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Risks and Mechanisms of Preeclampsia

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ABSTRACT

BACKGROUND: Preeclampsia is a specific pregnancy complication associated with a high cardiovascular risk in both mothers and neonates. Recent research has focused on understanding its underlying mechanisms, which involve differential methylation of cytosine-phosphate-guanine islands and alterations in microRNA expression, genetic and epigenetic factors, and various biomolecules involved in inflammation, oxidative stress, and angiogenesis, etc. Through all these mechanisms, preeclampsia-induced vascular abnormalities may be linked with the pathogenesis of potential cardiovascular diseases. This review explores the diverse mechanisms underlying preeclampsia and the associated cardiovascular changes in pregnant women. The review findings may inform potential strategies for early diagnosis and targeted treatment of preeclampsia.

AIM: to analyze published data on the risks and pathophysiological mechanisms of preeclampsia.

The review was conducted in 2024 using the eLibrary and PubMed databases. The following search queries were used: риски развития преэклампсии (risks of preeclampsia), механизмы развития преэклампсии (mechanisms of preeclampsia), осложнения при преэклампсии (complications of preeclampsia), and сердечно-сосудистые заболевания как осложнение преэклампсии (cardiovascular diseases as a complication of preeclampsia). Currently, there is no consensus regarding the true etiology of preeclampsia. It is often referred to as a disease of theories, which may reflect the fact that the primary biological mechanisms connecting clinical and epidemiological data with organ dysfunction, remain elusive. Despite the lack of definitive evidence, many experts favor the hypothesis that preeclampsia is a primary placental disease. Ongoing efforts are focused on developing effective strategies for screening, diagnosis, treatment, and improving maternal postpartum cardiovascular outcomes.

CONCLUSION: Preeclampsia is a pregnancy-specific complication with a multifactorial etiology, involving abnormal placentation, endothelial dysfunction, systemic inflammation, and oxidative stress. Despite advancements in understanding its underlying mechanisms, effective prevention and treatment options remain limited. The increased risk of cardiovascular diseases in women with preeclampsia may be associated with genetic predisposition, epigenetic modifications during pregnancy, and placental abnormalities.

Keywords: pregnancy; underlying mechanisms; preeclampsia; cardiovascular diseases; risk factors.

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Риски и механизмы развития преэклампсии

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АННОТАЦИЯ

Актуальность. Преэклампсия — это специфическое осложнение беременности, связанное с высоким риском возникновения сердечно-сосудистых заболеваний как у женщин, так и у их будущих детей. В настоящее время изучаются механизмы ее развития, связанные с дифференциальным метилированием цитозин-фосфат-гуанозиновых островов и изменением в экспрессии микроРНК, генетические и эпигенетические факторы, а также ряд биомолекул, участвующих в воспалении, окислительном стрессе, ангиогенезе и др. Все эти механизмы могут связывать нарушения сосудистого русла беременности при преэклампсии с патогенезом будущих сердечно-сосудистых заболеваний. В данном обзоре рассмотрены различные механизмы развития преэклампсии и изменения сердечно-сосудистой системы у беременных женщин с этим осложнением. Возможно, данные обзора представят потенциальные стратегии диагностики и лечения преэклампсии.

Цель — анализ имеющихся литературных данных о рисках и механизмах развития преэклампсии.

Обзор публикаций проведен в 2024 г. в базах eLibrary и PubMed. Использовались следующие поисковые запросы: «риски развития преэклампсии», «механизмы развития преэклампсии», «осложнения при преэклампсии», «сердечно-сосудистые заболевания как осложнение преэклампсии». Установлено, что все еще не существует единого мнения относительно истинной этиологии преэклампсии. Ее называют «болезнью теорий», вероятнее всего, это связано с тем, что основные биологические механизмы, связывающие клинические и эпидемиологические данные с дисфункцией органов при преэклампсии, пока недостаточно ясны. Несмотря на отсутствие последовательных доказательств, эксперты склоняются в пользу предположения, что преэклампсия является первичным плацентарным расстройством. В настоящее время все еще разрабатываются эффективные стратегии скрининга, диагностики, терапии и улучшения послеродового сердечно-сосудистого исхода у матери.

