

# The Concept of Preeclampsia in Biochemistry: Molecular Mechanisms, Oxidative Stress, and Emerging Biomarkers

Dunia Abbas Khudhair

Ammar Hatem Abdullateef

Abbas Hamza Khudhair

## REVIEW

# The Concept of Preeclampsia in Biochemistry: Molecular Mechanisms, Oxidative Stress, and Emerging Biomarkers

Dunia Abbas Khudhair <sup>a,\*</sup>, Ammar Hatem Abdullateef <sup>a</sup>, Abbas Hamza Khudhair <sup>b</sup>

<sup>a</sup> Department of Basic Sciences, College of Dentistry, University of Babylon, Babylon, Hilla, Iraq

<sup>b</sup> Department of Biochemistry, College of medicine, University of Babylon, Hilla, Iraq

## Abstract

Preeclampsia is a complex, pregnancy-related hypertension condition that significantly endangers mother and fetal health. While its clinical diagnosis is based on hypertension and proteinuria, its origins lie in a cascade of biochemical and molecular disturbances. This review highlights the central concept of preeclampsia from a biochemical perspective, with emphasis on abnormal placental development, oxidative stress, and endothelial dysfunction. Placental hypoxia and an excess of reactive oxygen species (ROS) are caused by inadequate spiral artery remodeling, which also leads to lipid peroxidation and systemic inflammation. A critical biochemical characteristic is the disparity between anti-antigenic (sFlt-1, sENG) and pro-antigenic (PIGF, VEGF) molecules, which leads to vascular damage and hypertension. The identification of novel biomarkers such as asymmetric dimethyl arginine, uric acid, and lipid peroxides holds promise for early diagnosis and targeted therapy. Understanding these biochemical pathways provides a foundation for developing personalized screening tools and improving therapeutic outcomes. This review integrates current advances in biochemical markers with clinical manifestations, aiming to refine preeclampsia early detection and management through a biomarker-driven approach.

**Keywords:** Preeclampsia, PIGF, VEGF, Enderlin, Soluble endoglin, sFlt-1

## 1. Introduction

Preeclampsia is a perilous obstetric illness that may result in substantial short- and long-term health repercussions for both the mother and the fetus. Its pathophysiology is still not fully understood, despite improvements in obstetric treatment. Preeclampsia is a major area of clinical and translational study due to the variety of clinical manifestations and underlying causes. This study aims to provide a comprehensive scientific overview suitable for postgraduate research in clinical life sciences.

Preeclampsia without severe features: Previously, moderate preeclampsia was defined as preeclampsia without severe symptoms. Nonetheless, it is

acknowledged that preeclampsia is a spectrum condition that can quickly worsen [1].

The systolic blood pressure (SBP) of a previously normotensive woman with proteinuria is more than 140 mm Hg, and after 20 weeks of pregnancy, the diastolic blood pressure (DBP) is 90 mm Hg or higher. When none of the aforementioned characteristics are present, preeclampsia without severe symptoms is the term used: severe thrombocytopenia (less than 100,000 platelets per microliter), neurological symptoms (such as headache or blurred vision), discomfort in the right upper quadrant or epigastrium, serum transaminase levels at least twice the normal range, pulmonary edema, and two separate episodes of systolic blood pressure of 160 mm Hg or higher and/or

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\* Corresponding author.

E-mail addresses: [den302.dunaa.abbas@uobabylon.edu.iq](mailto:den302.dunaa.abbas@uobabylon.edu.iq) (D. A. Khudhair), [dent.ammar.hattem@uobabylon.edu.iq](mailto:dent.ammar.hattem@uobabylon.edu.iq) (A. H. Abdullateef), [hamza9.abbas9@gmail.com](mailto:hamza9.abbas9@gmail.com) (A. H. Khudhair).

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diastolic blood pressure of 110 mm Hg or greater separated by at least four hours [2].

A subgroup of preeclampsia patients with considerable hypertension and/or certain end-organ dysfunction symptoms is referred to as having severe preeclampsia (formerly known as severe preeclampsia), which represents the extreme end of the preeclampsia range. Severe situations (at least two readings separated by at least four hours) when the systolic blood pressure is 140 mm Hg and/or the diastolic blood pressure is 90 mm Hg. It was determined that HELLP syndrome was a sufficient condition to be included in the severe classification [3].

