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The etiology of preeclampsia

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Abstract

A fundamental task in medicine is the understanding of the causes of diseases. Preeclampsia and eclampsia, an enigmatic and elusive disorder, have been labeled the “disease of theories.” Preeclampsia is one of the “great obstetrical syndromes” in which multiple and sometimes overlapping pathologic processes activate a common pathway composed of endothelial cell activation, intravascular inflammation, and syncytiotrophoblast stress. This article addresses the potential etiologies, or causal explanations, for preeclampsia. The role of uteroplacental ischemia is well established, based upon a solid body of clinical and experimental evidence. A causal role for microorganisms has gained recognition through the realization that periodontal disease and

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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 appears to be causally linked to preeclampsia are reviewed as well as the mechanisms whereby this viral infection can cause this syndrome. Particular etiological 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, while another, such as placental aging, may operate largely through syncytiotrophoblast stress. This article also examines the nature of the association between gestational diabetes mellitus and maternal obesity in preeclampsia. The various roles of autoimmunity, fetal diseases, and endocrine disorders are also discussed. A greater understanding of the etiologic factors of preeclampsia is essential to improve treatment and prevention.

Condensation:

This article describes the causal risk factors, or etiology, of preeclampsia.

Keywords

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 anti-fetal 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 in medicine is the understanding of the causes of diseases. Preeclampsia and eclampsia, the enigmatic, elusive disorders of pregnancy, have been labeled the "diseases of theories". Preeclampsia and eclampsia are among the "great obstetrical syndromes" in which multiple and sometimes overlapping pathologic processes activate a common pathway that leads to the clinical recognition of these disorders. 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 are preeclampsia and eclampsia. Their common pathway consists of endothelial cell activation, intravascular inflammation, and syncytiotrophoblast stress, and the diagnosis has traditionally rested in the detection of hypertension and proteinuria, although professional organizations had recently recommended that the diagnosis can be made in the absence of proteinuria when patients have evidence of multi-systemic involvement.

A rich body of literature describes the risk factors for preeclampsia and eclampsia (ie the conditions that increase the likelihood of these syndromes but are not necessarily causal). However, the elucidation of etiologic, or causal, factors is necessary to successfully treat and prevent disease. This article reviews the evidence linking these etiologic factors with preeclampsia and eclampsia, which is 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 of 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.[1] This theory was based on the demonstration that placental infarctions were observed in patients with eclampsia and on animal studies that showed subcutaneous injections of extracts of the autolyzed human placenta into guinea pigs elicited convulsions, hepatic focal necrosis, and renal lesions, similar to those observed in women who died of eclampsia.[1] 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 adrenaline.[2] Therefore, the search for the causes of preeclampsia and eclampsia and for the identity of the circulating “toxins” began more than 100 years ago.

Additional evidence supporting a role for uteroplacental ischemia came from studies by Ogden, Hildebrand, and Page who reported that clamping of the abdominal aorta below the renal arteries (to avoid renovascular hypertension) in dogs reduced uteroplacental perfusion; furthermore, this response was followed by maternal hypertension that resolved after the clamp was released.[3] Because this hypertensive response was not observed in non-pregnant animals, the investigators concluded that the signals responsible for hypertension must have originated within the gravid uterus.[3] Another observation buttressed this interpretation: after removal of the pregnant uterus, the clamping of the aorta did not elicit hypertension (Figure 2).[3, 4]

Subsequent studies strengthened this concept, demonstrating that placental ischemia, generated by placing silver clips in the uterine arteries of pregnant dogs, led to hypertension and proteinuria.[5] Two lines of evidence supported the view that placental ischemia rather than uterine ischemia was key. First, patients with an abdominal pregnancy were known to develop preeclampsia given that the implantation site was outside of the uterus.[6] Second, the placement of a Z suture through the placenta to generate ischemia resulted in the development of hypertension and proteinuria (Figure 3A-3C).[7] Moreover, the existence of a circulating “toxin,” supported by the observation that the administration of blood from a rabbit with experimental placental ischemia caused by the Z suture, resulted in hypertension in non-pregnant animals (Figure 3D).[7]

The first in vivo evidence indicating that women with preeclampsia had decreased maternal-placental blood flow was reported by McClure Browne and Veall,[8] who described the injection of radioactive sodium into the choriodecidual space of women with a normal pregnancy and in those affected by preeclampsia. The investigators noted that the blood flow at term was 600 mL/minute, but it was substantially lower in patients with preeclampsia. These observations have been confirmed with different radioactive tracers in subsequent studies.[9-13] For example, Lunell et al [13] 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 implemented 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] In addition, this effect led to a reduction in placental blood flow by approximately 40%, an increase in arterial blood pressure by 20-25 mm Hg by day 19 of pregnancy, increased vascular resistance, decreased cardiac output and glomerular filtration rate, and the frequent appearance of proteinuria.[14] This model recapitulated two of the many findings of preeclampsia: (1) 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, and (2) a rise in the concentrations of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6). A similar non-human 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 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, George, and Granger[17] 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 more recently, a dysfunctional maternal cardiovascular system has been implicated.[20] The developmental abnormalities include failure of physiologic transformation of the spiral arteries which are 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 failure of physiologic transformation are more likely to develop *atherosis* (Figure 4), which also narrows the vessel lumen and further compromises placental perfusion.[21-26] Atherosis is a lesion specific to the spiral arteries, which is 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 the deposition of fat droplets detected with oil red-O stain. 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) is four-fold to seven-fold higher in patients with preeclampsia than in those with a normal pregnancy.[27] A comprehensive review of the failure of physiological transformation and spiral artery atherosis by Staff et al [28] 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,[29] preterm labor,[30] preterm prelabor rupture of the membranes,[31] fetal growth restriction,[32, 33] and fetal death.[25, 29] 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 insult may explain the clinical occurrence of different obstetrical syndromes.[34]

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;[3, 5, 7] (2) uterine blood flow is lower in patients with preeclampsia than in normal pregnant women;[8, 11, 13] (3) placental histopathologic lesions indicative of ischemia (often referred to as maternal vascular malperfusion) are frequent, consistent findings in preeclampsia and eclampsia; [27] (4) the failure of physiologic transformation of the spiral arteries and atherosis are typical features of preeclampsia;[28, 35] (5) the pulsatility index of the uterine artery (a parameter to assess resistance to flow) is higher in patients with preeclampsia than in normal pregnant women; this finding can be observed during the midtrimester of pregnancy, weeks or even months before the development of the disease;[36, 37] (6) the maternal plasma placental growth factor (PlGF)/sFlt-1 ratio, a non-invasive marker of lesions of maternal vascular malperfusion, is elevated at the time of the onset of disease and prior to the development of preeclampsia;[38-44] and (7) a blockade of sFlt-1 mRNA reduces hypertension and proteinuria.[16] The frequency of placental lesions of maternal vascular malperfusion, of abnormalities in the uterine artery Doppler, and of alterations of biomarkers (eg PlGF/sFlt-1) is higher in preterm preeclampsia than in term preeclampsia, suggesting that ischemia plays a different role in early-onset versus late-onset preeclampsia.[45-48]

The case for ischemia as an etiologic factor could be even more persuasive if the treatment of ischemia could prevent the occurrence of preeclampsia. This evidence is difficult to generate in pregnant humans. Nonetheless, it can be argued that the efficacy of aspirin in reducing the rate of preterm preeclampsia[49] is achieved through the prevention of arterial thrombosis in the spiral arteries and intervillous space, as this is the proposed mechanism for 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 seems to play a lesser role.

Maternal infection

Maternal infection has been implicated in the etiology for preeclampsia and eclampsia since the beginning of the 20th century. Albert[51] 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, a 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, eg a fever, of an infectious disease. 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 reemerged recently based on the relationship between periodontal disease, urinary tract infection, SARS-CoV-2 infection, and maternal gut dysbiosis.

Periodontal disease—The best evidence to support a relationship between microorganisms and preeclampsia derives from studies of periodontal disease, which increases the risk of developing this pregnancy-related syndrome (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 and seed 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 denotes that 1) microorganisms found in the periodontal space can cause bacteremia;[59] 2) bacteria from the oral cavity have been found in atheromatous plaques;[60] and 3) periodontal infections can induce vascular lesions in the aorta and coronary arteries.[57, 61] In an animal model of hyperlipidemia, ie 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 and periodontal pathogens.[62] The etiologic role of periodontal disease in preeclampsia is predicated on the same mechanisms linking periodontal disease and atherosclerosis.

Offenbacher, Beck, Boggess, and Murtha[63] 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 (CRP) concentration are at increased risk for the development of preeclampsia compared to those without periodontal disease (adjusted relative risk (aRR) 5.8; 95% CI 1.2–26.9).[63] An elevated CRP would indicate that periodontal disease has led to a systemic inflammatory process, thus it provides a link between periodontal disease and preeclampsia.

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).[54] However, the case definitions have been broad and have included pyelonephritis, lower urinary tract infections, and asymptomatic bacteriuria as a group.[64, 65] 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,[66] could cause preeclampsia. Isolated cases have documented instances in which preeclampsia is associated with malaria,[67-69] cytomegalovirus (CMV),[70, 71] human immunodeficiency virus,[72, 73] but the evidence is insufficient to support causality.

Experimental observations supporting a causal relationship between infection and systemic inflammation and preeclampsia indicate that intravenous low-dose endotoxin administration in pregnant rats on day 14 of gestation results in the development of high blood pressure, proteinuria, low platelet count, and glomerular fibrinogen deposits.[74] Bacterial endotoxin is a method utilized to induce a systemic inflammatory response and the activation of thrombin through the release of tissue factor. These mechanisms are implicated in the pathogenesis of preeclampsia.

SARS-CoV-2 Infection—Early during the COVID-19 pandemic, it was recognized that a subset of non-pregnant patients developed hypertension,[75-77] proteinuria,[78-81]

thrombocytopenia,[82, 83] and elevated liver enzymes,[84, 85] which resemble preeclampsia and 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).[86] In addition, there is a dose-response relationship between SARS-CoV-2 infection and the subsequent development of preeclampsia (Figure 7).[87] Patients with severe COVID-19 had a 5-fold greater risk of preeclampsia than those with asymptomatic COVID-19.[87] 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).[88]

One mechanism whereby SARS-CoV-2 infection can be causally linked to preeclampsia has been proposed to involve endothelial dysfunction. Indeed, SARS-CoV-2 can infect endothelial cells that normally express angiotensin-converting enzyme 2 (ACE2), one of the cell entry receptors for the virus, leading to endothelitis.[89, 90] Endothelial infection can induce the activation of thrombin, intravascular inflammation (ie a cytokine storm), and damage of the microvasculature in target organs; this susceptibility ultimately leads to the multi-systemic nature of the syndrome, which includes not only renal involvement but also central nervous system dysfunction and seizures.[91-93] Therefore, an infectious process, which targets the endothelium, could lead to a syndrome similar to preeclampsia and eclampsia (Figure 8).