Заключение. Преэклампсия — это специфическое осложнение беременности с многофакторным происхождением, включающее аномальную плацентацию, эндотелиальную дисфункцию, системное воспаление и окислительный стресс. Несмотря на достижения в понимании ее патофизиологии, эффективные стратегии профилактики и лечения остаются ограниченными. Риски развития сердечно-сосудистых заболеваний при преэклампсии, вероятнее всего, связаны с существующим семейным генетическим фоном, эпигенетическими изменениями во время беременности, а также аномалиями развития плаценты.

Ключевые слова: беременность; механизмы развития; преэклампсия; сердечно-сосудистые заболевания; факторы риска.

Как цитировать

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BACKGROUND

According to the World Health Organization (WHO), preeclampsia is a leading pregnancy complication, affecting approximately 4%–5% of pregnant women worldwide. It ranks first among the causes of maternal and perinatal mortality, significantly contributing to the decompensation of maternal cardiovascular diseases (CVD) [1].

Currently, preeclampsia is considered a placental and maternal dysfunction. Genetic, angiogenic, structural, and metabolic mechanisms play a critical role in the development of this complication, including spiral artery remodeling, placental oxygenation, maternal–fetal redox balance, immune tolerance, and the balance between angiogenic and antiangiogenic factors. Certain antiangiogenic proteins have become key pathogenic mediators of preeclampsia. Their discovery has enabled the development of novel diagnostic tools such as risk calculators, prediction models, and triage instruments. Moreover, these antiangiogenic proteins have emerged as attractive therapeutic targets. Several strategies for their inhibition, removal, and blockade are currently under development, *in vitro* and *in vivo* [2, 3].

According to WHO estimates, preeclampsia and eclampsia account for over 50,000 maternal deaths annually worldwide, with considerable variation in incidence across geographic regions. In industrialized countries, the prevalence of hypertensive disorders during pregnancy has increased, with African–American women being at higher risk compared with Hispanic, American–Indian, White, Asian, and Pacific Islander women. Based on a national hospital discharge survey that tracked approximately 39 million deliveries over 10 years, the prevalence of hypertensive disorders in the United States during pregnancy is 5.9%. The investigation also demonstrated that women with preeclampsia or eclampsia had a 3- to 25-fold higher risk of severe complications such as placental abruption, disseminated intravascular coagulation, pulmonary edema, and aspiration pneumonia [4–6].

The heterogeneity of preeclampsia remains debatable, as its epidemiology, clinical manifestations, and associated morbidity differ between early-onset "placental" preeclampsia (before 34 weeks) and late-onset "maternal" preeclampsia (after 34 weeks). Early-onset preeclampsia is strongly associated with fetal growth restriction, whereas late-onset disease is often linked to maternal obesity and infants large for gestational age. Although clinical manifestations differ between the early- and late-onset subtypes, transcriptional profiling investigations show a common maternal blood gene signature for both subtypes, indicating that the mechanisms of maternal vascular injury may be more similar than previously thought [1, 4].

The determinants of preeclampsia include family history, genetic predisposition, duration of sexual cohabitation, maternal smoking, parity, maternal age, use of *in vitro* fertilization, and maternal health status (e.g., preexisting hypertension, congenital and acquired heart disease, cardiac arrhythmias, diabetes mellitus, chronic kidney disease, and obesity). The genetic heritability of preeclampsia is estimated at 55%, with maternal and fetal genetic contributions of 30%–35% and 20%, respectively. A large genome-wide association study provided evidence that variants near the fms-like tyrosine kinase 1 locus in the human fetal genome may underlie the development of preeclampsia [6–8].

