Review

The Etiopathogenesis of Preeclampsia: Where Do We Stand Now?

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Review

The Etiopathogenesis of Preeclampsia: Where Do We Stand Now?

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Abstract

Preeclampsia is a multisystem disorder whose development during pregnancy is associated with many severe complications both for the pregnant woman and her infant. The exact etiology of preeclampsia remains unclear, and it is often referred to as a disease of theories and hypotheses. A better understanding of the condition's precise etiology holds promise for the development of new options for early diagnosis, effective prevention, and modern causal treatment of preeclampsia to reduce the risk of severe complications in affected patients.

Keywords: preeclampsia; etiopathogenesis; fetal growth restriction (FGR); pregnancy complication; placenta

1. Introduction

Over the past few decades, enormous research efforts have been devoted to deciphering the etiology of preeclampsia. Numerous groundbreaking studies have been conducted to better understand this condition, which is specific to human pregnancy. However, the etiology of preeclampsia remains unclear, often being referred to as a disease of theories and hypotheses.

Preeclampsia is a multisystem disorder whose development during pregnancy is associated with the abnormal adaptation of a woman's cardiovascular system and impaired placental development. Maternal, placental, and fetal factors, as well as genetic, immunological, and metabolic predispositions, underlie its development. The development of preeclampsia requires the presence of the placenta, and the characteristic features result from involvement of the blood vessels and vascular endothelium, the largest organ, leading to multi-organ damage.

A modified two-stage model of preeclampsia development assumes that stress on the placental syncytiotrophoblast plays a key role in its development [2,3]. Changes and abnormalities occur in the first trimester of pregnancy, when the pregnancy appears to be progressing normally and the patient shows no clinical signs of disease. In the first stage, there is abnormal and insufficient trophoblast invasion and abnormal spiral artery remodeling [2,3].

However, the resulting clinical symptoms, known as "maternal syndrome," are characterized by an excess of antiangiogenic factors [4–7] and appear in the second half of pregnancy, specifically in the second and third trimesters [2].

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2. Text

2.1. Stage 1: Abnormal Placental Development and Trophoblast Invasion

The mechanism of abnormal placentation is controversial, but animal models have shown that uteroplacental ischemia leads to hypertension and multi-organ failure, which are observed in maternal preeclampsia [7]. Placental hypoperfusion leads to the production and release of vasoactive factors, resulting in the activation and damage of the vascular endothelium [8]. Excessively shallow trophoblast invasion, along with impaired transformation of the uterine spiral arteries and abnormalities in placental villi development, leads to placental dysfunction. This results in increased oxidative stress parameters and systemic vascular endothelial dysfunction. These changes manifest as clinical symptoms in later stages of the disease.

Normal placental development is characterized by the migration of highly invasive trophoblast cells beyond the chorion into the uterine mucosa. These cells then penetrate to a depth of approximately one-third of the uterine muscle. This process results in the remodeling of spiral arterioles into a low-resistance vascular system. This transformation ensures normal fetal growth and progression of the pregnancy [9].

An adequate oxygen concentration gradient between the placenta and maternal arteries is critical for this process to function properly. It has been suggested that the abnormal trophoblast invasion and placental hypoxia observed in preeclampsia result from an imbalance of oxygen and disorders of the methionine-homocysteine cycle [9]. The branched vascular network is crucial for the development of the placenta. This network depends on factors such as vascular endothelial growth factor (VEGF), placental growth factor (PlGF), angiopoietin-1 (Ang-1), angiopoietin-2 (Ang-2), soluble fms-like tyrosine kinase 1 (sFlt-1), and soluble endoglin (sEng) to regulate blood vessel growth[10]. Imbalances in these factors can lead to abnormal placental vascular development. Imbalances in these factors can lead to abnormal placental vascular development. During pregnancy, these factors are released into the maternal circulation to adapt the cardiovascular system to the demands of pregnancy [10].

