The etiology of preeclampsia

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Preeclampsia is one of the “great obstetrical syndromes” in which multiple and sometimes overlapping pathologic processes activate a common pathway consisting of endothelial cell activation, intravascular inflammation, and syncytiotrophoblast stress. This article reviews the potential etiologies of preeclampsia. The role of uteroplacental ischemia is well-established on the basis of a solid body of clinical and experimental evidence. A causal role for microorganisms has gained recognition through the realization that periodontal disease and maternal gut dysbiosis are linked to atherosclerosis, thus possibly to a subset of patients with preeclampsia. The recent reports indicating that SARS-CoV-2 infection might be causally linked to preeclampsia are reviewed along with the potential mechanisms involved. Particular etiologic factors, such as the breakdown of maternal-fetal immune tolerance (thought to account for the excess of preeclampsia in primipaternity and egg donation), may operate, in part, through uteroplacental ischemia, whereas other factors such as placental aging may operate largely through syncytiotrophoblast stress. This article also examines the association between gestational diabetes mellitus and maternal obesity with preeclampsia. The role of autoimmunity, fetal diseases, and endocrine disorders is discussed. A greater understanding of the etiologic factors of preeclampsia is essential to improve treatment and prevention.

Key words: angiotensin receptor II, atherosclerosis, autoantibodies, Ballantyne syndrome, body mass index, COVID-19, Cushing’s syndrome, endothelial cell dysfunction, genetic incompatibility, gestational diabetes mellitus, hydatidiform mole, hydrops fetalis, hyperaldosteronism, hyperparathyroidism, hypertension, infection, inflammation, insulin resistance, intestinal dysbiosis, maternal antifetal rejection, metabolic syndrome, mirror syndrome, molar pregnancy, obesity, placental aging, placental ischemia, placental lesions of maternal vascular malperfusion, primipaternity, proteinuria, SARS-CoV-2, sleep-disordered breathing, sleep disorders, snoring, tolerance

Introduction

A fundamental task of medicine is establishing the causes of diseases. Preeclampsia, an enigmatic and elusive disorder of pregnancy, has been labeled the “disease of theories.” This condition is one of the “great obstetrical syndromes” in which multiple and sometimes overlapping pathologic processes activate a common pathway that leads to their clinical recognition. Just as the syndrome of preterm labor is recognized by the clinical manifestations of activation of the common pathway of parturition (ie, increased uterine contractility, cervical remodeling, and membrane and decidual activation), so is preeclampsia. The common pathway of preeclampsia consists of endothelial cell activation, intravascular inflammation, and syncytiotrophoblast stress. The diagnosis of preeclampsia has traditionally relied on the detection of hypertension and proteinuria, although professional organizations have recently suggested that, in the presence of multisystemic involvement, the diagnosis of preeclampsia can be made in the absence of proteinuria. A rich body of literature describes the risk factors for preeclampsia and...
eclampsia, thus providing insight on the conditions that increase the likelihood of these syndromes but which are not necessarily causal. However, the elucidation of etiologic factors is necessary to successfully treat and prevent disease. This article reviews the evidence linking such etiologic factors with preeclampsia and eclampsia, as summarized in Figure 1.

**Uteroplacental ischemia**

The principal mechanism of disease implicated in the etiology of preeclampsia and eclampsia is uteroplacental ischemia. In 1914, James Young proposed that interference with the uterine blood supply to the placenta would lead to placental infarctions that, in turn, would release toxins into the maternal circulation, thus causing eclampsia. This theory was based on the observation of placental infarctions in patients with eclampsia and on animal studies showing that subcutaneous injections of autolyzed human placental extracts into guinea pigs elicited convulsions, hepatic focal necrosis, and renal lesions, similar to those observed in women who died of eclampsia. Dixon and Taylor reported that intravenous injections of extracts of fresh human placenta induced an increase in blood pressure in cats, rabbits, and dogs, resembling the effects of adrena-line. Therefore, the search for the causes of preeclampsia and eclampsia and for the identity of the circulating “toxins” began more than a century ago.

Additional evidence supporting a role for uteroplacental ischemia in preeclampsia or eclampsia came from Ogden et al, who reported that clamping of the abdominal aorta below the renal arteries in dogs led to maternal hypertension that resolved after the clamp was released. Since this hypertensive response was not observed in nonpregnant animals, the investigators concluded that the signals responsible for hypertension must have originated within the gravid uterus. This interpretation was buttressed by the observation that, after removal of the pregnant uterus, clamping of the aorta did not elicit hypertension (Figure 2).

Subsequent studies reinforced this
Two lines of evidence support the view that placental ischemia rather than uterine ischemia is key. First, patients with an abdominal pregnancy can develop preeclampsia, even though the implantation site is outside of the uterus. Second, the placement of a Z-suture through the placenta to generate ischemia results in the development of hypertension and proteinuria (Figure 3, A–C),7 which can be attributed to the presence of a circulating “toxin.” Indeed, the transfusion of blood from a pregnant rabbit with experimental placental ischemia and hypertension (caused by the placement of a Z-suture) could induce hypertension in a non-pregnant rabbit (Figure 3, D).7

The first in vivo evidence indicating that women with preeclampsia had a decreased maternal placental blood flow was reported by Browne and Veall,8 who described the injection of radioactive sodium into the choriodecidual space of women with a normal pregnancy and in those with preeclampsia. The investigators noted that the blood flow at term was 600 mL/min, but it was substantially lower in patients with preeclampsia. These observations have been confirmed in subsequent studies using different radioactive tracers.9–13 For example, Lunell et al13 reported that uteroplacental blood flow was reduced by 50% in patients with preeclampsia and that the reduction was greater in those with severe preeclampsia than in those with mild disease.