At present, the definitive treatment for preeclampsia is delivery, although ongoing research into new therapeutic methods appears promising. Management includes preconception counseling; perinatal blood pressure monitoring; treatment of complications, particularly in patients with CVD; timely delivery; and postpartum follow-up. The American College of Obstetricians and Gynecologists (ACOG) recommended preconception counseling for all women with a history of preeclampsia [1–3].

The recommendations for postpartum follow-up of women with gestational hypertension and preeclampsia include inpatient blood pressure monitoring or equivalent outpatient follow-up for at least 72 h, followed by monitoring at 7–10 days postpartum or earlier in women with high blood pressure and in those with cardiovascular disease. All postpartum women, not only those with preeclampsia, are advised to receive discharge instructions about the signs and symptoms of this complication. Studies have shown that postpartum hypertension and preeclampsia are more common than previously assumed. Evidence indicates that angiogenic profiles in this group of women are similar to those of women with preeclampsia and may represent a group with subclinical or unresolved preeclampsia [6].

This study aimed to analyze published data on the risks and pathophysiological mechanisms of preeclampsia.

The investigation was conducted in two stages. The first stage involved a literature search in *eLIBRARY.RU* and *PubMed*. The following search queries were used: риски развития преэклампсии (*risks of preeclampsia*), механизмы развития преэклампсии (*mechanisms of preeclampsia*), осложнения при преэклампсии (*complications of preeclampsia*), and сердечно-сосудистые заболевания как осложнение преэклампсии (*CVD as a complication of preeclampsia*).

The review included studies of any design published in the specified databases over the past 10 years. Initially, 321 publications were identified, of which 106 remained after the removal of duplicates, abstracts, and summaries without available full-text versions.

The second stage incorporated reviewing the publications and excluding those that did not meet the inclusion criteria. The inclusion criteria covered publications addressing the risks and mechanisms of preeclampsia and the mechanisms of cardiovascular disease development in pregnant women with preeclampsia.

Preeclampsia is a human-specific disease. This specificity is believed to be due to the disproportionately high brain-to-body mass ratio of the human fetus, which requires 60% of maternal nutrient exchange in the third trimester, compared with 20% in other mammals.

Ischemic Placenta Hypothesis

The characteristics of a preeclamptic placenta have been investigated for over a century. An analysis of >100 placental bed biopsy samples from women with various hypertensive disorders during pregnancy showed that samples from women with chronic hypertension demonstrated hyperplasia and arteriosclerosis with intimal and medial thickening of the basal and spiral arteries and frequent mural thrombi in the spiral arteries. These features differed markedly from those observed in preeclamptic and eclamptic placental bed samples, wherein vessels exhibited acute fibrinoid necrosis of the vessel wall and the presence of foam cells, indicating acute atherosis. Lipophage infiltration and complete thrombotic occlusion of vessels were also frequently found in preeclamptic placental beds [9, 10].

The ischemic placenta hypothesis was supported with the demonstration that in preeclampsia, physiological changes in the spiral arteries are limited to the decidua, whereas in normal pregnancy, they extend proximally into the myometrium. In addition, in a series of placental bed biopsy samples, the mean spiral artery diameter in preeclamptic samples was only 200 μm compared to 500 μm in placentas from normal pregnancies. This superficial invasion into the decidua leads to narrow, nondilated proximal segments of the spiral arteries, ultimately causing uterine hypoperfusion and increased blood flow velocity in the intervillous space. These findings were confirmed by a study that demonstrated a severe defect in spiral artery remodeling in the myometrium, which was particularly common when preeclampsia was accompanied by significant fetal growth restriction [9–11].