Of interest, pregnant women with COVID-19 infection who developed preeclampsia-like symptoms: their recovery from SARS-CoV-2 infection, followed by the resolution of hypertension, occurred without the delivery of the fetus and placenta.[94] It remains an open question whether preeclampsia, after SARS-CoV-2 infection, may or may not require placental involvement. Serum and plasma concentrations of sFlt-1, a marker of endothelial dysfunction, were elevated in non-pregnant subjects with COVID-19.[95] This finding is consistent with another study in pregnant women with severe COVID-19 who presented an elevated maternal plasma concentration of sFlt-1 and a high sFlt-1/PlGF ratio.[96] Genetic susceptibility may explain why some women with COVID-19 infection develop preeclampsia but others do not.[97, 98]

Maternal intestinal dysbiosis—The human gut microbiota plays an important role in host nutrition, harvesting of energy, and immune responses to potential pathogens.[99-103] 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. Remodeling of the gut microbiota during normal human pregnancy, reported for the third trimester of pregnancy, indicated an overall increase in *Proteobacteria* and *Actinobacteria* and a reduction in microbial richness.[104] When the intestinal content from normal pregnant women in the third trimester was administered to germ-free mice, it increased adiposity and insulin resistance,[105] which have been attributed to the proinflammatory effects of the gut microbiota.[104]

Gut dysbiosis, or an imbalance among the human gut's microbial communities, is now implicated in the development of atherosclerosis,[106, 107] hypertension,[108, 109] proteinuria,[110] cardiometabolic syndrome,[111, 112] and recently, preeclampsia.[113-117] A causal link between gut dysbiosis and cardiovascular disease has been derived from an observation that the transplant of fecal material from hypertensive, non-pregnant, 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 (eg apolipoprotein E null mice).[118] This effect has been attributed, at least in part, to trimethylamine-N-oxide (TMAO), 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 human gut microbiota have been reported in preeclampsia,[114, 115, 117, 119] which persist 6 weeks postpartum.[120] The changes include a reduction in microbial burden with *Firmicutes, Clostridia, Clostridiales,* and *Ruminococcus* and an increase in *Bacteroidetes, Proteobacteria, Actinobacteria, Bacteroidia, Gammaproteobacteria, and Enterobacteriaceae* (Figure 9A).[119] Moreover, the study provides evidence to support causality: fecal transplants from pregnant women with preeclampsia into mice led to the development of the syndrome.[115] The experimental paradigm required the administration of fecal material from pregnant women with and without preeclampsia to non-pregnant mice that had received antibiotics for 5 days (to change gut flora); the mice were housed in pathogen-free facilities.[115] Six weeks after the first fecal inoculation, mice were mated.[115] Pregnant mice that had received the fecal microbiota transplantation from mothers with preeclampsia developed high systolic blood pressure and proteinuria, and they delivered less live pups than mice that receive fecal microbiota transplantation from women with normotensive pregnancy (Figure 9B).[115] Collectively, this evidence suggests a role for gut dysbiosis in preeclampsia. However, further investigation into the precise mechanisms that may explain this phenomenon as well as the susceptibility of some pregnant women compared to others is necessary.

Gestational diabetes mellitus, maternal obesity, and the 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 had also been linked to the development of preeclampsia: a systematic review reported that diabetes mellitus prior to pregnancy was associated with an increased risk of preeclampsia (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 1-SD increase in glucose concentrations (fasting, one hour, and two hours after a 75mg glucose tolerance test) ranged from 1.21 to 1.28.[125]

A causal role was strengthened by the observation that the treatment of gestational diabetes mellitus with diet,[126] insulin,[127, 128] and metformin[129-132] 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 (RR 0.68; 95% CI 0.48–0.95)[131] and prolongation of gestation in women with preterm preeclampsia (median, 18 days).[133] Prenatal exercise has also been reported to decrease the rate of gestational diabetes mellitus by 38% and preeclampsia by 41% based on the results of a systematic review and meta-analysis.[134]

Collectively, the evidence suggests a causal relationship between gestational diabetes mellitus and preeclampsia given the consistency of association, its magnitude, 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/m^2 or more, is strongly associated with preeclampsia.[135-137] 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 even higher in severe obesity (BMI ≥ 35 kg/m^2; aOR 4.14; 95% CI 3.61-4.75).[138] A similar finding was reported overweight women (BMI: 26.1-29.0 kg/m^2) who had an increased risk of preeclampsia in comparison to women with a normal BMI (RR 1.57; 95% CI 1.49-1.64).[139]

Moreover, a dose-dependent relationship was found between pre-pregnancy BMI and the risk of preeclampsia in both nulliparous and parous women in a large epidemiological study (41,000 nulliparous and 29,000 multiparous) (Figures 10).[140] Data from the USA Collaborative Perinatal Project indicated similar results for Caucasian and for African-American women (severe preeclampsia: African American, OR 3.2, 95% CI 2.5-5.0; Caucasian, OR 3.4, 95% CI 2.1-5.6).[141] Most studies considered that obesity predisposes mainly to late-onset preeclampsia.[123, 141] 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/m^2 or greater: early-onset disease, aRR 2.18, 95% CI 2.12–2.24; late-onset disease: aRR 3.93, 95% CI 3.91–3.96).[142] In addition, preconceptional maternal weight loss, either with lifestyle modification or by bariatric surgery, was shown to be effective in reducing the risk of preeclampsia (OR 0.67; 95% CI 0.51-0.88).[143]

Metabolic syndrome—The term “metabolic syndrome” refers to a cluster of metabolic abnormalities that includes central obesity, insulin resistance, atherogenic dyslipidemia, and hypertension.[144, 145] This syndrome is strongly associated with systemic inflammation, oxidative stress, and endothelial dysfunction, all of which are features of preeclampsia.[146-149] A retrospective cohort study of 212,463 women showed that the presence of pre-pregnancy metabolic syndrome was associated with an increased risk of preeclampsia (aOR 1.48; 95% CI 1.26-1.74).[150] Preeclampsia is also a risk factor for the

subsequent development of metabolic syndrome after delivery.[151-154] Moreover, bariatric surgery performed before pregnancy as a treatment for metabolic syndrome was associated with a lower rate of preeclampsia or eclampsia (aOR 0.2; 95% CI 0.09-0.44).[155]

The mechanisms whereby insulin resistance predisposes to the development of preeclampsia are related to intravascular inflammation and endothelial cell dysfunction,[156, 157] 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 other, 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, during pregnancy is a risk factor of preeclampsia. 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 were associated with an increased risk of preeclampsia (OR 2.80; 95% CI 2.38-3.30);[158] 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 the restless legs syndrome (OR 1.83; 95% CI 1.04-3.21).[158]

Snoring is defined as the vibration of respiratory structures resulting from turbulent flow when the upper airway narrows during sleep.[159] It is more common in pregnant women than in non-pregnant women (14%-23% vs 4%)[160, 161] and increases the risk of hypertension,[162] and new-onset snoring during pregnancy is associated with preeclampsia (OR 1.59; 95% CI 1.06-2.37).[163] Evidence supporting a causal relationship between snoring and preeclampsia indicated that treatment with nasal continuous positive airway pressure (CPAP) improved blood pressure in women with preeclampsia.[164, 165] Edwards et al[164] reported that autosetting nasal CPAP administered through sleep resulted in a marked reduction in blood pressure (before treatment: mean systolic 146 mm Hg and mean diastolic 92 mm Hg; after treatment: mean systolic 128 mm Hg and mean diastolic 73 mm Hg). Recently, Bourjeily et al[166] reported that pregnant women with obstructive sleep apnea presented a higher maternal plasma sFlt-1/PlGF concentration ratio than those in a control group and that maternal sFlt-1 concentrations were decreased after CPAP treatment.[167]

In normal pregnancy, blood pressure has a circadian rhythm and is at its highest during the daytime. A reversed diurnal blood-pressure rhythm (ie the nocturnal blood pressure was higher than the diurnal blood pressure) has been reported in preeclampsia.[168, 169] Sleep architecture, using polysomnography, has shown that patients with preeclampsia had altered sleeping patterns,[170] specifically spending more time in slow-wave sleep, in comparison to those with a normal pregnancy (43 ± 3 vs 21 ± 2; $p < 0.001$).[170] One possible explanation for this finding is that cytokines, such as IL-1 and TNF-α, can increase the amount of slow-wave sleep,[170] as they are elevated in the maternal circulation of those with preeclampsia.[171-173] Collectively, the proposed mechanisms linking sleep disorders and preeclampsia involve intravascular inflammation and endothelial cell dysfunction.

Molar pregnancy

A hydatidiform mole, a gestational trophoblastic disease characterized by abnormal proliferation of trophoblast and hydropic changes of the chorionic villi, is associated with preeclampsia[174] and sometimes presents before 20 weeks of gestation.[175-178] The frequency of preeclampsia in patients with a hydatidiform mole ranges from 27% to 40% and is probably higher in patients who are left untreated until the second trimester.[175-178]

The mechanism whereby a complete hydatidiform mole causes preeclampsia involves the excess production of sFlt-1. Maternal serum sFlt-1 concentrations were 2-fold to 3-fold higher in patients with a hydatidiform mole than in those with a gestational age-matched control;[179] an increased expression of sFlt-1 within the molar tissue has also been reported.[180] Moreover, placentas with a hydatidiform mole had an increased expression of LIGHT (TNFSF14, or TNF superfamily member 14), which was co-localized with sFlt-1 in the molar tissue.[181] Chorionic villi in the molar tissue are edematous or hydropic, which are often avascular or display markedly reduced vessel density.[175] These villus capillary changes may lead to excessive production of sFlt-1 that enters maternal circulation and, consequently, to the development of the preeclampsia syndrome.