The role of placental ischemia in the pathogenesis of preeclampsia is now well-established. Indeed, the most frequently used animal model of the syndrome is chronic reduction of uteroplacental perfusion in pregnant rats, generated by the placement of a constriction clip around the aorta below the renal arteries and before the origin of the uterine arteries at 14 days of gestation.14 This maneuver leads to a reduction in placental blood flow by approximately 40%, an increase in arterial blood pressure by 20 to 25 mm Hg by the 19th day of gestation, increased vascular resistance, decreased cardiac output and glomerular filtration rate, and the frequent appearance of proteinuria.14 This animal model recapitulates many of the findings of preeclampsia, including an increase in circulating concentrations of soluble vascular endothelial growth factor receptor-1 (sVEGFR-1; also known as soluble fms-like tyrosine kinase-1 [sFlt-1]) and endoglin, as well as a rise in the concentrations of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin (IL)-6. A similar nonhuman primate model of preeclampsia, developed in pregnant baboons by selective ligation of one uterine artery, led to the development of hypertension, proteinuria, and increased production of sFlt-1.15 Importantly, the administration of short interfering RNAs, which silence three of the sFlt-1 messenger RNA (mRNA) isoforms, suppressed sFlt-1 overexpression and reduced hypertension and proteinuria.16 These studies suggest that the soluble factor or “toxin” responsible for hypertension is, at least in part, sFlt-1. The reader is referred to the review by Bakrania et al17 in this Supplement for more details about the model and the pathophysiologic events caused by uteroplacental ischemia.

What is the cause of placental ischemia in women with preeclampsia? The traditional explanation has been that a defect in placentation leads to ischemia,18,19 but recently, a dysfunctional maternal cardiovascular system has been implicated.20 The developmental abnormalities include failure of physiologic transformation of the spiral arteries, which is characterized by a narrow diameter and retention of the muscle in the media of the vessel wall.18,19 The persistence of the muscular coat is thought to make the vessels susceptible to the effect of vasoconstrictive agents. In addition, arteries affected by the failure of physiologic transformation are more likely to develop atherosclerotic plaques (Figure 4), which also narrows the vessel lumen and further compromises placental perfusion.21,23–27
Atherosis is a lesion specific to the spiral arteries, equivalent to the atherosclerotic lesions observed in the coronary arteries. Figure 5 illustrates the typical lesions of atherosis in the spiral arteries and shows lipid-laden macrophages with deposition of fat droplets detected with Oil Red O staining. A systematic review and meta-analysis showed that placental lesions consistent with maternal vascular malperfusion (eg, placental infarction, failure of physiologic transformation of the spiral arteries, acute atherosis) are 4- to 7-fold more frequent in patients with preeclampsia than in those with a normal pregnancy. A comprehensive review of failure of physiologic transformation of the spiral arteries and atherosis by Staff et al is available as part of this Supplement. Atherosis is not specific to preeclampsia, and this type of lesion has been reported in other pregnancy-related conditions, such as spontaneous abortion, preterm labor, preterm prelabor rupture of membranes, fetal growth restriction, and fetal death. We have proposed that placental ischemia is a major mechanism of disease in various obstetrical syndromes and that the timing, severity, and duration of the process may explain the clinical occurrence of different obstetrical syndromes.

In summary, the following evidence supports a causal link between placental ischemia and preeclampsia: (1) experimentally induced ischemia in several animal models leads to hypertension and proteinuria; (2) uterine blood flow is lower in patients with preeclampsia than in women with a normal pregnancy; (3) placental histopathologic lesions indicative of ischemia (often referred to as maternal vascular malperfusion) are frequent and consistent findings in preeclampsia and eclampsia; (4) failure of physiologic transformation of the spiral arteries and atherosis are typical features of preeclampsia; (5) the pulsatility index of the uterine artery (a parameter to assess resistance to flow) is higher in patients with preeclampsia than in women with a normal pregnancy; this can be observed during the midtrimester of pregnancy, weeks or even months before the development of disease; (6) the maternal plasma placental growth factor (PIGF) to sFlt-1 ratio, a noninvasive marker of lesions of maternal vascular malperfusion, is elevated at the time of disease onset and before the development of preeclampsia; and (7) a blockage of sFlt-1 mRNA reduces hypertension and proteinuria. The frequency of placental lesions of maternal vascular malperfusion, of abnormalities in the uterine...
**FIGURE 4**
Physiologic transformation of the spiral arteries, failure of physiologic transformation, and atherosis

A, Diagram of the maternal blood supply to the placenta. A1, The spiral arteries undergo physiologic changes in normal pregnancy (gray). A2, In preeclampsia, the myometrial segment of the spiral artery fails to undergo physiologic transformation (blue), which is thought to explain the utero-placental ischemia observed in preeclampsia. A3, Nontransformed spiral arteries are prone to atherosis (yellow), characterized by the presence of lipid-laden macrophages within the lumen. B, C, and D: Placental basal plate spiral arteries with hematoxylin-eosin stain. B, Transformed spiral arteries are characterized by the presence of intramural trophoblasts (arrowheads) and fibrinoid degeneration (arrows) of the arterial wall. C, Nontransformed spiral arteries lack intramural trophoblasts and fibrinoid degeneration, and retain smooth muscle. Arrowheads indicate the presence of trophoblasts in myometrium, but not in the wall of the spiral artery. D, Acute atherosis in a decidual spiral artery. Many lipid-laden macrophages (arrows) are seen in the spiral artery with the lack of invasion of the trophoblast (arrowhead) into a myometrial segment of the spiral artery. Images (B, C, and D) stained with cytokeratin 7 (brown) and periodic acid—Schiff (pink), original magnification ×200. E, F, and G: Immunohistochemistry of placental basal plate spiral arteries. E, Endothelium (arrow, blue) in vessels with normal trophoblastic invasion, original magnification ×640. F, A non-transformed spiral artery with endothelium (blue, arrowhead) and smooth muscle cells (green, arrow), original magnification ×640. G, Atherosis lesions show numerous CD36-positive macrophages (red, blue arrow) and smooth muscle cells in the vessel wall (green, yellow arrow), original magnification ×400. Asterisk represents lumen of spiral artery. Modified from McMaster-Fay,21 Espinoza et al,22 and Labarrere et al.23