An increased secretion of antiangiogenic factors can lead to an antiangiogenic state in the mother, which contributes to pregnancy pathologies such as preeclampsia and fetal growth restriction (FGR). There are many theories regarding the causes of placental dysfunction, including oxidative stress, abnormal natural killer cells at the maternal-fetal interface, and genetic and environmental influences. Numerous studies confirm that an abnormal placenta releases soluble toxic factors into the maternal circulation, causing inflammation, vascular endothelial dysfunction, and systemic maternal disease [5,6,11,12].

During a normal pregnancy, cytotrophoblast cells migrate into the maternal uterine spiral arteries as the placenta implants. These cells form vascular sinuses that provide the fetus with adequate nutrition and oxygenation. This infiltration progresses deep into the spiral arteries, reaching the level of the myometrium. This results in the extensive remodeling of the maternal spiral arterioles into low-resistance, high-capacity, high-flow vessels [4,11,13,14].

In pregnancies complicated by preeclampsia, abnormal placentation occurs when the cytotrophoblast fails to transform from a proliferative epithelium to an invasive endothelium. This leads to incomplete remodeling of the spiral arteries [15]. Inadequate remodeling of the spiral arteries leads to maternal vasoconstriction and relative placental ischemia [16]. Narrow spiral arteries are susceptible to atherosclerotic changes, including the presence of lipid-laden macrophages in the vessel lumen, fibrinous necrosis of the arterial wall, and mononuclear perivascular infiltrates [17]. These changes further compromise placental perfusion.

These changes are detected during a non-invasive Doppler ultrasound examination of the uterine arteries. They are characterized by a significant impairment of diastolic flow with a distinct notch in the waveform, as opposed to the normal, strong, undisturbed flow in both systolic and diastolic uterine arteries typically observed during physiological pregnancy. These abnormalities are

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observed in the preclinical phase and may be used to stratify patients into risk groups, indicating the initiation of preeclampsia prophylaxis [18,19].

Trophoblast abnormalities alone are believed to lead to shallow invasion and abnormal spiral artery transformation, resulting in placental ischemia and preeclampsia[15]. In pregnancies complicated by preeclampsia, atherogenic changes have also been observed in the radial arteries supplying the decidual arteries [20,21]. Decidual vasculopathy with acute atherosclerotic changes, medial hyperplasia, and perivascular lymphocytes is observed in placental insufficiency. This condition is associated with poorer clinical prognoses, higher diastolic blood pressure, impaired renal function, and an increased risk of fetal death [22].

In the third trimester of a normal pregnancy, the vessels of the decidua are characterized by a flat endothelium and a loss of vascular smooth muscle. However, in preeclampsia, secondary atherosclerotic changes occur in the decidual vessels: edematous and loosely arranged vascular endothelium; hypertrophy of the intima and media; and a lack of modification of vascular smooth muscle. This is a characteristic feature of decidual vasculopathy [20]. The question remains whether decidual vasculopathy is the cause of stage 1 in the pathogenesis of preeclampsia, or whether these changes result from systemic damage to the maternal vascular endothelium secondary to the observed changes [20].

Another factor that appears to lead to preeclampsia is the abnormal transformation of the endometrium and decidua [23]. Absent or abnormal decidualization in vitro, as well as genetic defects, have been observed in patients with preeclampsia, which indicates a genetic influence [24]. It has been suggested that cells from the decidua may play an important role in reducing trophoblast invasion.

Hypoxia is also thought to play a key role in the pathogenesis of preeclampsia [25]. The low-oxygen environment during the early stages of gestational sac implantation favors trophoblast proliferation and blastocyst implantation in the uterus. The connection between the trophoblast and the spiral arteries creates spaces called intervillous sinuses, which allow for the inflow of maternal blood. This leads to an increase in oxygen tension and generates oxidative stress. Thus, it enables the differentiation of the proliferative trophoblast into an invasive phenotype that disrupts and remodels the spiral arteries [26].