Fetal diseases

Specific fetal diseases associated with the development of preeclampsia include 1) Ballantyne or mirror syndrome;[225, 226] 2) Trisomy 13 or triploidy;[227, 228] and 3) a unique complication of multiple gestations (eg twin-to-twin transfusion syndrome or selective fetal growth restriction).[229] Ballantyne or mirror syndrome reflects the simultaneously edematous state of the mother, fetus, and placenta (also called triple edema).[230, 231] This syndrome has been observed in fetal hydrops caused by rhesus isoimmunization,[230] CMV,[232] or parvovirus 19 infections,[233] Ebstein's anomaly,[234] aneurysms of the vein of Galen,[235] fetal supraventricular tachycardia,[236, 237] and placental chorioangioma.[238] In mirror syndrome, the mother may develop proteinuria, hypertension, and even severe preeclampsia.[225, 226, 234, 239] The frequency of hypertension in patients with mirror syndrome is about 60%.[225, 226, 234, 239] The reversal of preeclampsia and Ballantyne syndrome can occur after intrauterine transfusion in parvovirus-induced hydrops without delivery.[240] All patients with mirror syndrome presented an increased maternal plasma concentration of sFlt-1 (above the 95th percentile for gestational age).[241] In addition, it has been shown that the maternal sFlt-1 concentration returns to normal after intrauterine transfusion.[242, 243]

Another example of preeclampsia with fetal disease is Trisomy 13 or triploidy.[227, 228, 244] A case control study of 25 cases with Trisomy 13 showed that the incidence of preeclampsia was significantly higher than detected in the normal karyotype control (44% vs 8%, p=0.001).[245] Women with a Trisomy 13 pregnancy have a higher serum concentration of sFlt-1/PlGF ratio,[246] and the placentas had an increased staining for sFlt-1 when compared to euploid as well as Trisomy 21.[247] Interestingly, sFlt-1 is located on chromosome 13, suggesting the possibility that an extra copy of chromosome 13 may lead to increased production of sFlt-1.[244, 247]

Multiple gestations with twin-to-twin transfusion syndrome or selective fetal growth restriction can also predispose to the development of preeclampsia.[229] Resolution of hypertension and proteinuria generally occur after the selective termination of pregnancy[248-251] or after the fetal death of one twin.[252] An improvement in angiogenic and anti-antiangiogenic profiles has also been demonstrated after selective termination or fetal demise of one twin.[253, 254] Collectively, these observations indicate that preeclampsia can resolve without delivery and suggest 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, a role for autoimmune mechanisms of disease has been investigated for several decades, given that patients with a systemic autoimmune disease, such as systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS), were at an increased risk for preeclampsia (SLE: RR 1.91, 95% CI 1.44-2.53; APS: RR 1.81, 95% CI 1.33-2.45).[255-258] Similarly, several studies have shown that some specific autoantibodies, such as anti-β2 glycoprotein-I (ab2GPI), anti-cardiolipin antibodies (aCL), or lupus anti-coagulant (LA), are associated with preeclampsia.[256, 259] However, the most compelling case for a role of an autoimmune mechanism is exemplified by antibodies against the angiotensin II receptor.

Nearly two decades ago, Wallukat et al[260] reported that women with preeclampsia had antibodies that bind to the angiotensin II type I receptor (AT1-AA). Subsequently, substantial evidence has accumulated that supports a role for AT1-AA in the pathogenesis of preeclampsia. Such evidence comprises the following findings: 1) 80% of women with preeclampsia have increased concentrations of AT1-AA in maternal serum at the time of diagnosis;[261] 2) the concentration of AT1-AA in maternal serum correlates with the severity of hypertension and proteinuria;[262] and 3) the administration of AT1-AA (either produced endogenously in response to transgenic expression of human renin and angiotensinogen, or administered by an injection of purified AT1-AA from women with preeclampsia) to pregnant rats led to hypertension, proteinuria, glomerular capillary endotheliosis,[263] and the increased production of sFlt-1 as well as soluble endoglin,[264] which can be attenuated by the administration of an AT1-receptor blocker (Losartan). However, one longitudinal study, conducted to determine whether the concentration of AT1-AA is increased before the onset of preeclampsia, did not produce such a result.[265]

What causes the production of AT1-AA? Placental ischemia after a reduction in uterine perfusion pressure has been shown to increase the concentration of serum AT1-AA.[266] Also, the inhibition of AT1-AA by the administration of an epitope-binding peptide (‘n7AAc’) can reduce maternal blood pressure and plasma concentrations of endothelin-1, sFlt-1, and isoprostanes, a marker of oxidative stress.[267] Moreover, the administration of the inflammatory mediators TNF-α,[266, 268] IL-6,[268, 269] and IL-17[270] to pregnant rats can induce preeclampsia and enhance AT1-AA activity, which is abrogated by an AT1-AA blockade.[267]

Placental Aging

Cells and organisms have a finite lifespan. Human cells in culture can multiply (mitosis) a limited number of times (Hayflick limit) before they stop dividing and, subsequently, undergo programmed cell death, or apoptosis.[271] The placenta is also thought to have a pre-specified lifetime, and as age advances, the functional capacity of placental cells declines. Placental aging has been described for several decades,[272, 273] and premature aging has been implicated as a mechanism of disease for obstetric outcomes, eg preeclampsia,[274, 275] fetal growth restriction,[274, 276] fetal death,[277] and preterm labor.[278]

Cytotrophoblasts are replicating cells, but the syncytiotrophoblast is generated by fusion and, therefore, is in a state of senescence (ie 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, 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.[279-281] Cindrova-Davies et al [280] 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,[274] and reduced telomerase activity.[282, 283] Redman et al [279] 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 pore size, leading to respiratory failure of the placenta (Figure 12) and contributing to intervillous hypoxia and syncytiotrophoblast stress.[284-286] A twilight placenta has been invoked as a potential cause for late pregnancy problems such as late-onset preeclampsia,[46, 287] unexplained term stillbirth, or fetal death in prolonged pregnancy.[277, 283, 288] 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,[289] 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 temporal coexistence of two individuals (mother and fetus) with different genetic makeup. The placenta and fetus together are viewed as the most successful semi-allograft (with maternal and paternal contributions), and the mechanisms responsible for the immune tolerance have been the subject of investigation for decades.[182-187] Two typical features of the adaptive immune system are memory and specificity.[188-190] A role for the immune system has been proposed because preeclampsia is more common in primigravidas than in parous women and in multigravidas with different fathers (primipaternity) than in subsequent pregnancies with the same father.[191, 192] The predilection for primigravidas has been attributed to a memory-like phenomenon that protects mothers against paternal antigens in subsequent pregnancies.[193] The higher frequency of preeclampsia in multigravidas whose pregnancy is from a different father supports the concept that the immune phenomenon is specific to paternally derived

antigens.[194, 195] Moreover, this syndrome is more common in pregnancies that occur from an egg donation in which the placenta and fetus represent a full allograft rather than a semi-allograft.[196]

The placenta and fetus express both paternal and maternal antigens; they are a semiallograft.[197-199] The syncytiotrophoblast is in direct contact with maternal blood and the decidua, thus the maternal immune system is exposed to paternal antigens expressed by the fetus.[182] Immune tolerance is a requirement for a successful pregnancy,[185, 200, 201] and a breakdown of tolerance leads to maternal anti-fetal rejection, placental damage, and pregnancy complications that may include preeclampsia. Placental lesions, which represent manifestations of maternal anti-fetal rejection, are villitis of unknown etiology,[202-205] massive perivillous fibrin deposition,[206, 207] chronic chorioamnionitis,[208-210] and chronic deciduitis of the placental basal plate.[209] The frequency of chronic villitis is higher in preeclampsia than in normal pregnancy (25% vs 17%).[203, 211] Massive perivillous fibrin deposition was present in 20% of patients with preeclampsia.[212]

Maternal-fetal genetic incompatibility has been implicated in 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-C (HLA-C) molecules (Figure 11).[213-216] Extravillous trophoblasts are specialized fetal cells that invade the decidua basalis, where they come into direct contact with maternal immune cells, eg dNK cells, macrophages, T cells, B cells, and dendritic cells.[217] Extravillous trophoblasts do not express major T-cell ligands such as HLA-A and HLA-B molecules. Instead, these fetal cells express HLA-C, HLA-E, and HLA-G.[218] The latter two are largely monomorphic, while HLA-C is polymorphic, and therefore will vary according to the genetic makeup of the father.[219] On the other hand, the dNK cells express the receptors for HLA-C proteins; these receptors are called KIRs.[220] Both maternal KIR and fetal HLA-C genes are highly polymorphic, and the interaction between HLA-C and KIR has a unique role in placentation through the facilitation of trophoblast invasion of the decidua and the physiologic transformation of the spiral artery. The molecular machinery implicated in this process involves chemokines (CXCL-10 and CXCL8, or IL-8) that can attract trophoblasts expressing their receptors (CXCR3 and CXCR1), metalloproteinases, and growth factors, including the angiogenic factors (PlGF, VEGF, etc.).[221, 222] Moffett et al [213-215] has 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 has the KIR AA genotype with additional 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, Staff et al [223] 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.[223] The mechanisms whereby a breakdown of maternal-fetal immune tolerance leads to preeclampsia appear 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 immunological mechanisms of preeclampsia, the reader is referred to the review article by Robillard et al [224] in this Supplement.

Endocrine disorders

An association among several endocrine disorders and preeclampsia has been reported,[290-297] yet the evidence for causality is the weakest among those reviewed in this article. Two explanations are plausible: the low frequency of endocrine disorders in pregnancy and the paucity of experimental evidence from animal studies of endocrine disorders. These investigations have not focused on the effect of such disorders in the development of preeclampsia. Hence, this section will review the evidence of an association and the proposed mechanism for activation of the common pathway.

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 30g of calcium, 20g of phosphorus, and 0.8g of magnesium, and 80% of calcium is deposited during the third trimester.[298] 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);[290] 2) low vitamin D concentration in early pregnancy is associated with a 5-fold increased risk for preeclampsia;[299] 3) hyperparathyroidism is commonly found in pregnant women with low calcium and vitamin D;[300, 301] 4) patients diagnosed with parathyroid adenoma are at an increased risk for preeclampsia (OR 6.89; 95% CI 2.30-20.58);[291] 5) the absence of a vitamin D prophylaxis in the mother's childhood is associated with a subsequent higher risk of preeclampsia;[302] and 6) the administration of vitamin D combined with calcium or a multivitamin supplement has been shown to reduce blood pressure and the frequency of preeclampsia in a randomized trial.[303, 304] The proposed mechanisms whereby primary hyperparathyroidism leads to preeclampsia are thought to involve endothelial cell damage, increased insulin resistance, left ventricular hypertrophy, and dyslipidemia.[305, 306]

Cushing's syndrome, aldosteronism, pheochromocytoma, and paraganglioma —Cushing's syndrome is associated with an increased risk of preeclampsia (aOR 2.20; 95% CI 1.18–4.41).[292, 293] In non-pregnant subjects, the chronic glucocorticoid excess of Cushing's syndrome is commonly associated with an increased cardiometabolic risk through an increase in pro-inflammatory adipokine production, alteration of coagulation and thrombosis factor, platelet function, and endothelial activation.[307-309]

Primary aldosteronism is the most common form of endocrine hypertension, and it can be caused by aldosterone-producing adenoma or bilateral adrenal hyperplasia.[310, 311] Increased aldosterone secretion suppresses renin activity, leading to hypertension, hypokalemia, and hypernatremia.[312, 313] Twenty-five percent of women with this disorder develop preeclampsia.[294, 295]

Pheochromocytoma and paraganglioma are rare catecholamine-producing tumors, with a reported frequency of 1/54,000 pregnancies.[314] An excess of catecholamine released by these tumors can elicit signs or symptoms similar to preeclampsia (eg hypertension, headache, and proteinuria), making the diagnosis of pheochromocytoma during pregnancy difficult.[314, 315] A recent meta-analysis that included 204 pregnant patients with pheochromocytoma paraganglioma showed that 20% of patients are initially misdiagnosed

as preeclampsia.[316] Maternal and fetal mortality are as high as 28% and 27%, respectively, when there is a delay in diagnosis and treatment.[316, 317] Only a few studies have reported that patients with pheochromocytoma developed superimposed preeclampsia;[296, 297] therefore, the existence of such a relationship is not clear yet.[316]

Conclusion

Multiple and sometimes overlapping insults can induce an adaptive homeostatic vascular response in pregnancy, which can be recognized clinically by the presence of hypertension and proteinuria (or other signs of multi-systemic involvement). When this response becomes maladaptive, it can cause target organ damage and becomes potentially life-threatening to the mother and fetus. This article has reviewed the etiological factors responsible for preeclampsia and eclampsia.