artery Doppler, and of alterations in biomarkers (eg, PlGF/sFlt-1) is higher in preterm preeclampsia than in term preeclampsia, suggesting that ischemia plays a different role in early-onset vs late-onset preeclampsia.45 The case for ischemia as an etiologic factor in preeclampsia could be even more persuasive if the treatment of ischemia could prevent the occurrence of preeclampsia. This evidence is difficult to obtain in humans. Some have argued that the efficacy of aspirin in reducing the rate of preterm preeclampsia may be due to the prevention of arterial thrombosis in the spiral arteries and intervillous space, given that this is the proposed mechanism of aspirin in the prevention of myocardial infarction in atherosclerosis.50 This interpretation would also explain the lack of efficacy of aspirin in preventing preeclampsia at term, given that ischemia plays a lesser role in such cases.

Maternal infection
Maternal infection has been implicated in the etiology of preeclampsia and eclampsia since the beginning of the 20th century. Albert51 proposed that the “toxins” responsible for eclampsia were the product of putrefactive changes in the uterine cavity caused by the action of bacteria (“a latent microbic endometritis”). Indeed, the microorganism “Bacillus eclampsiae” was proposed to be the cause.52,53 This view progressively fell out of favor because preeclampsia and eclampsia do not present the typical features of an infectious disease (eg, fever). Nonetheless, the idea that microorganisms may be involved in the genesis of preeclampsia and eclampsia recurs in the literature every few years, and it has recently reemerged on the basis of research on the relationship between preeclampsia and periodontal disease, urinary tract infection, SARS-CoV-2 infection, or maternal gut dysbiosis.

Periodontal disease
The best evidence to support a relationship between microorganisms and preeclampsia is derived from studies of periodontal disease, a condition that increases the risk of developing preeclampsia (odds ratio [OR], 1.76; 95% confidence interval [CI], 1.43–2.18).54 The term periodontal disease refers to an inflammatory condition caused by immune dysfunction initiated by bacteria within the oral cavity.55 The spectrum of disease ranges from gingivitis (inflammation of the soft tissues only) to the destruction of the connective tissue attachment and alveolar bone, which can eventually lead to tooth loss.55 Bacteria in the periodontal space can be released during dental procedures or in the course of severe disease, leading to a systemic inflammatory response that can cause damage as well as seeding sites in the cardiovascular system.56 Indeed, strong evidence indicates that periodontal disease is a risk factor for atherosclerotic cardiovascular diseases, including atherosclerosis, coronary artery disease, stroke, and atrial fibrillation.57,58 In brief, such evidence includes the following: (1) microorganisms found in the periodontal space can cause bacteremia59; (2) bacteria from the oral cavity are found in atheromatous plaques60; and (3) periodontal infections can induce vascular lesions in the aorta and coronary arteries.57,61 In an animal model of hyperlipidemia (apolipoprotein E-null mice), an oral infection with Porphyromonas gingivalis led to plaque in the aorta (Figure 6).61 Similar findings have been reported in an integrin β6-null mice model with polymicrobial infection with periodontal pathogens.62 The etiologic role of periodontal disease in preeclampsia is predicated on the same mechanisms linking periodontal disease and atherosclerosis.

Ruma et al63 have provided clinical, epidemiologic, and experimental evidence that periodontal disease is causally linked to preeclampsia. For example, women with periodontal disease who have an elevated C-reactive protein
concentration are at higher risk for the development of preeclampsia than women without periodontal disease (adjusted relative risk [aRR], 5.8; 95% CI, 1.2–26.9). An elevated C-reactive protein can provide a link between periodontal disease and preeclampsia by indicating that periodontal disease has led to a systemic inflammatory process.

**Urinary tract infection**

The relationship between microbial colonization of the maternal urinary tract and preeclampsia has also been reported. A systematic review noted that urinary tract infections are associated with preeclampsia (OR, 1.57; 95% CI, 1.45–1.70). However, the case definitions have been broad and have included pyelonephritis, lower urinary tract infections, and asymptomatic bacteriuria as a group. When subgroup analysis is performed, evidence for the association with preeclampsia either weakens or disappears. We have doubts that asymptomatic bacteriuria, which is not associated with a systemic inflammatory response, could cause preeclampsia.

**Other infections**

Isolated reports have documented instances in which preeclampsia was associated with malaria, cytomegalovirus, and human immunodeficiency virus, but the evidence is insufficient to support causality.

**Animal experiments**

Experimental observations supporting a causal relationship between infection and systemic inflammation and preeclampsia include that the administration of low-dose endotoxin in pregnant rats on the 14th day of gestation results in the development of high blood pressure, proteinuria, a low platelet count, and glomerular fibrinogen deposits. Bacterial endotoxin induces a systemic inflammatory response and activates thrombin through the release of tissue factor. These mechanisms have been implicated in the pathogenesis of preeclampsia.

**SARS-CoV-2 infection**

Early during the COVID-19 pandemic, it was recognized that a subset of nonpregnant patients developed hypertension, proteinuria, thrombocytopenia, and elevated liver enzymes. This resembled preeclampsia and the hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. A recent meta-analysis demonstrated that SARS-CoV-2 infection during pregnancy is associated with a significant increase in the odds of developing preeclampsia (OR, 1.58; 95% CI, 1.39–1.8), preeclampsia with severe features (OR, 1.76; 95% CI, 1.18–2.63), eclampsia (OR, 1.97; 95% CI, 1.01–3.84), and HELLP syndrome (OR, 2.01; 95% CI, 1.48–2.97). In addition, there is a dose-response
The relationship between SARS-CoV-2 infection and the subsequent development of preeclampsia (Figure 7). Patients with severe COVID-19 had a 5-fold greater risk of preeclampsia than those with asymptomatic COVID-19. The median interval between maternal SARS-CoV-2 infection and the subsequent development of preeclampsia is 3.8 weeks (interquartile range, 0.29–11.5). Therefore, SARS-CoV-2 infection meets several of the epidemiological postulates for causality.