The molecular mechanisms mediating spiral artery remodeling remain under investigation. Investigations have shown that during normal placentation, cytotrophoblasts differentiate from an epithelial to an endothelial phenotype – a process called “pseudovasculogenesis” or “vascular mimicry”; however, this transformation does not occur in preeclampsia. Cytotrophoblasts that do not invade maternal spiral arterioles cannot express endothelial adhesion markers such as VE-cadherin and the integrins α1β1 and αVβ3, which are expressed by normal invasive cytotrophoblasts. These cytotrophoblast differentiation defects in the placenta of women with preeclampsia indicate that mechanisms contributing to placental ischemia are initiated very early in pregnancy [12–16].

Role of HIF1α in the Pathogenesis of Preeclampsia

Experimental studies of placental metabolic profiles throughout pregnancy have demonstrated that energy demand in the first trimester does not decrease despite relative hypoxia. Moreover, in human villous explants at 5–8 weeks, low oxygen tension triggers cytotrophoblast proliferation through mechanisms involving the hypoxia-inducible transcription factor 1α (HIF1α). HIF1α and HIF2α are products of a shared oxygen-sensitive pathway. They regulate the expression of hypoxia-inducible genes, including erythropoietin, vascular endothelial growth factor (VEGF), and nitric oxide synthase (NO synthase). HIF1α expression in the human placenta increases during the first trimester and decreases at approximately 9 weeks, when blood flow and fetal oxygenation increase [16, 17].

Persistent increase of HIF1α may indicate placental stress and contribute to the development of preeclampsia. Preeclamptic placentas have been shown to overexpress HIF1α and HIF2α and fail to suppress their expression upon oxygenation. In addition, pregnant mice with HIF1α overexpression exhibit several features of preeclampsia, including increased blood pressure, proteinuria, intrauterine growth restriction, glomerular endotheliosis, HELLP syndrome, and increased levels of antiangiogenic factors such as soluble fms-like tyrosine kinase 1 (sFlt1), also known as sVEGFR1, and soluble endoglin (sEng). Hypoxia-induced increases in sFlt1 have been determined in models of placental hypoxia *in vitro* and *in vivo*, including in early first-trimester placentas from women living at high altitudes and from women with preeclampsia [16].

HIF1α appears to be a pathogenic mediator in preeclampsia. The reason for persistently increased HIF expression in the preeclamptic placenta remains unclear and may be related to an upstream pathway involving 2-methoxyestradiol (2-ME) formation via catechol-O-methyltransferase (COMT). Moreover, 2-ME is an estradiol metabolite whose concentration increases throughout pregnancy and destabilizes, thereby inhibiting HIF1α. Current data regarding placental COMT expression levels in women with preeclampsia are inconsistent. Some small reports have revealed decreased COMT levels in the placenta during hypertensive pregnancy, whereas others have found no differences in COMT expression between hypertensive and normotensive pregnancies. Clinical evaluations measuring circulating 2-ME and other estrogen metabolites are required to clarify the role of the COMT pathway in the development of preeclampsia [17].

In preeclampsia, there is an imbalance between antioxidant and pro-oxidant mechanisms. Consistent with this hypothesis, *in vitro* experiments have demonstrated increased reactive oxygen species levels in human placental tissue following ischemia and reperfusion. These findings were further corroborated by an experiment that showed increased oxidative stress in pregnant rats with decreased uterine perfusion pressure (a model of hypertensive pregnancy) [16, 18, 19].