Combining preeclampsia with chronic hypertension: The standard diagnostic criteria for preeclampsia in patients who already have chronic hypertension (hypertension that predates pregnancy, is documented at least twice before the 20th week of gestation, or lasts for more than 12 weeks after giving birth) [4].

A patient with persistent hypertension may exhibit significant new end-organ dysfunction after 20 weeks of pregnancy or after giving birth, the onset or sudden increase of proteinuria, and the exacerbation or refractory nature of hypertension, especially in an acute setting [5].

HELLP syndrome, defined by hemolysis, increased liver enzymes, and thrombocytopenia, manifests in 10 to 20% of women experiencing severe preeclampsia or eclampsia; this incidence is roughly 100 times that of all pregnancies. It seems to be a severe subtype of preeclampsia where the main characteristics are thrombocytopenia, hemolysis, and elevated liver enzymes [6].

There may also be renal failure, central nervous system dysfunction, and/or hypertension. Most patients, but not all, suffer from proteinuria and/or hypertension [7].

## 2. Epidemiology

Preeclampsia is a pregnancy-related illness that disrupts liver function in extreme situations and affects the heart as well as other bodily organs including the kidneys and lungs. It is believed that between 2% and 10% of pregnancies globally result in preeclampsia [8].

Preeclampsia incidence varies by geography, with the eastern Mediterranean having a 1.0% rate and Africa having a 5.6% incidence. When income is taken into account, upper middle-income nations have the greatest incidence rates of preeclampsia, whereas lower middle-income countries seem to have higher rates of eclampsia [9].

It was estimated that 6.7% of teenage pregnancies had preeclampsia or eclampsia [10].

Preeclampsia is a critical worldwide maternal health issue that substantially contributes to foetal prematurity and the long-term cardiovascular disease (CVD) of mothers, along with severe morbidity and mortality in both mothers and babies [11].

Preeclampsia was more common in Iraqi women (4.79%) than in other nations like Iran (4%), Jordan (1.3%), and others [12].

## 3. Pathophysiology

Although its precise etiology is yet unknown, preeclampsia is thought to have a two-phase pathophysiology. While the second stage is marked by an abnormal maternal endothelium response that causes oedema, proteinuria, and high blood pressure, the first stage is initiated by the placenta [13].

### 3.1. First stage (Placental phase)

One important contributing element to the development of preeclampsia is acknowledged to be the placenta. Only during pregnancy can preeclampsia develop, and it goes away when the placenta is expelled. It may also appear when there isn't a viable fetus, as in molar pregnancies, as is known [14].

The placenta obtains its blood supply from the spiral arteries, which are branches of the uterine arteries; optimal fetal growth relies on the meticulously regulated process of placental development [15].

The remodeling of spiral arteries occurs in stages throughout pregnancy, commencing approximately at the moment of implantation. The arteries undergo remodeling, transforming from low-flow, high-resistance vessels to high-flow, low-resistance vessels essential for optimal placental development (Fig. 1). The pathophysiology of preeclampsia is thought to be considerably affected by dysfunctional remodeling of spiral arteries [16].

The development of connecting channels between the blastocyst and spiral arteries indicates that intervillous flow begins around week seven or eight of pregnancy. Around 10–12 weeks of pregnancy, the cytotrophoblastic cells of the growing placenta then invade the decidua regions of the spiral arteries, and at 15–16 weeks, they invade the segments of the myometrium. The trophoblastic then enters the maternal spiral arteries and passes through the endothelium and muscular tunica medium. [17].

In preeclampsia, cytotrophoblast invades the decidual portion of the spiral blood vessels but not the myometrium portions; hence, the spiral arteries