One mechanism whereby SARS-CoV-2 infection can be causally linked to preeclampsia is endothelial dysfunction. Indeed, SARS-CoV-2 can infect endothelial cells that normally express angiotensin-converting enzyme 2, one of the cell entry receptors for the virus, leading to endotheliitis. Endothelial infection can induce the activation of thrombin, intravascular inflammation (ie, a cytokine storm), and damage of the microvasculature in target organs; this ultimately leads to the multisystemic nature of the syndrome, which includes not only renal involvement but also central nervous system dysfunction and seizures.

Therefore, an infectious process, which targets the endothelium, could lead to a syndrome similar to preeclampsia and eclampsia (Figure 8).

A fascinating observation is that the recovery from COVID-19 has been followed by the disappearance of hypertension and proteinuria without delivery of fetus and placenta. It remains to be determined whether preeclampsia after SARS-CoV-2 infection requires placental involvement or, merely, endothelial cell dysfunction and intravascular inflammation.

Serum and plasma concentrations of sFlt-1, a marker of endothelial dysfunction, are elevated in nonpregnant patients with COVID-19. This finding is consistent with another study in which pregnant women with severe COVID-19 had an elevated maternal plasma concentration of sFlt-1 and a high sFlt-1/PIGF ratio. Genetic susceptibility may explain why some women with COVID-19 infection develop preeclampsia but others do not.

**Maternal intestinal dysbiosis**

The human gut microbiota plays an important role in host nutrition, harvesting of energy, and immune response to potential pathogens. Normal pregnancy represents a state in which a major reorganization of energy distribution (harvesting, storage, and expenditure) is related to the need to support the growth and development of the fetus and placenta. Studies of the gut microbiota in the third trimester of pregnancy showed that there is an overall increase of *Proteobacteria* and *Actinobacteria* coupled with a reduction in microbial richness. When the intestinal content from women with a normal pregnancy in the third trimester was administered to germ-free mice, it increased adiposity and insulin resistance, which have been attributed to the proinflammatory effects of the gut microbiota.

Gut dysbiosis, or an imbalance among the human gut’s microbial communities, is now implicated in the development of atherosclerosis, hypertension, proteinuria, cardiometabolic syndrome, and recently, preeclampsia. A causal link between gut dysbiosis and
FIGURE 8
Placental ischemia and SARS-CoV-2 infection can elicit intravascular inflammation and endothelial cell dysfunction

Placental syncytiotrophoblast stress induces excessive release of sFlt-1 into the maternal circulation. sFlt-1 binds to free PlGF or VEGF (angiogenic factors) with high affinity, thus preventing their interaction with their cell-surface receptors (i.e., VEGFR-1) on the endothelial cells, leading to endothelial dysfunction. SARS-CoV-2 also targets the endothelium which normally expresses ACE-2, one of the cell entry receptors for the virus, leading to endothelitis, which can induce intravascular inflammation (i.e., cytokine storm) and endothelial dysfunction.

ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; sFlt-1, soluble fms-like tyrosine kinase-1; VEGFR-1, vascular endothelial growth factor receptor-1.


cardiovascular disease has been proposed based on observations that the transplantation of fecal material from hypertensive and nonpregnant human subjects to germ-free mice led to hypertension.108 Similarly, fecal transplants from mice prone to atherosclerosis can transmit the condition to susceptible mice (e.g., apolipoprotein E-null mice).118 This effect has been attributed, at least in part, to trimethylamine N-oxide, a bacteria-derived metabolite from choline and carnitine that is present in gut dysbiosis and has been shown to accelerate the development of atherosclerosis.107,118

Changes in the composition of human gut microbiota have been reported in preeclampsia114,115,117,119 and persist up to six weeks postpartum.120 These changes included a reduction in the microbial burden of Firmicutes, Clostridia, Clostridiales, and Ruminococcus and an increase in Bacteroidetes, Proteobacteria, Actinobacteria, Bacteroidia, Gammaproteobacteria, and Enterobacteriaceae (Figure 9, A).119 Importantly, fecal transplantation from pregnant women with preeclampsia to mice led to the development of the syndrome, and this provides evidence of causality.115 The experimental paradigm consisted of the administration of fecal material from pregnant women with and without preeclampsia to nonpregnant mice that had received antibiotics for five days (to change gut flora).115 Six weeks after the first fecal inoculation, mice were mated.115 Pregnant mice that had received the fecal microbiota transplant from mothers with preeclampsia developed high systolic blood pressure and proteinuria, and they delivered fewer live pups than mice that received fecal microbiota transplants from women with a normotensive pregnancy (Figure 9, B).115 Collectively, this evidence suggests a role for gut dysbiosis in preeclampsia. However, further investigation of the precise mechanisms that may explain this phenomenon and the different levels of susceptibility among pregnant women is necessary.

Gestational diabetes mellitus, maternal obesity, and metabolic syndrome

Gestational diabetes mellitus

Gestational diabetes mellitus is an independent risk factor for preeclampsia, after adjusting for confounders.121,122 In a retrospective study of 647,392 pregnancies, women with gestational diabetes had an increased risk of preeclampsia (adjusted odds ratio [aOR], 1.29; 95% CI, 1.19–1.41).121 Preexisting diabetes mellitus has also been linked to the development of preeclampsia as reported in a systematic review (aRR, 3.56; 95% CI, 2.54–4.99).123 Diabetes mellitus is considered to be strongly associated with late-onset rather than early-onset preeclampsia (early-onset: aOR, 1.87; 95% CI, 1.6–2.18; late-onset: aOR, 2.46; 95% CI, 2.32–2.61).124 The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Cooperative Research Group reported a significant positive association between the degree of maternal hyperglycemia and preeclampsia: the odds ratio for each standard deviation increase in glucose concentrations (fasting, 1 hour, and 2 hours after a 75 mg glucose tolerance test) ranged from 1.21 to 1.28.125

The case for a causal role is strengthened by the observation that the treatment of gestational diabetes mellitus with diet,126 insulin,127,128 and metformin129–132 reduces the risk of preeclampsia. Two randomized clinical trials have shown that the treatment of gestational diabetes mellitus with insulin reduces the risk of preeclampsia (adjusted treatment effect: 0.70; 95% CI, 0.51–0.95).127,128 Metformin is associated with a reduced risk of preeclampsia...
Relative risk [RR], 0.68; 95% CI, 0.48–0.95) and prolongation of gestation in women with preterm preeclampsia (median, 18 days). Prenatal exercise has also been reported to decrease the rate of preeclampsia by 41% in a systematic review and meta-analysis.