Hypoxia-inducible factors (HIFs) are highly expressed in the proliferating trophoblast tissues and placentas of women with preeclampsia. Using a mouse model, researchers observed that overexpressing HIF-1α disrupts the trophoblast's transformation from a proliferative state to an invasive state. This leads to hypertension, proteinuria, and restricted fetal growth [27]. Conversely, inhibiting HIF-1α with the estradiol metabolite 2-methoxyestradiol blocks the production of sFlt-1 (soluble fms-like tyrosine kinase 1), a potent antiangiogenic factor responsible for the clinical symptoms of preeclampsia [28].

Studies have confirmed an association between lower placental perfusion fraction and fetal growth restriction, Doppler flow abnormalities in maternal and fetal vessels, lower neonatal weight, and higher sFlt1 levels [29]. Additionally, the significance of oxidative stress in the trophoblast invasion process for the development of normal pregnancies or those complicated by preeclampsia has been highlighted.

Proper oxygen delivery through maternal blood flow after prior oxygen restriction is necessary for normal placentation. However, periodic changes in hypoxia and reoxygenation may lead to poor or overly shallow invasion of the spiral arteries and oxidative stress [11].

Another factor that occurs in preeclampsia is an imbalance between enzymes that generate reactive oxygen species (ROS) and antioxidants. This imbalance favors the enzymes that generate ROS, which contributes to the inhibition of trophoblast invasiveness. This occurs through increased expression and activity of ROS-generating enzymes and the inhibition of the Wnt/β-catenin pathway. It also promotes antiangiogenic factors, such as sFlt1 11,28. Furthermore, decreased expression of superoxide dismutase and glutathione peroxidase, along with impaired antioxidant mechanisms, has

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been observed in women experiencing preeclampsia during pregnancy compared to healthy pregnant women [11].

Increased reactive oxygen species may result from mitochondrial stress. Zsengellér et al. [30] demonstrated reduced activity of the mitochondrial electron transport chain (ETC) and cytochrome C oxidase in syncytiotrophoblast cells of placentas from preeclamptic pregnancies, which correlated with increased sFLT1 expression in the placenta. Additionally, damage caused by sequential ischemia and reflow leads to endoplasmic reticulum (ER) stress in the decidua and placentas from pregnancies complicated by preeclampsia or fetal growth restriction (FGR), resulting in apoptosis of the decidua and cytotrophoblast cells, as well as reduced transcription of placental growth factor (PlGF), a key proangiogenic factor essential for normal pregnancy development [31–34].

In rodents, the induction of heme oxygenase (HO-1) has been shown to have beneficial effects, including a reduction in blood pressure and an increase in the ratio of vascular endothelial growth factor (VEGF) to soluble fms-like tyrosine kinase 1 (sFlt-1) in the placenta [35].

Physiologically, the trophoblast coats the outer wall of the decidual capillaries and the interendometrial branches of the spiral arteries, forming the outer sheath of these vessels.

Trophoblast cells infiltrate the capillary walls from the outside in, forming loose clusters within them. During the next phase of cytotrophoblast invasion, the endothelium and most of the musculoelastic fibers are lost. The endothelial cells of the spiral arteries are partially replaced by extravillous trophoblast cells within the blood vessels.

Remodeling of the spiral arteries occurs. During a normal pregnancy, the diameter of their lumen increases four- to six-fold, and they become insensitive to vasopressors due to nerve fiber degradation. These changes affect the spiral arteries in both the decidual and myometrial portions. The vascular endothelium layer is restored, and wide uteroplacental arteries form. This ensures low-pressure, low-resistance blood flow, which promotes proper perfusion and oxygenation of the intervillous space [36–38].