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, while late-onset preeclampsia appears to be related to the mismatch between maternal perfusion and feto-placental demands, together with a maternal predisposition to cardiovascular disease. However, it is necessary to identify the fundamental causes of the vascular dysfunction responsible for preeclampsia and 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 as a result of SARS-CoV-2 infection can induce preeclampsia brings 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 and the effect of interventions to prevent this syndrome. A greater understanding of the differences in the etiology of each subtype of preeclampsia and the pathophysiology of other great obstetrical syndromes are required in order to improve the understanding of this elusive disease.

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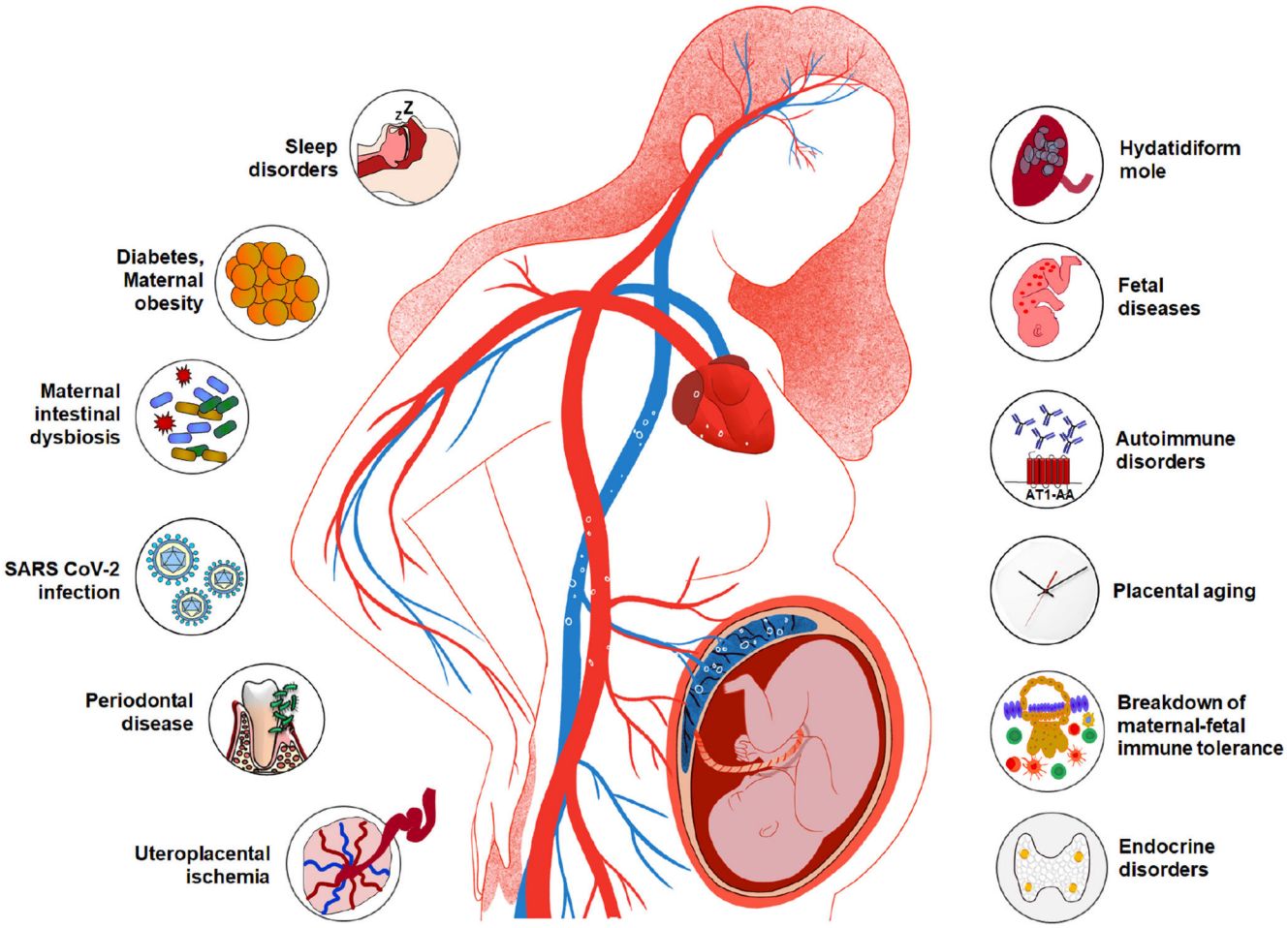

Figure 1.

Multiple etiologies implicated in preeclampsia. Uteroplacental ischemia, maternal infection and inflammation (eg periodontal disease, urinary tract infection, COVID-19), maternal intestinal dysbiosis, maternal obesity, sleep disorders, hydatidiform mole, fetal diseases (eg hydrops fetalis, viral infection, Trisomy 13, and unique complications of multiple gestation), autoimmune disorders, placental aging, breakdown of maternal-fetal immune tolerance, and endocrine disorders (eg hyperparathyroidism, Cushing's syndrome, hyperaldosteronism).

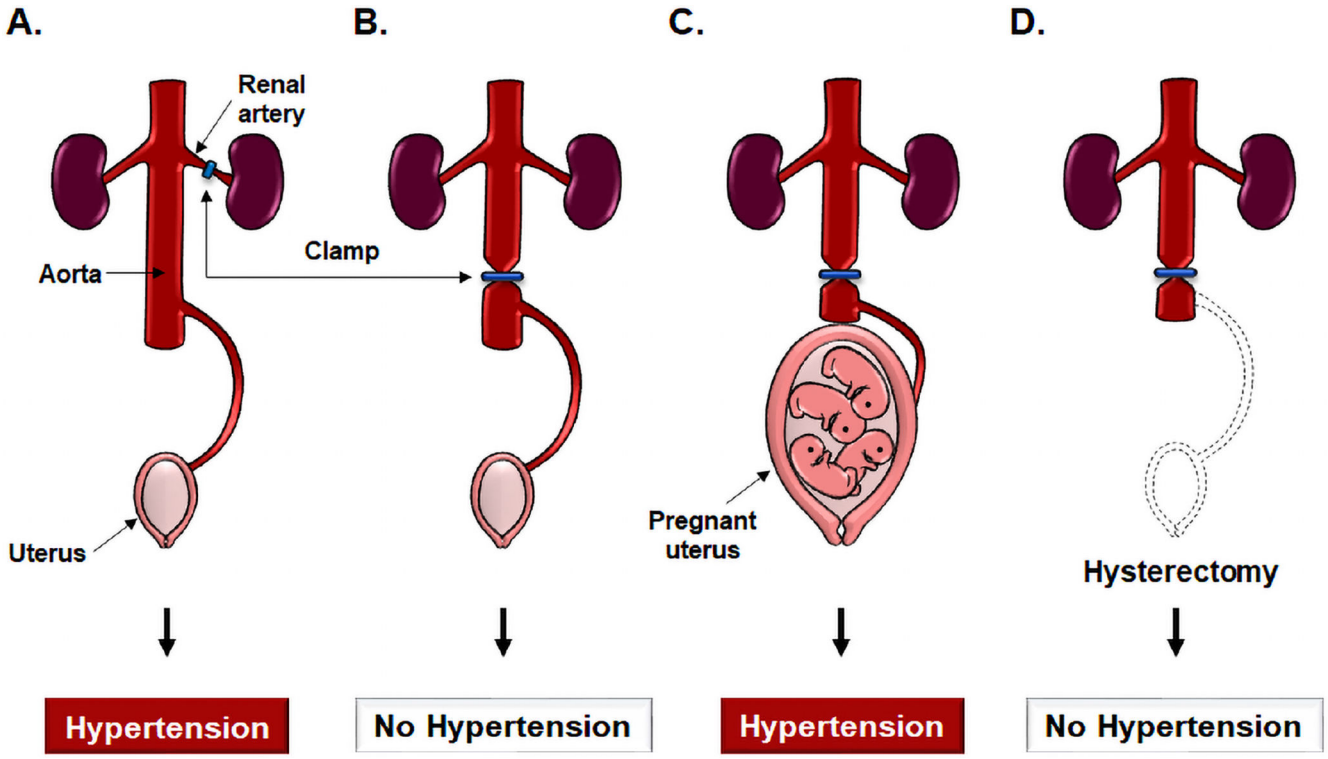

Figure 2.