Collectively, the evidence suggests a causal relationship between gestational diabetes and preeclampsia given the consistency of association, the temporal relationship, and the efficacy of interventions, such as insulin and metformin, in reducing the rate of preeclampsia.

**Maternal obesity**

Obesity, defined by a body mass index (BMI) of ≥30.0 kg/m², is strongly associated with preeclampsia. A meta-analysis of 29 prospective cohort studies (1,980,761 participants and 67,075 cases of preeclampsia) showed that maternal obesity was significantly associated with the development of preeclampsia (aOR, 2.93; 95% CI, 2.58–3.33), and the risk was higher in severe obesity (BMI ≥35 kg/m²; aOR, 4.14; 95% CI, 3.61–4.75). A similar finding was reported in overweight women (BMI, 26.1–29.0 kg/m²) who had a higher risk of preeclampsia than women with a normal BMI (RR, 1.57; 95% CI, 1.49–1.64).

A dose-dependent relationship has been reported between prepregnancy BMI and the risk of preeclampsia in both nulliparous and parous women in a large epidemiologic study (41,000 nulliparous and 29,000 multiparous women) (Figure 10). Data from the US Collaborative Perinatal Project indicated similar results for White and African American women (severe preeclampsia: African American, OR, 3.2; 95% CI, 2.5–5.0; White, OR, 3.4; 95% CI, 2.1–5.6). Most studies report that obesity predisposes mainly to late-onset preeclampsia. However, a recent population-based study, which used US vital statistics data and included 15.8 million women (48,007 cases of early-onset disease and 777,715 cases of late-onset disease), demonstrated that maternal obesity is associated with an increased risk of both early-onset and late-onset disease (eg, BMI ≥40 kg/m²: early-onset disease, aRR, 2.18; 95% CI, 2.12–2.24; late-onset disease, aRR, 3.93; 95% CI, 3.91–3.96). In addition, preconceptional maternal weight loss, either by lifestyle modification or bariatric surgery, is effective in reducing the risk of preeclampsia (OR, 0.67; 95% CI, 0.51–0.88).

**Metabolic syndrome**

The term “metabolic syndrome” refers to a cluster of metabolic abnormalities, including central obesity, insulin resistance, atherogenic dyslipidemia, and hypertension. This syndrome is strongly associated with systemic inflammation, oxidative stress, and endothelial dysfunction, all of which are features of preeclampsia. A retrospective cohort study of 212,463 women showed that the presence of prepregnancy metabolic syndrome is associated with an increased risk of preeclampsia (aOR, 1.48; 95% CI, 1.26–1.74). Preeclampsia is also a...
risk factor for the subsequent development of metabolic syndrome after delivery. Moreover, bariatric surgery performed before pregnancy as a treatment for metabolic syndrome is associated with a lower rate of pre-eclampsia (aOR, 0.2; 95% CI, 0.09–0.44). The mechanisms whereby insulin resistance predisposes to the development of preeclampsia are related to intravascular inflammation and endothelial cell dysfunction, which is the common pathway of the syndrome. Nonetheless, insulin resistance is neither required nor sufficient for the development of preeclampsia. The reason why some but not all patients with insulin resistance develop preeclampsia is unknown.

Sleep disorders
Sleep-disordered breathing, a term encompassing obstructive sleep apnea, snoring, periodic episodes of hypoxia, central apnea, and sleep hypopnea, is a risk factor for preeclampsia during pregnancy. A systematic review and meta-analysis of 120 studies, which included a total of 58,123,250 pregnant women, indicated that maternal sleep disturbances during pregnancy are associated with an increased risk of preeclampsia (OR, 2.80; 95% CI, 2.38–3.30); these disturbances included subjective sleep-disordered breathing (OR, 3.52; 95% CI, 2.58–4.79), obstructive sleep apnea (OR, 2.36; 95% CI, 2.00–2.79), and restless legs syndrome (OR, 1.83; 95% CI, 1.04–3.21).

Snoring is defined as the vibration of respiratory structures resulting from turbulent flow when the upper airway narrows during sleep. It is more common in pregnant women than in nonpregnant women (14%–23% vs 4%). Snoring increases the risk of hypertension and new-onset snoring during pregnancy is associated with preeclampsia (OR, 1.59; 95% CI, 1.06–2.37). Evidence supporting a causal relationship between snoring and preeclampsia is that treatment with nasal continuous positive airway pressure (CPAP) improved blood pressure in women with preeclampsia. Edwards et al reported that autosetting nasal CPAP administered during sleep resulted in a marked reduction in blood pressure. Of interest, Bourjeily et al reported that pregnant women with obstructive sleep apnea presented a higher maternal plasma sFlt-1/PlGF ratio than those in a control group and that maternal sFlt-1 concentrations were decreased after CPAP treatment.