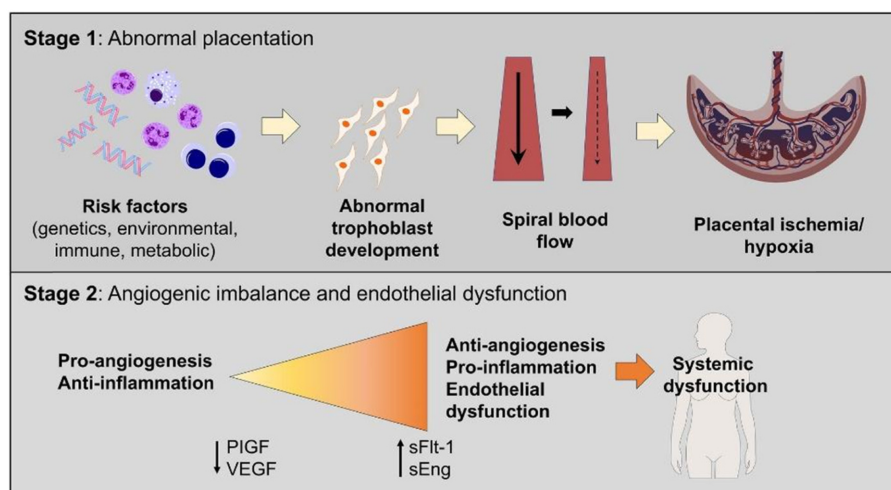


Fig. 1. Two-stage pathogenesis model for preeclampsia.

remain constricted, leading to a diminished blood supply to the foetus. As pregnancy progresses, the effects on the fetus worsen because the uterine vasculature cannot keep up with the increasing volume of blood and nutrients needed for fetus growth. The etiology of preeclampsia's poor uteroplacental circulation development is still unclear and hotly debated. Genetic, environmental, and vascular variables all seem to be involved [18].

Impaired placental development seems to be linked to decreased placental perfusion caused by aberrant spiral artery remodeling. According to this view, the risk of aberrant placentation and Preeclampsia is increased by vascular insufficiency-related illnesses such as hypertension, diabetes, systemic lupus erythematosus (SLE), and renal disease [19].

Placental ischemia is caused by hypoperfusion of the developing placenta; apheresis, fibroid necrosis, thrombosis, and placental infarction are pathological signs of ischemia. While not all pre-ecliptics women exhibit the usual placental pathological features, their presence does seem to be associated with the severity of the condition [20].

### 3.2. Second stage (Maternal syndrome):

The second stage of Preeclampsia development is distinguished from a normal pregnancy by a pro-inflammatory state and enhanced maternal endothelial activation [21].

Placental hypoxia leads to the effusion of substances from the intervillous space into the maternal circulation, oxidative stress, and the degradation of syncytial structure. the remnants of maternal trophoblasts. Circulation contains syncytiotrophoblastic membrane microparticles and syncytiotrophoblast-

produced substances including soluble endoglin (sENG) and the soluble version of the vascular endothelial growth factor receptor (sFLT 1) [22].

Alongside endothelial dysfunction and heightened vascular reactivity, these and other unspecified mechanisms lead to the generation of inflammatory cytokines in the maternal bloodstream. The restoration of physiological vascular alterations during pregnancy, along with the subsequent hypertension, proteinuria, and edema, is regulated by the deterioration of maternal endothelial integrity (Fig. 2) [23]

Cytotrophoblasts in preeclampsia individuals exhibit an absence of the invasive phenotype required for the formation of robust anastomoses, leading to diminished and superficial endovascular invasion of the spiral arteries. The diminutive diameter of these anomalous blood vessels results in placental ischemia and inadequate oxygen delivery [24]. This is seen in the Stage 1 section of Fig. 1.

Moreover, individuals with preeclampsia have elevated levels of many pro-inflammatory substances such as natural killer cells and more general indicators of inflammation [25].

## 4. Biochemical perspectives on preeclampsia pathogenesis

The major disturbances in maternal and placental biochemistry that characterize preeclampsia are primarily brought on by oxidative stress, endothelial dysfunction, and an imbalance between pro- and anti-angiogenic molecules, as seen in (Fig. 3). During the first trimester, abnormal placental development results in inadequate spiral artery remodelling, which reduces uteroplacental perfusion and creates an ischemic and hypoxic environment within the placenta