Heme Oxygenase Pathway as a Key Factor in the Pathogenesis of Preeclampsia

The heme oxygenase (HO) pathway is a crucial mediator of oxidative stress. HO exists as an inducible isoform (HO1), a constitutive isoform (HO2), and an isoform of unknown function (HO3). Using transcriptional profiling and immunohistochemistry, studies have demonstrated that HO1 is localized in the perivascular smooth muscle layer of human placental vessels and that its induction attenuates tumor necrosis factor (TNF)-mediated cellular injury. They also reported that HO1 protein levels were significantly decreased in preeclamptic placentas compared with placentas from normotensive control pregnancies. Interestingly, adenoviral overexpression of HO1 in endothelial cells inhibited the release of antiangiogenic factors from the placenta, whereas the induction of HO1 using cobalt protoporphyrin in an animal model of preeclampsia attenuated placental ischemia-induced hypertension, indicating a role for HO1 in the downstream effects of such ischemia on maternal endothelium. Consistent with these findings, HO1 knockout mice had lower birth weight and litter size than controls. HO1 heterozygotes exhibited increased maternal diastolic blood pressure and sFlt1 levels compared with wild-type pregnant mice, despite a compensatory increase in HO expression. These data exhibit the role of the HO system as a critical mediator of oxidative stress in normal pregnancy and as a key factor in the pathogenesis of abnormal placentation in preeclampsia [20, 21].

Endoplasmic Reticulum Stress

Data regarding endoplasmic reticulum (ER) stress in placental tissue from patients with preeclampsia have also been obtained. Further investigations are warranted to determine whether ER stress is a consequence of placental hypoxia or a causal factor contributing to abnormal placentation in preeclampsia. Decreased expression of activating transcription factors, which are highly expressed in the placenta, contributes to preeclampsia through aberrant placental expression of HIF and antiangiogenic factors. However, the molecular basis of this dysfunction remains unclear [21].

Immunological Aspects of Preeclampsia Pathogenesis

Identifying the primary cause of defective placentation requires understanding of maternal–fetal immune tolerance. Decidual natural killer (dNK) cells play a key role in spiral artery remodeling. *In vivo* experiments have shown that dNK cell administration in immunodeficient mice with increased uterine artery resistance decreases this resistance, indicating improved placentation. Thus, appropriate activation of dNK cells is required for normal placentation [22].

Another immune-related aspect of preeclampsia involves the major histocompatibility complex (i.e., HLA). Normal fetal trophoblast cells express HLA-C molecules that interact with killer immunoglobulin-like receptors (KIR) expressed on maternal uterine natural killer cells. HLA-C is inherited from both the mother and father. Certain KIR haplotypes are more frequently expressed in preeclamptic pregnancies than in normal pregnancies. This finding demonstrates that normal placentation requires allorecognition of paternal HLA-C63 by maternal KIR and that the higher frequency of preeclampsia in first pregnancies, changes in paternity, shorter durations of sexual cohabitation, and use of barrier contraception are associated with decreased paternal antigen exposure [22, 23].

Preeclampsia is characterized by a T-cell profile imbalance with predominance of T-helper cells and associated cytokines, such as IFNγ and TNF. This imbalance potentially contributes to poor placentation and, consequently, endothelial dysfunction [22–24].

Complement activation is linked to preeclampsia and fetal growth restriction. Lynch et al. prospectively measured the complement activation fragment Bb, a marker of the alternative pathway, in human pregnancy before 20 weeks. They found that women with increased Bb levels had a fourfold increased risk of developing preeclampsia compared with those with lower levels. These data provide strong evidence for complement involvement in preeclampsia pathogenesis. In experimental models of preeclampsia, an imbalance of angiogenic factors appears to precede complement activation. Complement activation is believed to be critical in the development of severe preeclampsia, such as HELLP syndrome. Indeed, dysregulation of complement occurs in atypical hemolytic–uremic syndrome and thrombotic microangiopathy (TMA) with histological resemblance to preeclampsia [13, 25].

Nature of Endothelial Lesions in Preeclampsia

At the histological level, pathological lesions in preeclampsia and eclampsia are characterized by endothelial damage in multiple organ layers. Autopsy of 317 mothers who died from eclampsia revealed brain lesions with

perivascular edema in 68.4% of women, hemorrhage in 36.8%, hemosiderin in 31.6%, small-vessel thrombosis in 10.5%, parenchymal necrosis in 15.8%, liver lesions with perivascular edema and portal necrosis in 72.2%, and medial necrosis of the hepatic artery in 44.4%. Renal tissue exhibited signs of glomerular endotheliosis similar to those reported in previous investigations. Thrombosis is a characteristic finding in most cases of TMA, but is usually absent in glomerular endotheliosis. However, severe preeclampsia with vascular thrombosis often indicates a combination with non-preeclamptic TMA or HELLP syndrome [25].