In normal pregnancy, blood pressure has a circadian rhythm with highest values at daytime. A reversed diurnal blood pressure rhythm (ie, nocturnal blood pressure is higher than diurnal pressure) has been reported in preeclampsia. Polysomnography has shown that patients with preeclampsia have altered sleeping patterns, specifically spending more time in slow-wave sleep than patients with a normal pregnancy (percentage of time spent in slow-wave sleep: 43±3 vs 21±2; P<.001). One possible explanation for this finding is that cytokines, such as IL-1 and TNF-α, can increase the amount of slow-wave sleep; these cytokines are elevated in the maternal circulation of patients with preeclampsia. The proposed mechanisms linking sleep disorders and preeclampsia involve intravascular inflammation and endothelial cell dysfunction.

Molar pregnancy
Hydatidiform mole, a gestational trophoblastic disease characterized by abnormal proliferation of trophoblastic and hydropic changes of the chorionic villi, is associated with preeclampsia that sometimes presents before 20 weeks of gestation. The frequency of preeclampsia in patients with hydatidiform mole ranges from 27% to 40% and is higher in patients untreated until the second trimester.
The mechanism whereby a complete hydatidiform mole causes preeclampsia is thought to involve an excessive production of sFlt-1. Maternal serum sFlt-1 concentrations are 2- to 3-fold higher in patients with hydatidiform mole than in gestational age-matched controls. An increased expression of sFlt-1 in the molar tissue has also been reported. Placentas with hydatidiform mole have increased expression of LIGHT (TNFSF14, or tumor necrosis factor superfamily member 14), which is colocalized with sFlt-1 in the molar tissue. Chorionic villi in molar tissue are edematous or hydropic and are often avascular or display markedly reduced vessel density. These villus capillary changes may lead to excessive production of sFlt-1 and preeclampsia.

Fetal diseases
Specific fetal diseases associated with the development of preeclampsia include: (1) Ballantyne or mirror syndrome, (2) trisomy 13 or triploidy, and (3) unique complications of multiple gestations (eg, twin-to-twin transfusion syndrome or selective fetal growth restriction). Ballantyne or mirror syndrome reflects a simultaneous edematous state of the mother, fetus, and placenta (also called triple edema). This syndrome has been observed in rhesus isoimmunization, cytomegalovirus, parvovirus B19 infection, Ebstein’s anomaly, aneurysms of the vein of Galen, fetal supraventricular tachycardia, and placent chorioangiomas. In mirror syndrome, the mother may develop proteinuria, hypertension, and even severe preeclampsia. Approximately 60% of patients with mirror syndrome have hypertension. The reversal of preeclampsia and Ballantyne syndrome can occur after intrauterine transfusion in parvovirus-induced hydrops without delivery. Patients with mirror syndrome can have an increased maternal plasma concentration of sFlt-1 that can return to normal after intrauterine transfusion.

Another example of preeclampsia associated with fetal disease is trisomy 13, or triploidy. In a case control study, the frequency of preeclampsia was higher in cases with trisomy 13 than in the control group with normal karyotype (44% vs 8%, P=.001). Women with a trisomy 13 pregnancy have a higher serum sFlt-1/PlGF ratio, and their placentas show greater staining for sFlt-1 than those of euploid and trisomy 21 pregnancies. Interestingly, sFlt-1 is located on chromosome 13, suggesting that an extra copy of chromosome 13 may lead to increased production of sFlt-1.

Multiple gestations complicated by twin-to-twin transfusion syndrome or selective fetal growth restriction are at a greater risk for preeclampsia. Selective termination of pregnancy, or the death of one twin, can lead to the resolution of hypertension and proteinuria as well as to the improvement in the angiogenic and antiangiogenic profiles. These observations suggest that preeclampsia can resolve without delivery and that fetal compromise may induce the syndrome in some cases.

Autoimmune mechanisms: a role for antibodies against angiotensin II type I receptor
Preeclampsia is not traditionally considered an autoimmune disorder. However, the possibility of an autoimmune mechanism of disease has been investigated for several decades, given that patients with systemic autoimmune diseases such as systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS) are at increased risk for preeclampsia (SLE: RR, 1.91; 95% CI, 1.44–2.53; APS: RR, 1.81; 95% CI, 1.33–2.45). Similarly, several studies have shown that specific autoantibodies, such as anti-β2 glycoprotein-I (ab2GPI), anticardiolipin antibodies (aCL), or lupus anticoagulant (LA), are associated with preeclampsia. However, the most compelling case for the role of an autoimmune mechanism in the pathogenesis of preeclampsia can be made with antibodies against the angiotensin II receptor.

Nearly two decades ago, Wallukat et al reported that women with preeclampsia had antibodies that bind to the angiotensin II type I receptor (AT1-AA). Subsequently, substantial evidence has accumulated supporting the role of AT1-AA in the pathogenesis of preeclampsia. Such evidence includes: (1) 80% of women with preeclampsia have increased concentrations of AT1-AA in maternal serum at the time of diagnosis; (2) the concentration of AT1-AA in maternal serum correlates with the severity of hypertension and proteinuria; and (3) the administration of AT1-AA to pregnant rats leads to hypertension, proteinuria, glomerular capillary endotheliosis, an increased production of sFlt-1 and soluble endoglin. The increase in mean arterial pressure can be attenuated by the administration of an AT1-receptor blocker (losartan). It is noteworthy that a longitudinal study did not find that the maternal plasma concentration of AT1-AA increased prior to the diagnosis of preeclampsia.

What causes the excessive production of AT1-AA? Placental ischemia, caused by a reduction in uterine perfusion pressure, has been shown to increase the concentration of serum AT1-AA in pregnant rats. The importance of this in preeclampsia has been inferred by the observation that inhibition of AT1-AA by the administration of an epitope-binding peptide can reduce maternal blood pressure and plasma concentrations of endothelin-1, sFlt-1, and isoprostanes, which are markers of oxidative stress.

Other factors that can modify the activity of AT1-AA are cytokines. Indeed, the administration of TNF-α, IL-6, IL-6, and IL-17 to pregnant rats enhances AT1-AA activity and can induce preeclampsia, which is prevented by AT1-AA blockade.