A diagrammatic depiction of experiments demonstrating that uterine ischemia in pregnant animals, but not in non-pregnant animals, can cause hypertension. **A**. In the Goldblatt model of renovascular hypertension, clamping the renal artery leads to development of hypertension through renal ischemia and the release of renin in non-pregnant animals. **B**. By contrast, clamping the aorta below the renal arteries does not induce hypertension in non-pregnant animals. **C**. Clamping of the aorta in pregnant animals below the renal arteries leads to hypertension. **D**. The hypertension disappears after a hysterectomy has been performed; this suggests that the source of the signals leading to maternal systemic hypertension are derived from the gravid uterus. *Modified from Chaiworapongsa T. et al. Pre-eclampsia part 1: current understanding of its pathophysiology. Nat Rev Nephrol. 2014 Aug; 10 (8):466-80.*

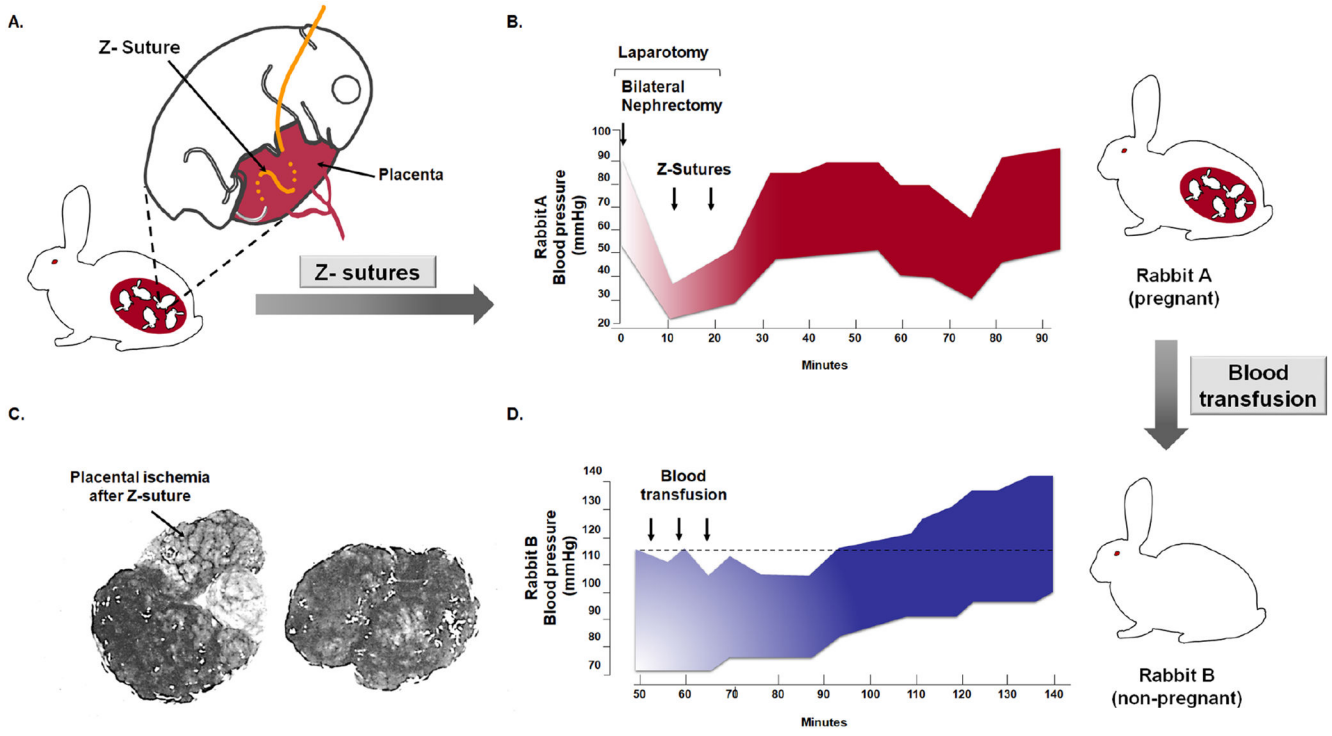

Figure 3.

Experimental demonstration that placental ischemia causes maternal hypertension and that a soluble factor in the blood of an animal with placental ischemia can induce hypertension in a non-pregnant animal. **A**. The Z suture is placed in the uterus to generate placental ischemia. **B**. Placental ischemia causes hypertension. Rabbit A had undergone a bilateral nephrectomy; therefore, the kidney is not a cause of the hypertension. After Z sutures were placed through several placentas, hypertension developed. **C**. Gross evidence that the suture has caused a placental infarction. The pale portion of the placenta with the arrow represents a large infarction. A control placenta of the same animal is illustrated on the right. **D**. Transfusions of blood from Rabbit A (a pregnant rabbit with placental ischemia) to a non-pregnant rabbit (Rabbit B) caused hypertension; this suggests that a circulating factor generated after placental ischemia is present in the maternal blood and that it can induce hypertension in a non-pregnant rabbit. *Modified from Berger M. and Cavanagh D. Toxemia of pregnancy: The hypertensive effect of acute experimental placental ischemia. Am J Obstet Gynecol. 1963 Oct 1;87:293-305.*

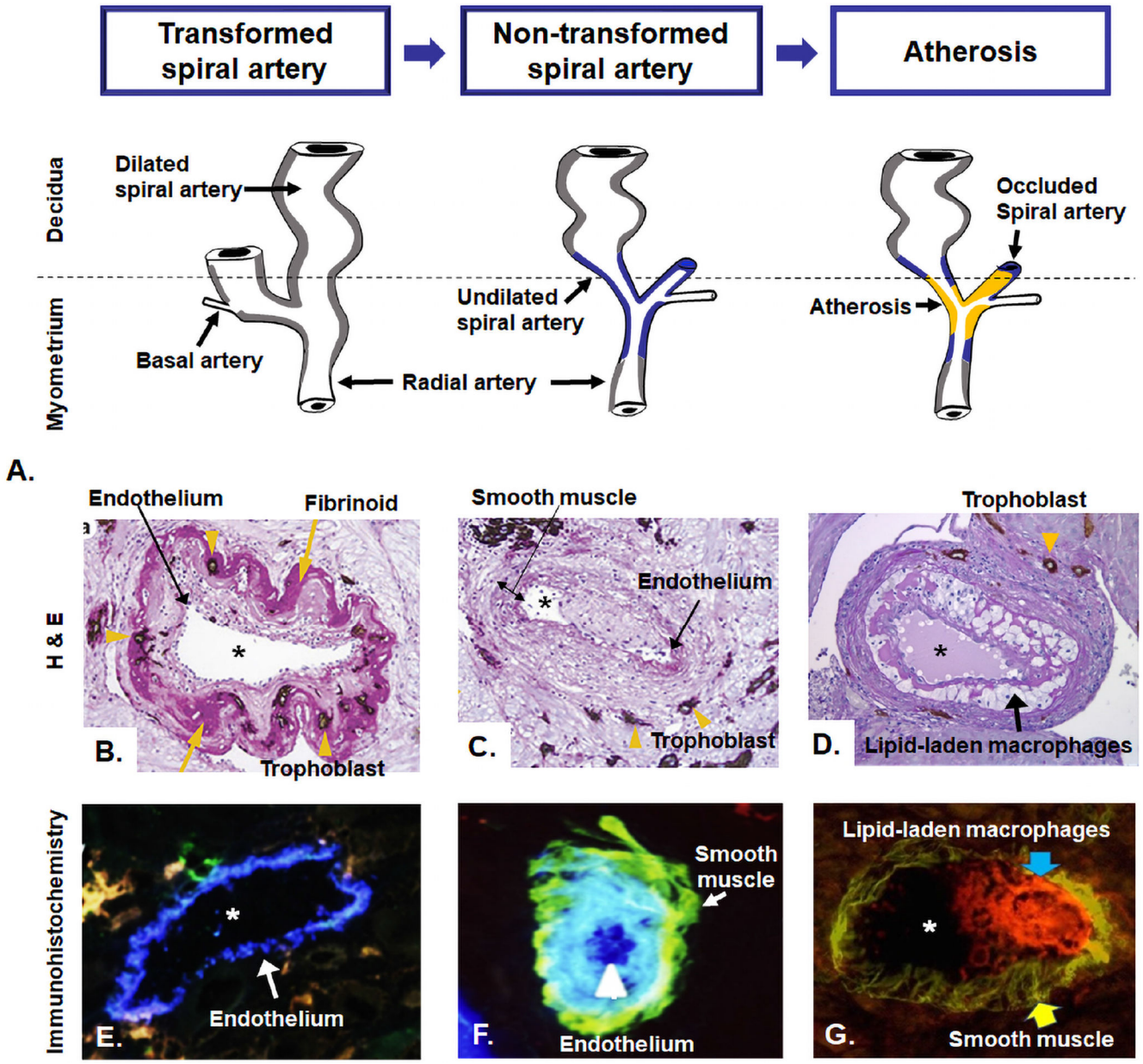

Figure 4.

A. Diagram of maternal blood supply to the placenta. The spiral arteries undergo physiologic changes in normal pregnancy (grey). In preeclampsia, the myometrial segment of the spiral artery fails to undergo physiological transformation (blue), which is thought to explain the uteroplacental ischemia observed in preeclampsia. Moreover, non-transformed spiral arteries are prone to atherosis (yellow), characterized by the presence of lipid-laden macrophages within the lumen. Placental basal plate spiral arteries with hematoxylin-eosin stain (B, C, and D). **B**. Transformed spiral arteries are characterized by the presence of intramural trophoblasts (arrowheads) and fibrinoid degeneration (arrows) of the arterial wall. **C**. Non-transformed spiral arteries lack intramural trophoblasts and fibrinoid degeneration, and they retain smooth muscle. Arrowheads indicate the presence of trophoblasts in

myometrium, but not in the wall of the spiral artery. **D**. Acute atherosis in decidual spiral artery. Many lipid-laden macrophages (arrows) are seen in the spiral artery with the lack of invasion of the trophoblast (arrowhead) into myometrial segment of the spiral artery. Images (B, C, and D) stained with cytokeratin 7 (brown) and periodic acid–Schiff (pink), original magnification ×200. Immunohistochemistry of placental basal plate spiral arteries (E, F, and G). **E**. Presence of endothelium (arrow, blue) in vessels with normal trophoblastic invasion, original magnification × 640. **F**. spiral artery with presence of endothelium (blue, arrowhead) and smooth muscle cells (green, arrow), original magnification ×640. **G.** Atherosis lesions show the presence of numerous macrophages CD36-reactive (red reactivity, blue arrow) and smooth muscle cells in the vessel wall (green reactivity, yellow arrow), original magnification x400. *lumen of spiral artery. *Modified from McMaster-Fay RA. Uteroplacental vascular syndromes: theories, hypotheses and controversies. Clin Obstet Gynecol Reprod Med 2018;4:1–5. Espinoza J et al. Normal and abnormal transformation of the spiral arteries during pregnancy. J Perinat Med. 2006;34(6):447-58. Labarrere CA et al. Failure of physiologic transformation of spiral arteries, endothelial and trophoblast cell activation, and acute atherosis in the basal plate of the placenta. Am J Obstet Gynecol. 2017 Mar;216(3):287.e1-287.e16.*