In preeclampsia, pseudovasculogenesis fails, causing cytotrophoblast cells to fail to adopt an invasive endothelial phenotype. Consequently, the invasion of spiral arteries is incomplete and limited to the decidua, failing to reach the intrauterine myometrium. These arteries remain small-diameter, high-resistance vessels, which leads to placental ischemia [11].

Abnormal spiral arteries are narrower but retain their reactivity. Placental perfusion and the maternal-placental-fetal exchange surface are reduced, and the volume of placental villi shrinks. Blood flow is high-resistance, with variable velocity and turbulence during inflow, which further damages the villi surface [36–38]. Oxidative stress increases, leading to the release of proinflammatory cytokines and vasoactive factors, which in turn activate and dysfunction the vascular endothelium [39]. Both early- and late-onset preeclampsia result from stress on the placental syncytiotrophoblast [2].

2.2. Stage 2 Involves an Imbalance in Circulating Angiogenic Factors and Underlies the Development of Maternal Syndrome

An imbalance in circulating angiogenic factors is responsible for the maternal symptoms of preeclampsia. Currently, elevated levels of soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), along with significantly reduced levels of placental growth factor (PlGF), are believed to play a key role in the development of preeclampsia symptoms.

These substances are primarily produced in the syncytiotrophoblast and secreted into the maternal circulation [39–43]. Overly shallow placentation and abnormal vascular remodeling, along with the associated ischemic processes and placental damage, are responsible for the increased secretion of antiangiogenic factors into the maternal circulation [40–43]. An imbalance of these factors leads to vascular changes and microangiopathy in vital organs, especially those with fenestrated endothelium, such as the brain, kidneys, or liver.

sFlt1 is a soluble protein that exerts anti-angiogenic effects by binding to and inhibiting the biological activity of pro-angiogenic proteins such as VEGF and PlGF [11,49]. VEGF is important for

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maintaining endothelial cell function. PlGF, on the other hand, plays an essential role in angiogenesis and selectively binds to VEGFR1/sFLT1, but not to VEGFR2 [48,49]. The administration of exogenous sFlt1 to rodents resulted in hypertension, proteinuria, and glomerular endotheliosis - hallmarks of preeclampsia. In contrast, reducing sFlt1 levels or antagonizing sFlt1 in experimental animal models of preeclampsia attenuated clinical symptoms [44,45] or led to their spontaneous resolution when sFlt1 levels were reduced by half or more by treating underlying placental conditions such as fetal hydrops or by removing diseased placentas in multiple pregnancies [46–49].

Soluble endoglin (sEng), another antiangiogenic protein that has been extensively studied in preeclampsia, is an endogenous inhibitor of TGF-β1 (transforming growth factor β1) [50]. Elevated levels of soluble endoglin (sEng), an endogenous inhibitor of transforming growth factor β1 (TGF-β1), have been detected in the serum of women with preeclamptic pregnancies as early as two months before the onset of clinical symptoms. These levels correlate with disease severity, leading to fetal growth retardation, thrombocytopenia, and, in combination with sFlt1, cerebral edema [51,52].

Cytokines and Changes in Immune Cells

Preeclampsia is well-known to be a proinflammatory condition; however, the responsible mechanism has not yet been fully elucidated. It seems that syncytiotrophoblast microvesicles and exosomes, which are rich in sFlt1 and endoglin, may initiate an inflammatory response [53,54]. A normal pregnancy is characterized by a shift in the T cell phenotype toward Th2 versus Th1 [55,56]. However, in pregnancies complicated by preeclampsia, an abnormal shift toward the Th1 phenotype is observed, which leads to insufficient trophoblast invasion [57]. Additionally, a preeclampsia-like syndrome can be induced in healthy pregnant rats by transferring CD4+ cells derived from RUPP models.

Studies on the peripheral blood mononuclear cells of women with preeclampsia have shown reduced IL-10 secretion. This may lead to impaired T lymphocyte differentiation because IL-10 is a cytokine that induces T lymphocyte differentiation into the Th2 phenotype (T helper type 2). IL-10 has properties that neutralize proinflammatory cytokines, AT1-AA (autoantibodies against the angiotensin II receptor 1), and placental ROS (reactive oxygen species) and ET-1 (endothelin-1) [55–61].