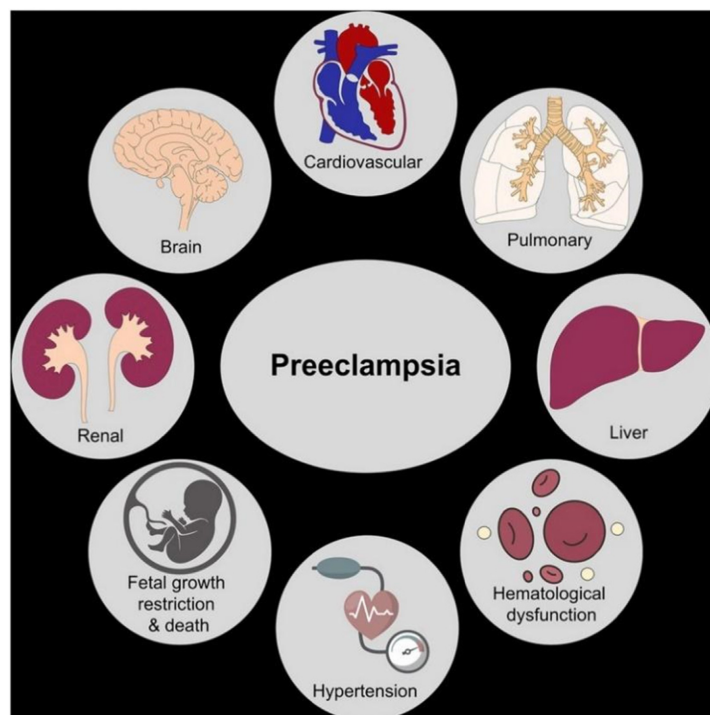


Fig. 2. The impact of preeclampsia on organ systems.

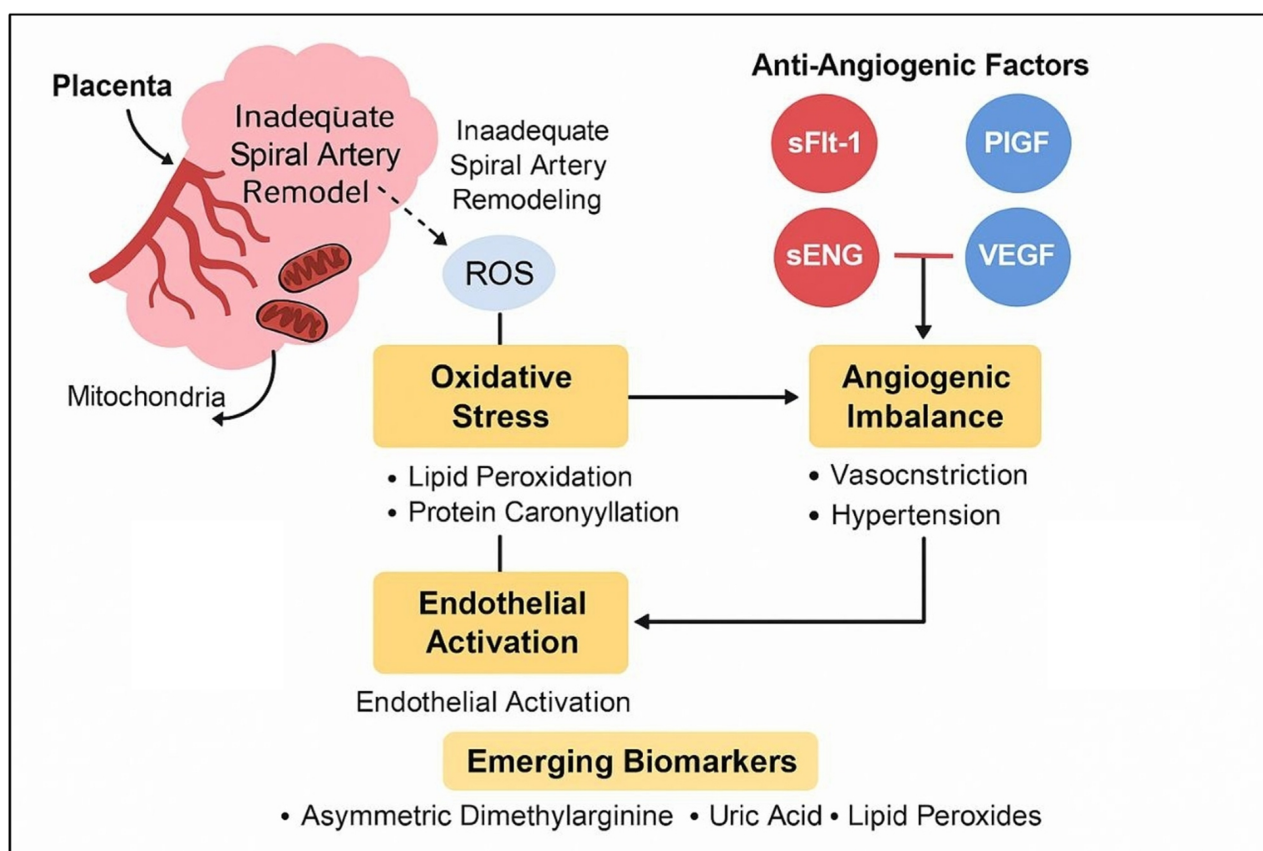


Fig. 3. Biochemical perspectives on preeclampsia pathogenesis.