Placental aging
Cells and organisms have a finite lifespan. Human cells in culture can multiply (mitosis) a limited number of times (the Hayflick limit) before they stop dividing and, subsequently, undergo programmed cell death, or apoptosis. The placenta is also thought to have a prespecified lifetime, and as age advances, the functional capacity of placental cells declines.
Placental aging has been described for several decades, and premature aging has been implicated as a mechanism of disease for obstetrical outcomes, e.g., preeclampsia, fetal growth restriction, fetal death, and preterm labor.

Cytotrophoblasts are replicating cells, but the syncytiotrophoblast is generated by fusion and, therefore, is in a state of senescence (defined as the inability to multiply). Evidence supporting the concept that senescence is present in the normal syncytiotrophoblast includes the following findings: (1) high lysosomal activity indicated by staining with beta-galactosidase; (2) increased expression of cyclin-dependent kinase, p53, p21, and p16; and (3) the presence of syncytial knots, proposed to be equivalent to senescence-associated heterochromatic foci, which are clusters of chromatin in the nucleus of senescent cells. Cindrova-Davies et al. demonstrated that markers of senescence increase in normal placentas as a function of advancing gestational age.

Placentas of patients with preeclampsia exhibit greater expression of p53, p21, and p16, shorter telomeres, and reduced telomerase activity. Redman et al. have proposed that with advancing gestational age some patients develop a “twilight placenta,” a condition in which the organ is affected by senescence. When placental growth reaches its limits at term, terminal villi become overcrowded with diminished intervillous space, leading to respiratory failure of the placenta (Figure 11) and contributing to intervillous hypoxia and syncytiotrophoblast stress. A twilight placenta has been invoked as a potential cause for late pregnancy complications such as late-onset preeclampsia, unexplained term stillbirth, or fetal death in prolonged pregnancy. At present, there is not an easy or practical way to determine placental age; however, recent studies have identified an epigenetic clock for placental dating, which may be used to examine the role of placental aging in pregnancy complications in the future.

Breakdown of maternal-fetal immune tolerance
Viviparity involves the coexistence of two individuals (mother and fetus) with different genetic makeups. The placenta and fetus are viewed as the most successful transplant in biology (often referred to as a semiallograft because of maternal and paternal contributions), and the mechanisms responsible for immune tolerance have been the subject of investigation for decades. Two typical features of the adaptive immune system are memory and specificity. A role for the immune system in the pathogenesis of preeclampsia has been proposed as the syndrome is more common in primigravidas and in multigravidas with different fathers (primipaternity). A memory-like phenomenon that protects mothers against paternal antigens in subsequent pregnancies has been
invoked to explain the predilection for primigravidae. The higher frequency of preeclampsia in multigravidae with pregnancies from different fathers has been attributed to an immune process specific to paternally derived antigens. Additional evidence for this is that preeclampsia is more common in pregnancies resulting from egg donation in which placenta and fetus are complete grafts rather than semiallografts.

The placenta and fetus, express both paternal and maternal antigens. The syncytiotrophoblast is in direct contact with maternal blood, thus the maternal immune system is exposed to paternal antigens expressed by the placenta. Immune tolerance is considered important for successful pregnancy, and a breakdown of tolerance can lead to maternal antifetal rejection, placental damage, and pregnancy complications that may include preeclampsia. Placental lesions, which represent manifestations of maternal antifetal rejection, are villitis of unknown etiology (VUE), massive perivillous fibrin deposition, chronic choioamnionitis, chronic intervillositis, and chronic deciditis of the placental basal plate. In VUE, the battleground for immune damage is the chorionic villi, and maternal T-cells infiltrate the villous tree (Figure 12, A and B). The frequency of VUE is higher in late-onset preeclampsia than in normal pregnancy but not in early-onset preeclampsia (Figure 12, C). Massive perivillous fibrin deposition is characterized by extensive deposition of fibrinoid material in the intervillous space, hypoplasia, and sclerosis of the engulfed villi. This lesion is associated with preeclampsia in one in five cases.

Maternal-fetal genetic incompatibility has been implicated in the genesis of preeclampsia. Placentation is regulated by interactions between members of the killer cell immunoglobulin-like receptors (KIRs) expressed by decidual natural killer (dNK) cells and trophoblast human leukocyte antigen (HLA)-C molecules. Extravillous trophoblasts are specialized fetal cells that invade the decidua basalis, where they come into direct contact with maternal immune cells, such as dNK cells, macrophages, T cells, B cells, and dendritic cells. Extravillous trophoblasts do not express major classical MHC I molecules such as HLA-A and HLA-B. Instead, these cells express HLA-C and non-classical MHC I molecules (HLA-E and HLA-G). The latter two are largely monomorphic, whereas HLA-C is polymorphic and will vary according to the genetic makeup of the father. HLA-C molecules on the surface of extravillous trophoblasts are recognized by receptors of dNK cells called KIRs. Both maternal KIR and fetal HLA-C genes are highly polymorphic, and the interaction between HLA-C and KIRs has a unique role in placentation by facilitating trophoblast invasion of the decidua and the physiologic transformation of the spiral arteries.

Some maternal-fetal genotypes for HLA-C and KIR favor a well-developed placentation and others do not. Moffet al have shown that normal pregnancy is more common when a mother has the KIR BB genotype and the fetus has HLA-C1 genes, whereas preeclampsia is more frequent when a mother carries the KIR AA genotype with fetal HLA-C2 genes (HLA-C2 vs HLA-C1 in KIR AA mothers: 45% vs 20%; OR, 2.38; 95% CI, 1.45–3.90). By contrast, Johnsen et al reported that fetal HLA-C2 combined with maternal KIR BB was associated with placental lesions of acute atherosis. Patients with preeclampsia and acute atherosis presented this specific genetic combination in 60% of cases. The mechanism whereby a breakdown of maternal-fetal immune tolerance leads to preeclampsia seems to involve defective placentation, an example of the convergence of an immune disorder with uteroplacental ischemia. Such can be the case for other etiologic factors in preeclampsia. For further details of immunologic mechanisms of preeclampsia, the reader is referred to the review article by Robillard et al in this Supplement and to an upcoming publication by our group (Romero R, personal communication).