Preeclampsia has also been shown to be associated with elevated complement levels and C3 genetic mutations [62,63]. Animal studies have demonstrated that inhibiting complement component activity restores spiral artery capacitance and reduces sFlt1 production in this patient group [11.62,63]. The highest level of abnormal complement activity is observed in HELLP syndrome, which is similar to atypical hemolytic uremic syndrome, which is associated with uncontrolled complement activation [11].

Renin–Angiotensin–Aldosterone System

Increased sensitivity to angiotensin II has been reported both in clinically overt preeclampsia and in the preeclamptic period, despite reduced levels of circulating renin and angiotensin II compared with normal pregnancy [64–68].

Circulating anti-angiotensin II type 1 receptor (AT1) autoantibodies in women with preeclampsia may be a potential mechanism that increases sensitivity to angiotensin II [64–68]. These autoantibodies induce vasoconstriction via endothelin-1 (ET-1) activation, necrosis and apoptosis of umbilical vein endothelial cells, reduced trophoblast invasion, and increased reactive oxygen species (ROS) production, which stimulates tissue factors and leads to hypercoagulability [64–68].

Additionally, an increase in the number of CD19+CD5+ cells, as well as anti-Angiotensin II type 1 receptor antibody activity (AT1-AA), has been observed in the serum of patients with preeclampsia. This suggests that B lymphocytes play a role in the development of preeclampsia. Anti-AT1-AA antibodies, produced by the CD19+CD5+ subpopulation in response to placental ischemia and systemic inflammation, appear to contribute to hypertension and the production of antiangiogenic

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factors that characterize the maternal syndrome. Antibodies against the angiotensin type 1 receptor, produced in response to placental ischemia and inflammation, stimulate production of antiangiogenic factors, such as sFlt1 and sEng, in the placenta [11,67–70]. In animal models, elevated levels of circulating sFlt1 are sufficient to induce sensitivity to angiotensin II by interfering with the normal production of nitric oxide by the vascular endothelium.

Homocysteine

Reduced blood homocysteine levels are observed in pregnant women with normal pregnancies. Conversely, elevated homocysteine levels are associated with implantation disorders, embryogenesis abnormalities, neural tube defects, miscarriage, fetal death, premature placental abruption, hypertension, and fetal growth restriction (FGR) [2,11,69,70]. Furthermore, hyperhomocysteinemia leads to endothelial cell dysfunction, vascular wall damage, increased fibrosis, impaired blood flow, increased platelet activation, thrombosis, atherosclerotic changes, and abnormal placental function [69,70].

Nitric Oxide and ADMA

Nitric oxide (NO) is a key factor in regulating placental blood flow. It has potent vasodilatory effects and inhibits platelet aggregation and vascular smooth muscle proliferation. NO also reduces the release of free oxygen radicals and lowers vascular tone [69,70]. NO plays an active role in intravascular cytotrophoblast invasion and placental development due to its unique angiogenic properties [69,70].

Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthase (NOS) that has been associated with impaired endothelial function and uterine artery flow abnormalities observed in preeclampsia [69,70]. Elevated homocysteine (Hcy) levels in women with preeclampsia lead to increased ADMA levels due to Hcy's inhibitory effect on ADMA metabolism. Nitric oxide (NO) also increases the proangiogenic activity of vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) while decreasing the levels of soluble fms-like tyrosine kinase 1 (sFlt-1) in hypoxic human trophoblast cells [69,70]. In preeclampsia, reduced nitric oxide production in the fetoplacental unit leads to placental vasoconstriction, impaired placental perfusion, increased maternal blood pressure, and increased peripheral resistance [11,69,70].