The relationship between proteinuric preeclampsia and endotheliosis is unclear. Electron microscopy of preeclamptic podocytes showed minimal effacement of foot processes and minimal decrease in slit diaphragm frequency compared with normal podocytes. Some data demonstrate that proteinuria may occur solely due to endothelial dysfunction, possibly from loss of the endothelial glycocalyx. However, podocyturia observed during preeclampsia may also contribute to proteinuria. Further investigations are required to clarify the precise mechanisms underlying proteinuria in preeclampsia [25].

Imbalance of Circulating Angiogenic Factors

Experimental and epidemiological data confirm the pathological role of circulating angiogenic factor imbalance in the etiology of the "maternal syndrome." Excess levels of the antiangiogenic factor sFlt1, produced by the placenta and released into maternal circulation, cause maternal endothelial dysfunction, which leads to preeclamptic signs and symptoms. sFlt1 is a soluble splice variant of the membrane-bound VEGFR1 receptor that binds the proangiogenic proteins VEGF and placental growth factor (PlGF). Consequently, sFlt1 acts as a ligand trap and antagonizes ligand-mediated angiogenic signaling through cell-surface receptors. In rodents, sFlt1 overexpression induces preeclampsia-like symptoms; in humans, higher maternal sFlt1 levels are associated with more severe complications. Additionally, high plasma sFlt1–PlGF ratios are strong predictors of disease severity and adverse clinical outcomes [26, 27].

Agents that inhibit angiogenic signaling, such as VEGF-neutralizing drugs (bevacizumab [Genentech: Avastin]), VEGF-trap (aflibercept [Regeneron]) and small-molecule VEGF receptor inhibitors, are associated with major preeclampsia-like adverse effects, including hypertension, proteinuria, and glomerular changes. These data indicate that increased circulating sFlt1 levels and low circulating proangiogenic factors (VEGF and PlGF) create an antiangiogenic state that contributes to clinical manifestations of preeclampsia [26, 27].

Placental sFlt1 is associated with the matrix, which facilitates its access to systemic circulation. Currently, syncytial fragments released into maternal blood have been identified as a crucial source of circulating sFlt1 in preeclampsia and have been found to play a role in maternal endothelial dysfunction. Further investigation of the molecular machinery controlling syncytium formation and the release of syncytiotrophoblast fragments may elucidate the earliest mechanisms of preeclampsia [28, 29].

Role of the Antiangiogenic Protein sEng in Preeclampsia Pathogenesis

The antiangiogenic protein sEng, which inhibits transforming growth factor-β (TGFβ) signaling, has been extensively studied in preeclampsia. It is highly expressed in preeclampsia and eclampsia. Increased levels of both sEng and sFlt1 are associated with more severe forms of preeclampsia. The specific interaction between sFlt1 and sEng in producing a severe phenotype is unknown; however, sEng may inhibit the TGFβ signaling pathway and further reduce endothelial NO synthase (eNOS) activity, leading to decreased NO bioavailability and increased vascular permeability [29–31].

Antiangiogenic Factors and Agonistic Autoantibodies

Hypertension in preeclampsia does not appear to be mediated by the renin–angiotensin–aldosterone system. Rather, it may be mediated by antiangiogenic factors and agonistic autoantibodies that bind the angiotensin II type I receptor (AT1-AAs). These autoantibodies are produced in women with preeclampsia. AT1-AAs levels do not fully regress postpartum and may contribute to the increased cardiovascular risk in women with a history of preeclampsia. AT1-AAs have been shown to activate sFlt1 in pregnant women and restrict fetal growth. Further studies are warranted to assess the temporal relationship between AT1-AAs and antiangiogenic factor production. Upregulation of bradykinin B2 receptors and heterodimerization of B2 with angiotensin II type I (AT1) receptors may also contribute to enhanced angiotensin II sensitivity and hypertension during preeclampsia; however, definitive evidence for this mechanism is lacking [31].