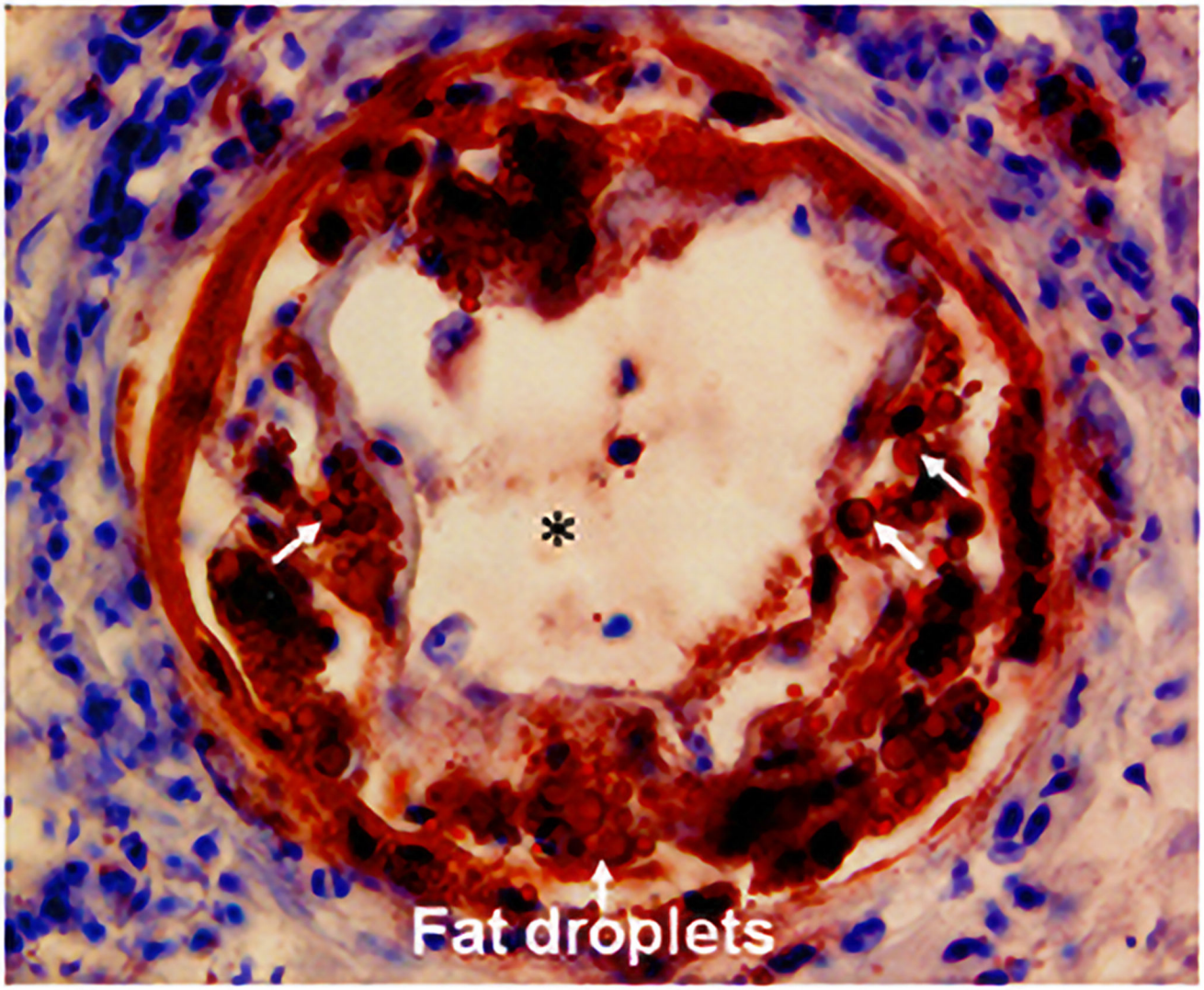

Figure 5.

Acute atherosis on oil-red O staining. Fat droplets (arrows) in the non-transformed spiral artery are stained red. *Lumen of spiral artery. *Cover, Am J Obstet Gynecol. November 2014 Yeon Mee Kim, Roberto Romero.*

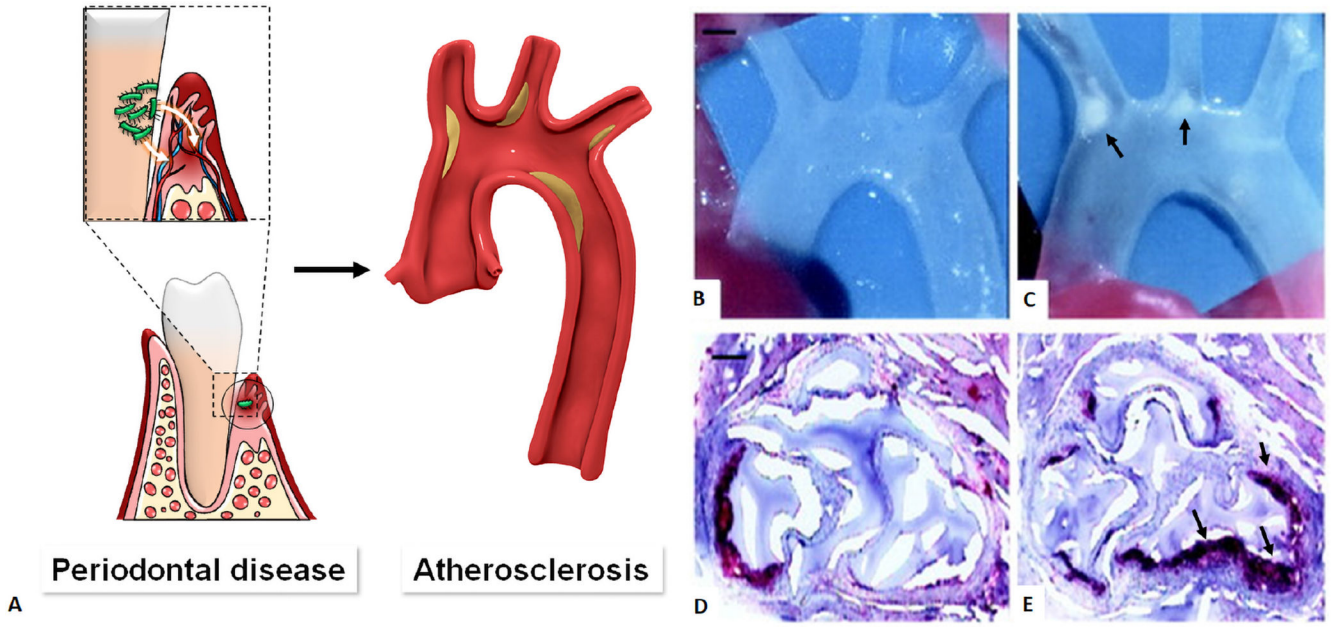

Figure 6.

Periodontal diseases and association with atherosclerotic disease. **A**. Bacteria found in the periodontal space can enter the bloodstream (bacteremia) and eventually the heart, resulting in atherosclerotic plaque in the heart blood vessels. Compared with uninfected control (B), periodontal infection with *Porphyromonas gingivalis* causes atherosclerotic aortic arch plaques (**C**, arrow) in apoE-null mice. Scale bar =1 mm. Oil red O staining of cryosections at the aortic sinus shows few small fatty streaks (control, **D**), whereas atherosclerotic lesions were greater in number and size (arrow) in infected animals (**E**). Scale bar=50 μm. *Modified from Hajishengallis G et al. Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities. Nat Rev Immunol. 2021 Jul;21(7):426-440 and Lalla E. et al, Oral infection with a periodontal pathogen accelerates early atherosclerosis in apolipoprotein E-null mice. Arterioscler Thromb Vasc Biol. 2003 Aug 1;23(8):1405-11.*

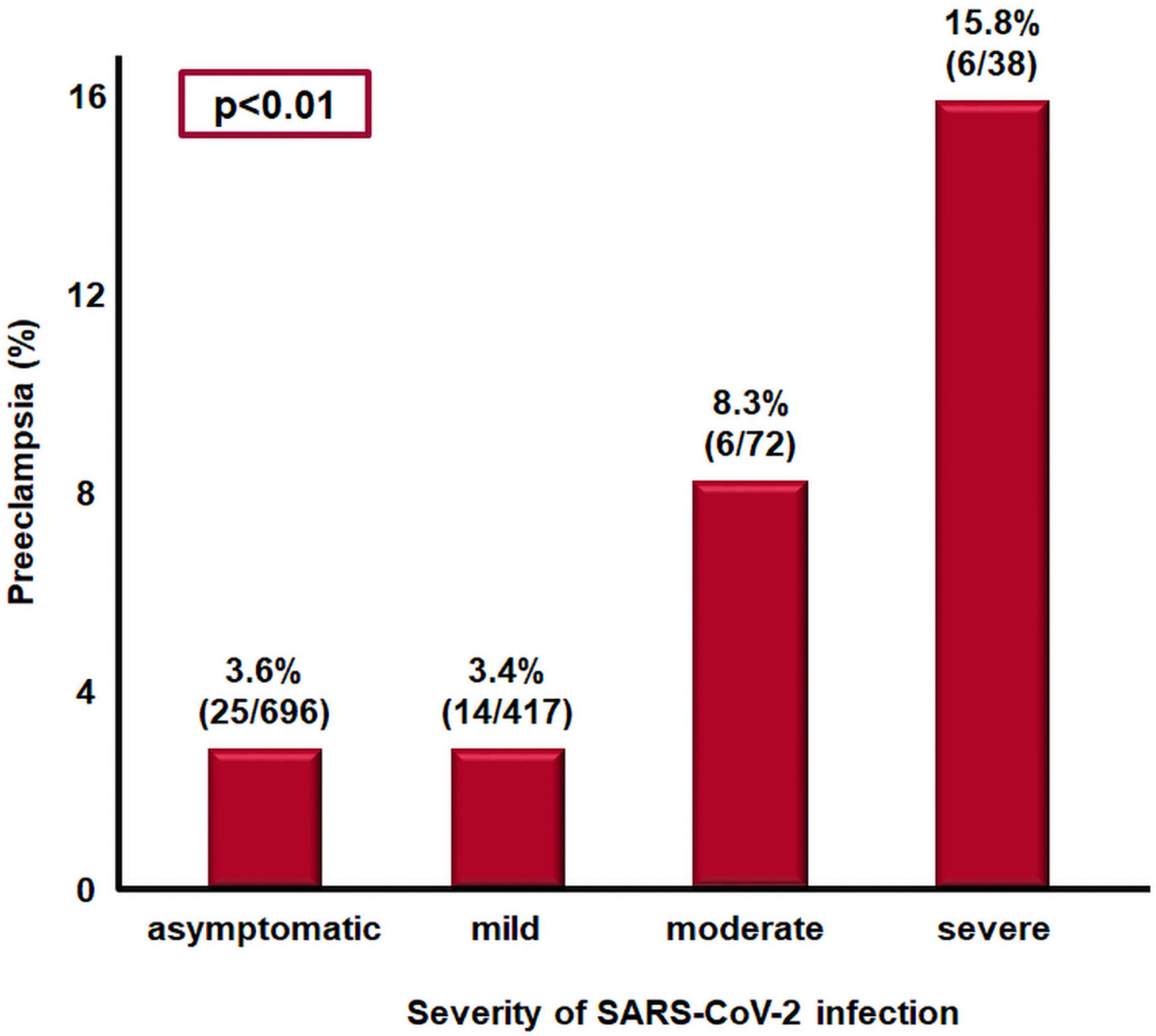

Figure 7.