Increased apoptosis and aponecrosis (a form of incomplete apoptosis) have also been reported in patients with preeclampsia. The continuous increase in villous turnover leads to intense proliferation and turnover of trophoblast cells, leading to increased flow of placental material into the maternal circulation, the presence of degenerative changes in the syncytiotrophoblast, and higher levels of fetal DNA in the maternal circulation.

The maternal immune system is thought to play a significant role in the development of preeclampsia. One cause of abnormal trophoblast invasion in early pregnancy is believed to be an altered immune response of the pregnant woman, characterized by abnormal tolerance of the maternal immune system, comparable to the rejection reaction of an allogeneic transplant.

Sack et al. and Borzychowski and Luppi described the excessive activation of neutrophils and monocytes, as well as the increased spontaneous production of proinflammatory cytokines, such as IL-1β, IL-6, and IL-8, in patients with preeclamptic pregnancies [71–73]. Furthermore, an increased tendency toward a proinflammatory response in CD4+ and CD8+ T lymphocytes, natural killer (NK) cells, and dendritic cells due to dysregulation of Toll-like receptors. This response was similar to that observed in non-pregnant women, but different from the immunosuppressive and anti-inflammatory response characteristic of healthy pregnant women [9,55,71–73]. Natural killer (NK) cells play an important role in regulating cellular interactions during physiological changes and promoting placental development and spiral artery transformation.

Decidual NK cells secrete fewer invasion-promoting factors in women with abnormal uterine artery flow examination results, which may explain the shallow invasion observed in pregnancies complicated by preeclampsia.

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Genetics is another factor that contributes to the development of preeclampsia. Variations in the incidence of preeclampsia have been observed based on race, geography, and socioeconomic status. Women with first-degree relatives with preeclampsia have a five-fold increased risk, while those with second-degree relatives have a two-fold increased risk, and a two-fold increased risk in patients who themselves were born to pregnancies complicated by preeclampsia [9].

Abnormal trophoblast invasion, which occurs early in pregnancy in patients with certain genetic or immunological predispositions, appears to lead to increased vascular resistance in the uteroplacental circulation and altered resistance in the uterine arteries.[9]

Persistent subperfusion leads to placental hypoxia, which induces local oxidative stress and increases apoptosis and necrosis of trophoblast villi. This, in turn, has fetal implications and may lead to the development of fetal growth restriction (FGR) or the release of vasoactive factors into the maternal circulation, leading to the next stage of preeclampsia, with a systemic inflammatory response and vascular endothelial dysfunction, which should be considered an interdependent, interactive process preceding the onset of clinically apparent preeclampsia symptoms [73].

The mechanisms responsible for abnormal placental development in preeclampsia (PE) remain incompletely understood. However, several factors have been suggested to play a role, including impaired maternal immune recognition, increased HIF-1α and HIF-2α, increased TGF-β3, altered soluble VEGF/PIGF receptor ratios, low levels of PIGF, and altered levels of angiogenic factors [9,11,12].

3. Conclusions

Despite numerous studies, the etiology of preeclampsia has not yet been fully elucidated. A better understanding of the condition's precise etiology holds promise for the development of new options for early diagnosis, prevention, and modern causal treatment of preeclampsia. Research on maternal angiogenic factor imbalances and their effect on vascular function has led to the development of methods for detecting and assessing the risk of early-onset preeclampsia. Levels of sFlt-1, sEng, and PlGF have proven to be particularly useful in predicting the occurrence and severity of preeclampsia [9,11,74].

Furthermore, clinical trials have demonstrated that preeclampsia symptoms can be alleviated and pregnancy can be safely prolonged through plasma apheresis, which removes antiangiogenic proteins [9,11,75–77]. Studies in animal models using recombinant human PlGF and siRNA have also shown promise as an effective therapy, particularly for early-stage preeclampsia. This therapy could help reduce the risk of severe complications and premature delivery in affected patients [9,11,75–77].

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