Vasodilatory and Antioxidant NO and Endothelin 1

Another critical mediator of endothelial dysfunction in preeclampsia is the potent vasodilator and antioxidant NO, which has been shown to mediate the effects of PlGF and VEGF *in vitro*. Circulating NO levels are decreased in women with preeclampsia, whereas restoration of bioavailable NO appears to lower increased sFlt1 and hypertension. Moreover, polymorphisms and changes in eNOS expression are involved in the development of preeclampsia [30, 31].

Endothelin 1 (ET1) is a potent vasoconstrictor, and hypertension and kidney injury caused by VEGF blockade

are mediated by ET1 system activation. ET1 levels are increased in women with preeclampsia. Experimental data have shown that ET1 production mediates hypertension induced by sFlt1 and AT1-AAs. AS ET1 blockers cross the placenta, ET1 signaling remains a less attractive target than other potential therapeutic options for preeclampsia [29, 30].

Endothelial dysfunction, manifested by decreased vasodilation, decreased circulating NO, and increased cholesterol levels, may precede pregnancy in women who later develop preeclampsia. This theory is supported by the fact that such endothelial dysfunction is also present in women with recurrent pregnancy loss who have CVD or an increased risk of CVD despite the absence of hypertension and target-organ damage observed in preeclampsia. Thus, preexisting endothelial dysfunction may represent the link between abnormal placentation and CVD [29, 31].

Obesity and Insulin Resistance

Extensive investigations have focused on obesity and insulin resistance in normal and complicated pregnancies with preeclampsia. Preeclampsia is associated with severe hyperinsulinemia, abnormal glycogen accumulation in the placenta, and impaired insulin signaling through the placenta. Insulin resistance acts synergistically with angiogenic factors, increasing the risk of preeclampsia [30, 31].

Imbalance of Angiogenic Markers

Angiogenic factors are crucial biomarkers of preeclampsia. An imbalance of these angiogenic markers plays a central role in the pathogenesis of preeclampsia. Four independent investigations have demonstrated that most complications can be explained by alterations in angiogenic pathways. PlGF, sFlt1, and sEng levels and the ratios of sFlt1 to PlGF and PlGF to sEng significantly differ between women with preeclampsia and those with normal pregnancies. Changes in sEng and sFlt1 levels between the first and second trimesters were predictive of early preeclampsia, whereas levels in the third trimester could identify women at risk of severe late preeclampsia. Angiogenic factor levels correlate with disease severity. Studies have shown that median plasma sFlt1 levels were higher in patients with early-onset and severe disease than in those with late-onset and mild disease. Alterations in PlGF and sFlt1 levels have been detected as early as 6–10 weeks before the onset of clinical manifestations of preeclampsia. Several studies have confirmed that sFlt1 and PlGF levels can be used as reliable predictive tests [31–33].

A landmark multicenter clinical trial demonstrated that the sFlt1–PlGF ratio can be used to rule out preeclampsia for 1 week in patients with suspected disease, with a negative predictive value >99%. Furthermore, a retrospective analysis indicated a negative predictive value of ~95% for ruling out preeclampsia occurring within 4 weeks of presentation. The improved diagnostic and prognostic capabilities provided by angiogenic marker levels make them clinically useful. In an analysis that used angiogenic markers to guide diagnosis and management, fewer women were misclassified at risk for preeclampsia, potentially decreasing average per-patient costs by avoiding unnecessary testing [34].

A decision-analytic model simulating 1,000 pregnant women receiving standard obstetric care in the UK and evaluating the economic impact of using angiogenic markers instead of standard diagnostic tests determined projected cost savings [35, 36].