Association between SARS-CoV-2 infection severity and subsequent development of preeclampsia. The most severe COVID-19, the greater the risk of preeclampsia. Modified from Lai J et al. SARS-COV-2 and the subsequent development of preeclampsia and preterm birth: evidence of a dose response relationship supporting causality. Am J Obstet Gynecol. 2021 Aug 26:S0002-9378(21)00947-9.

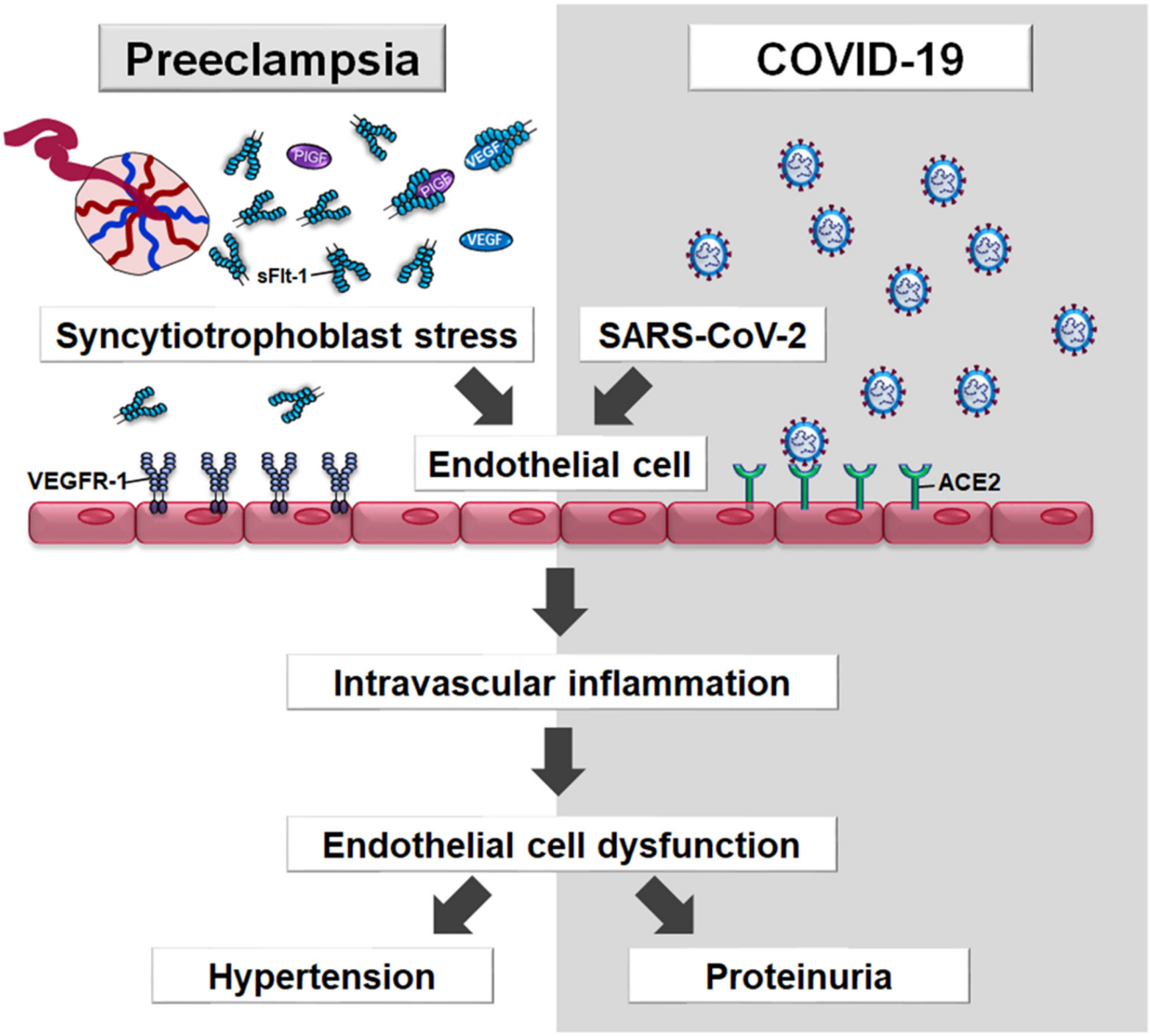

Figure 8.

Placental syncytiotrophoblast stress induces excessive sFlt-1 into the maternal circulation. sFlt-1 binds to free PlGF or VEGF (proangiogenic factors) with high affinity, thus preventing their interaction with their cell-surface receptors (i.e. VEGR-1) on the endothelial cells, leading to endothelial dysfunction. SARS-CoV-2 also targets the endothelium which normally express angiotensin-converting-enzyme 2 (ACE-2), one of the cell entry receptors for the virus, leading to endothelitis, which induces 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

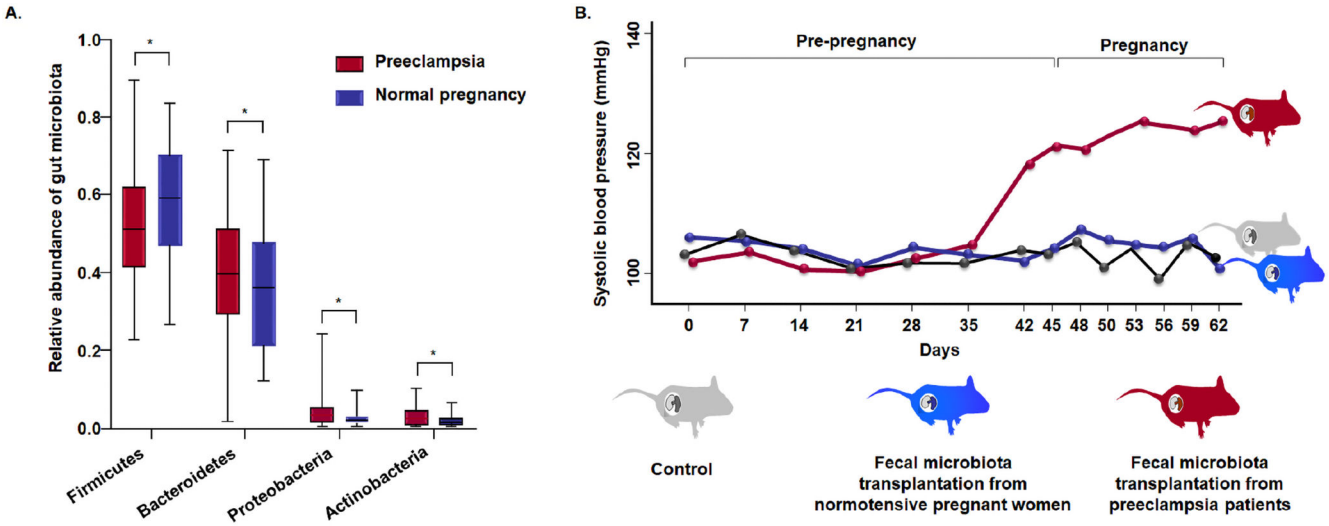

Figure 9.

(A) Gut microbiota in patients with preeclampsia (red) and those with normal pregnancy (blue). The significantly different genera (*Firmicutes, Bacteroidetes, Proteobacterias,* and *Actinobacteria*) at the phylum level in the two groups. The boxes represent the interquartile range (IQR) between first and third quartiles and the line inside represents the median. *$p < 0.05$. (B) Maternal intestinal dysbiosis and preeclampsia. Mice that received fecal microbiota from patients with preeclampsia (red) had higher systolic blood pressure than mice that received fecal microbiota from normotensive pregnant women (blue) or those that received the phosphate-buffered saline (control, grey). *Modified from Wang J et al. Gut Microbiota Dysbiosis and Increased Plasma LPS and TMAO Levels in Patients with Preeclampsia. Front Cell Infect Microbiol. 2019 Dec 3;9:409 and Chen X. et al. Gut dysbiosis induces the development of pre-eclampsia through bacterial translocation. Gut. 2020 Mar;69(3):513-522.*

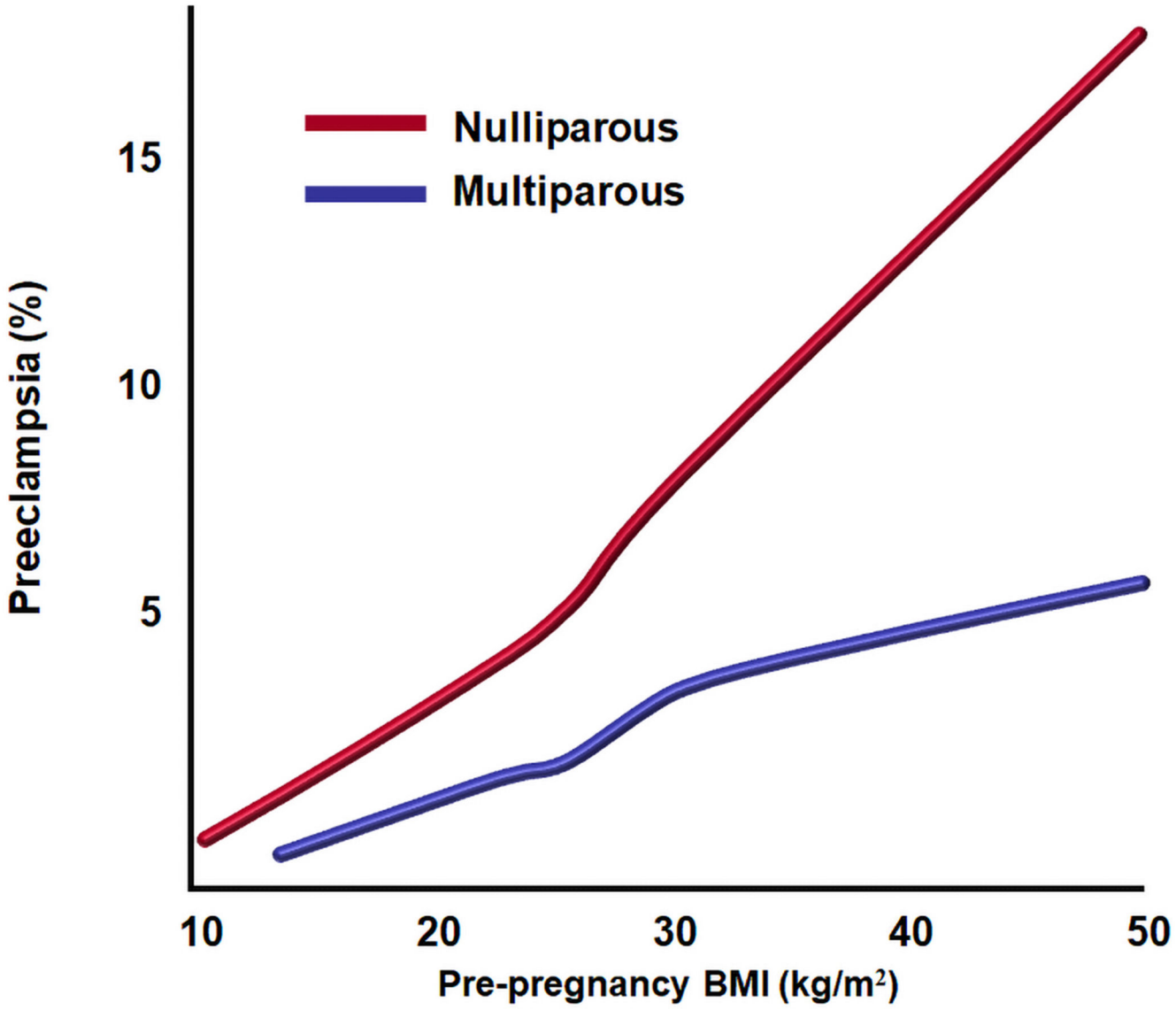

Figure 10.