**Endocrine disorders**

Several endocrine disorders have been associated with preeclampsia, however the evidence to support causality is not strong. This section will review the evidence in support of the association and the proposed mechanisms for activation of the common pathway of preeclampsia.

**Hyperparathyroidism**

Normal pregnancy is characterized by changes in maternal calcium hemostasis, which are thought to occur to meet fetal demands. By term, the fetus has 30 g of calcium, 20 g of phosphorus, and 0.8 g of magnesium, and 80% of calcium is deposited during the third trimester. The evidence that links altered calcium hemostasis to preeclampsia is as follows: (1) hypocalcemia is a risk factor for preeclampsia (OR, 7.63; 95% CI, 1.64–35.37); (2) low vitamin D concentration in early pregnancy is associated with a 5-fold increased risk for preeclampsia; (3) hyperparathyroidism is commonly found in pregnant women with low calcium and vitamin D; (4) patients diagnosed with parathyroid adenoma are at increased risk for preeclampsia (OR, 6.89; 95% CI, 2.30–20.58); (5) absence of vitamin D prophylaxis in the mother’s childhood is associated with a higher risk of preeclampsia; and (6) administration of vitamin D combined with calcium or multivitamin supplement has been shown to reduce blood pressure and the frequency of preeclampsia in a randomized trial. The proposed mechanisms whereby primary hyperparathyroidism leads to preeclampsia are endothelial cell damage, increased insulin resistance, left ventricular hypertrophy, and dyslipidemia.

**Cushing syndrome, aldosteronism, pheochromocytoma, and paraganglioma**

Cushing syndrome is associated with an increased risk of preeclampsia (aOR, 2.2; 95% CI, 1.18–4.41). In nonpregnant subjects, chronic glucocorticoid excess of Cushing syndrome is commonly associated with an increased cardiometabolic risk through an increase in proinflammatory adipokine production.
FIGURE 12
Villitis of unknown etiology as a pathologic manifestation of maternal anti-fetal rejection

A, Circulating maternal T cells entering the intervillous space can infiltrate the villous tree. After maternal T-cell infiltration, Hofbauer cells (fetal placental macrophages) are activated. This can be interpreted as evidence of semiallograft rejection because maternal T cells (recipient of the semiallograft) infiltrate the placenta (semiallograft). B, Normal chorionic villi showing the villous core with fetal vessels and stroma. The intervillous space contains maternal red blood cells. The rest of the image shows cross-sections of the villous tree of the placenta; chorionic villi are lined with syncytiotrophoblast. Inside the villi, fetal capillaries are observed. C, Destructive inflammation of the chorionic villus (asterisk). The inflammatory process is diagnosed by the presence of an infiltration of mononuclear cells. Obliteration of the villous capillaries is also seen in comparison to unaffected villi adjacent to the distorted villus (asterisk). Unaffected villi (black arrow). D, Destructive inflammation of the chorionic villi (asterisk). Immunoperoxidase staining for CD8+ T cells. Cells stained in brown express CD8 on their surface and are therefore cytotoxic lymphocytes. These cells are of maternal origin, and are derived from the intervillous space. Original magnification (B-D), 200 x. E, The frequency of villitis of unknown etiology is higher in late-onset preeclampsia than normal pregnancy (p<0.001). Modified from Kim et al. and Stanek et al.

alteration of coagulation, platelet function, and endothelial activation.305–307

Primary aldosteronism is the most common form of endocrine hypertension, and it can be caused by an aldosterone-producing adenoma or a bilateral adrenal hyperplasia.308,309 Increased aldosterone secretion suppresses renin activity, leading to hypertension, hypokalemia, and hypernatremia.310,311 Twenty-five percent of women with this disorder develop preeclampsia.302,293

Pheochromocytoma and paraganglioma are rare catecholamine-producing tumors, with a reported frequency of 1 in 54,000 pregnancies.312 An excess of catecholamines released by these tumors can elicit signs or symptoms similar to preeclampsia (e.g., hypertension, headache, and proteinuria), making the diagnosis of pheochromocytoma during pregnancy difficult.313,314 A recent meta-analysis that included 204 pregnant patients with pheochromocytoma and paraganglioma showed that 20% of patients were initially misdiagnosed with preeclampsia.314 Maternal and fetal mortality were as high as 28% and 27%, respectively, when there was a delay in diagnosis and treatment.314,315 Only a few studies have reported that patients with pheochromocytoma develop superimposed preeclampsia.294,295 Therefore, the existence of an association is not yet clear.314

Conclusion

Multiple and sometimes overlapping insults can induce an adaptive vascular response in pregnancy, which can be recognized clinically by the presence of hypertension and proteinuria (or other signs of multisystemic involvement). When this response becomes maladaptive, it can cause target organ damage and become potentially life-threatening to the mother and fetus.

At present, the classification of the syndrome is largely based on the gestational age at the time of diagnosis (early-onset vs late-onset preeclampsia). Early-onset preeclampsia is associated with defective placentation, whereas late-onset preeclampsia seems to be related to the mismatch between maternal perfusion and fetoplacental demands, along with a maternal pre-disposition to cardiovascular disease. Hence, the need to identify the fundamental causes of the vascular dysfunction responsible for preeclampsia to develop comprehensive predictive models and preventive interventions. This review highlights the multiple etiologies of the syndrome of preeclampsia. We propose that multiple etiologic factors converge to cause endothelial cell dysfunction, intravascular inflammation, and syncytiotrophoblast stress. The recognition that a viral infection such as COVID-19 can induce preeclampsia raises challenging questions of whether preeclampsia is a pregnancy-specific disorder caused by the placenta and cured only by delivery. Further research is required to assess the relative contribution of each cause of this elusive disease.

REFERENCES