Angiogenic biomarkers are also useful for differentiating preeclampsia from other disorders with similar signs and symptoms that may present during pregnancy, such as chronic kidney disease, gestational thrombocytopenia, and chronic hypertension, thereby potentially replacing invasive renal biopsy for diagnostic purposes. A cohort of approximately 500 pregnant women with lupus and/or antiphospholipid antibodies showed that circulating sEng, PlGF, and particularly sFlt1 were significantly higher in those who developed severe adverse outcomes, including early-onset preeclampsia, fetal death, and preterm delivery [37–40].

Circulating angiogenic factors have been evaluated as a screening tool for predicting preeclampsia onset. In a large UK-based analysis, the mid-trimester (~28 weeks) plasma sFlt1–PlGF ratio had a positive predictive value of 32% for preeclampsia in an unselected cohort of nulliparous women (n = 4099). Angiogenic markers have also been incorporated into several first-trimester prediction models that integrate maternal characteristics with biophysical and biochemical parameters. In women with singleton pregnancies, one first-trimester algorithm combined uterine artery pulsatility index, mean arterial pressure, pregnancy-associated plasma protein A, free serum PlGF, body mass index, and a history of preterm birth or preeclampsia. This approach identified 93.1% of cases of early-onset preeclampsia with a false-positive rate of 5%. A clinical trial that demonstrated that early aspirin prophylaxis was highly effective in preventing preeclampsia used an algorithm incorporating both biophysical and angiogenic risk factors to identify patients at increased risk for enrollment [41–44].

Proteomic Analyses

Current investigations are exploring the feasibility of proteomic profiling using mass spectrometry, protein microarrays, and urinary proteomics and metabolomics in detecting and predicting preeclampsia. Fetal RNA levels have been found to be approximately 10-fold higher in women with preeclampsia than in those with uncomplicated pregnancies; both fetal and placental RNAs are

being examined as potential biomarkers for early diagnosis of preeclampsia [45–47].

Long-Term Consequences of Preeclampsia

Increasing evidence indicates an increased risk of long-term adverse outcomes among women with a history of preeclampsia, particularly in the context of CVD. The American Heart Association recommends documenting pregnancy history as part of cardiovascular risk assessment in women. A meta-analysis that included approximately 200,000 cases of preeclampsia demonstrated an increased relative risk of hypertension and ischemic heart disease. A subsequent meta-analysis reported a threefold increase in chronic hypertension and a twofold increase in CVD and stroke among mothers with preeclampsia. The ACOG advises periodic assessment of blood pressure, lipid profile, fasting glucose, and body mass index in women with a history of early-onset or recurrent preeclampsia [48–52]. Furthermore, preeclampsia has been linked to peripartum cardiomyopathy. Evaluation of echocardiographic parameters and angiogenic markers in affected women has shown that myocardial dysfunction during preeclampsia is associated with circulating levels of angiogenic factors such as sFlt1 and sEng [53, 54].

CONCLUSION

Although knowledge of the pathogenesis of preeclampsia has substantially advanced, its true etiology remains unclear. Consequently, preeclampsia has been termed a “disease of theories,” possibly because the key biological mechanisms linking clinical and epidemiological observations to organ dysfunction in preeclampsia are insufficiently understood. Despite the lack of consistent evidence, experts tend to support the hypothesis that preeclampsia is primarily a placental disorder.

Preeclampsia and CVD share common risk factors, and preexisting CVD is the strongest risk factor (e.g., chronic hypertension and congenital heart defects) for developing preeclampsia. Current echocardiographic investigations and research on angiogenic markers indicated that cardiovascular dysfunction often precedes preeclampsia by several weeks or months.

Despite the severity of maternal and perinatal outcomes associated with preeclampsia, effective strategies for screening, diagnosis, treatment, and improvement of postpartum cardiovascular outcomes remain under development. These strategies will become clearer with understanding of the cardiovascular etiology of preeclampsia.

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