Probability of preeclampsia according to the pre-pregnancy body mass index in both nulliparous (top line, red) and multiparous (bottom line, blue) women. *Modified from Catov JM et al. Risk of early or severe pre-eclampsia related to pre-existing conditions. Int J Epidemiol. 2007 Apr;36(2):412-9.*

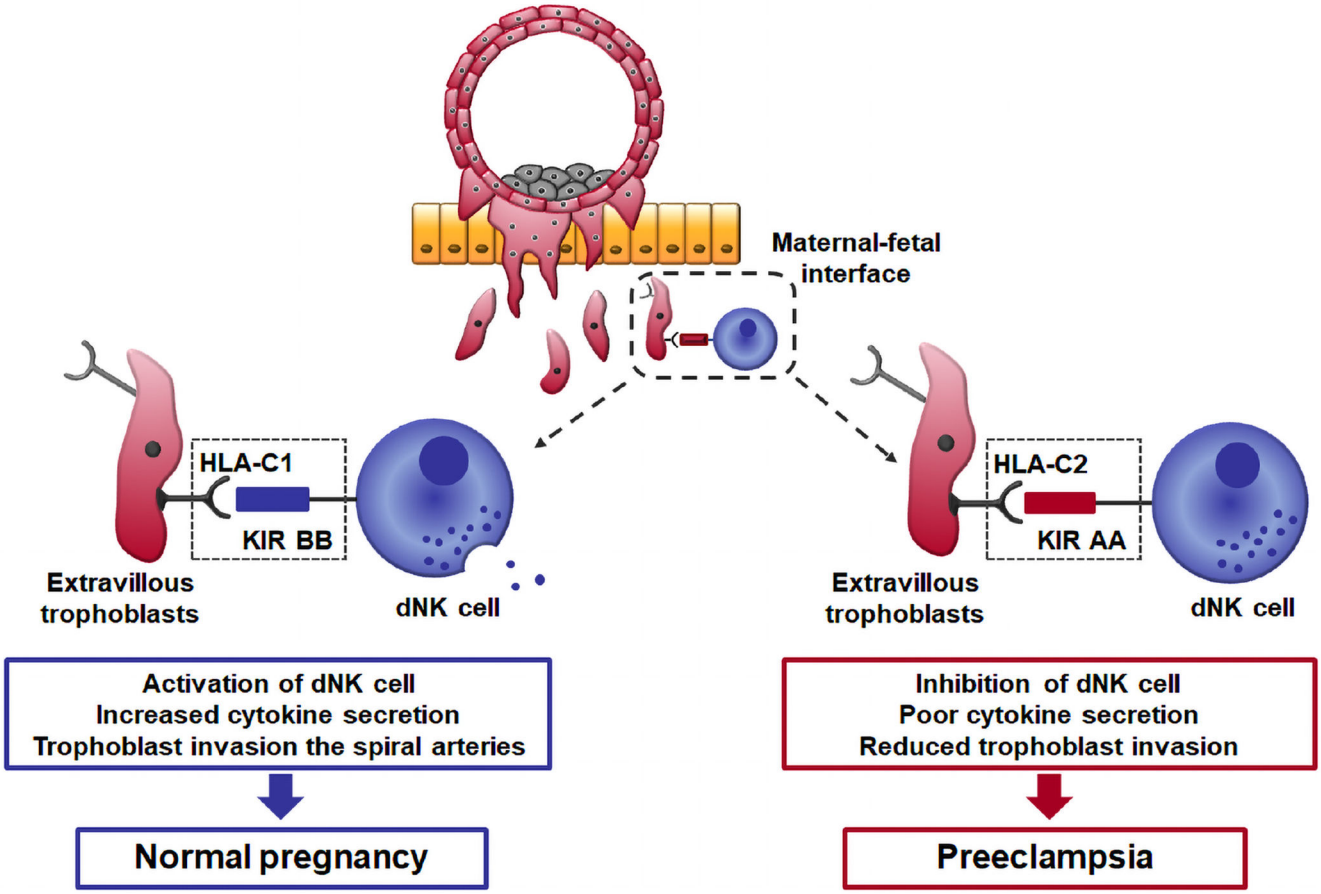

Figure 11.

Interactions between maternal KIR and fetal HLA-C at the site of placentation. If the mother has a KIR BB genotype, which binds to trophoblast HLA-C1 molecules, this activates dNK cells, producing increased levels of cytokines such as GM-CSF that can enhance placentation. In contrast, when the mother has a KIR AA genotype and fetal HLA-C2 alleles, this inhibits dNK cells, leading to defective placentation.

KIR; killer cell immunoglobulin like receptors, HLA; human leukocyte antigen, dNK; decidual natural killer cells, GM-CSF; granulocyte-macrophage colony-stimulating factor. *Modified from* https://www.ivi-rmainnovation.com/maternal-killer-immunoglobulin-receptors-predictive-live-birth-rate/

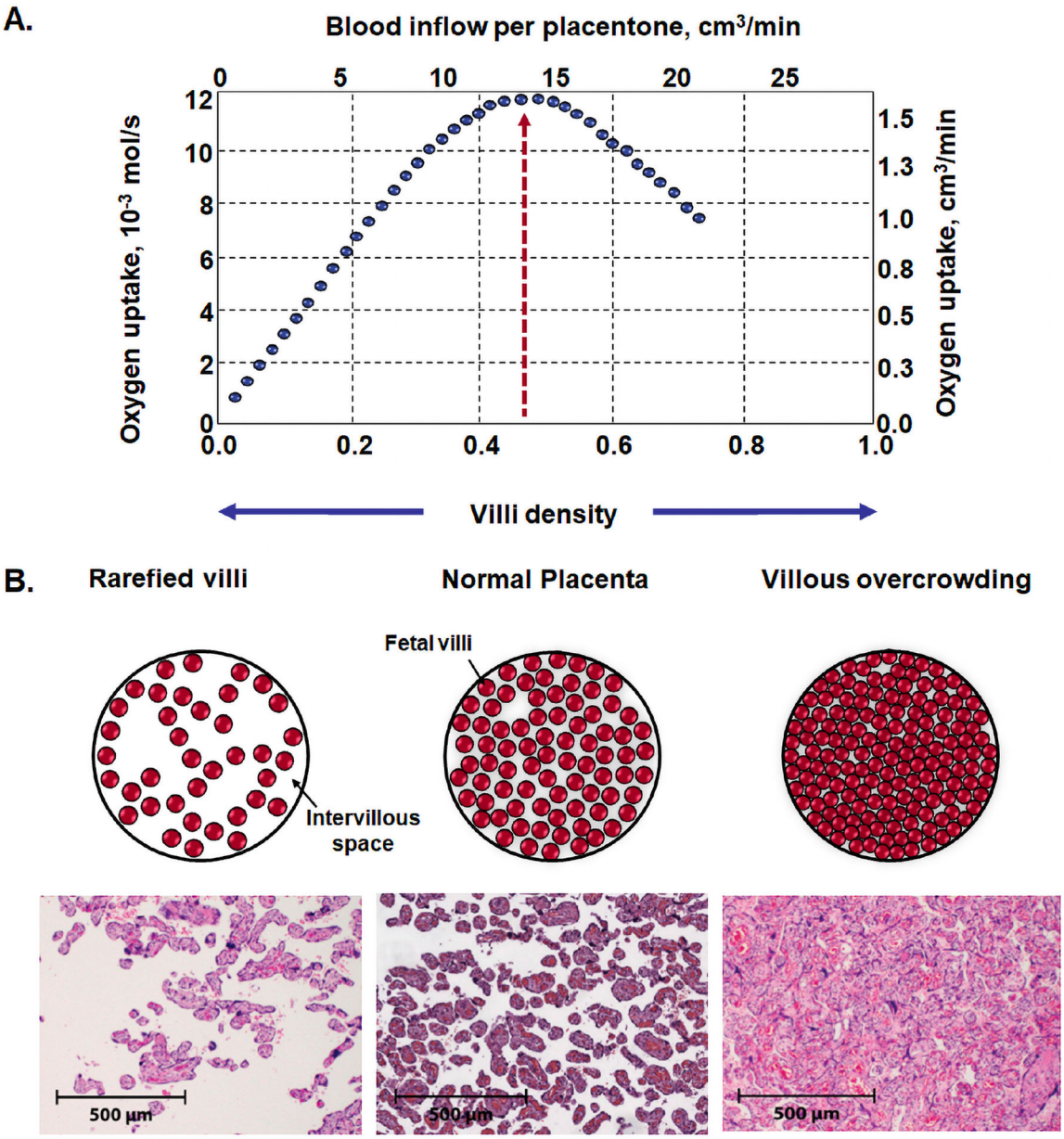

Figure 12.

A. Optimal villi density for maximal oxygen uptake in the human placenta. Placentas with low villi density (rarefied villi) have low oxygen uptake, as fetal villi are rare. By contrast, in placentas with high villous density (villous overcrowding), there is no space for intervillous space for oxygen exchange. The optimal villi density for the oxygen uptake was 0.47 ± 0.06, calculated from histomorphometrical data for villi and intervillous volumes of placentas.

B. Cross-section of the placenta: 1) rarefied villi in preeclampsia; 2) normal placenta; and 3) villous overcrowding in diabetes mellitus. H&E stained and scale represents 50 µm.

Modified from Serov AS et al. Optimal villi density for maximal oxygen uptake in the human placenta. J Theor Biol. 2015 Jan 7;364:383-96.