[28]. Trophoblasts respond to prolonged hypoxia by secreting bioactive chemicals into the maternal circulation, including soluble fms-like tyrosine kinase-1 (sFlt-1), soluble Enderlin (sENG), and inflammatory cytokines. This exacerbates vasoconstriction and systemic endothelial dysfunction [27].

**Oxidative Stress and Endothelial Activation:** The ischemic placenta produces an overabundance of reactive oxygen species (ROS) as a result of mitochondrial malfunction and diminished activity of placental antioxidant enzymes, including superoxide dismutase and catalase [19]. ROS enhance lipid peroxidation and protein carbonylation, leading to oxidative damage of placental and maternal endothelium. Endothelial injury in turn reduces nitric oxide bioavailability and increases endothelin-1 levels, resulting in vasospasm and hypertension characteristic of preeclampsia [28].

**Role of Angiogenic and Anti-angiogenic Factors:** According to biochemical profiling, women with preeclampsia had lower amounts of pro-angiogenic mediators like vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) and higher levels of anti-angiogenic factors like sFlt-1 and sENG in their blood. Nitric oxide-mediated vasodilation is hampered by the increased sFlt-1's binding to VEGF and PlGF, which blocks their interaction with endothelial receptors [33]. This metabolic imbalance is an initial occurrence in the aetiology of preeclampsia and may be identified prior to the emergence of clinical symptoms.

**Emerging Metabolomic and Proteomic Biomarkers:** Recent metabolomic and proteomic studies have identified a distinct molecular signature in preeclampsia, including increased serum levels of asymmetric dimethylarginine (ADMA), uric acid, and lipid peroxides, along with dysregulated metabolites involved in energy metabolism and inflammation [32]. These biochemical markers, combined with traditional indices such as proteinuria and liver transaminases, hold promise for early prediction of preeclampsia and tailoring personalized prophylactic strategies.

## 5. Effects on vital organs

**Kidneys:** Proteinuria and decreased renal clearance are caused by glomerular endotheliosis. **Liver:** Subcapsular hematomas and increased transaminases are two features of hepatocellular injury; the severe hepatic manifestation is known as HELLP syndrome. **Brain:** Vasospasm and cerebral edema raise the risk of stroke, intracranial bleeding, and seizures (eclampsia). **Cardiovascular system:** Pulmonary edema and chronic cardiovascular illness may arise from elevated cardiac afterload caused by increased systemic

vascular resistance. Fetal growth limitation, placental abruption, and stillbirth are caused by impaired perfusion in the **placenta** and **fetus** [26].

## 6. Symptoms and signs of preeclampsia

Preeclampsia is often defined by elevated blood pressure, proteinuria, or further indicators of renal or other organ impairment. It is conceivable that you might not have any symptoms. Regular prenatal visits with a healthcare provider are often associated with the identification of early preeclampsia symptoms [29]. Preeclampsia symptoms and indicators, in addition to elevated blood pressure, may include [30]:

- Hypertension
- Proteinuria – Elevated protein levels in urine

High blood pressure alone does not indicate Preeclampsia; rather, the combination of protein in urine and higher blood pressure serves as definitive indications of the condition.

- Reduced platelet count in the blood (thrombocytopenia) - Elevated liver enzymes indicative of hepatic dysfunction
- Intense cephalalgia - Visual disturbances, including transient visual loss, impaired vision, or photophobia; dyspnoea due to pulmonary oedema
- Discomfort in the upper abdomen, often under the ribs on the right side - Queasiness or emesis

## 7. Risk factors

Preeclampsia risk factors that only appear during pregnancy include [31]:

- A history of Preeclampsia in the family.
- Primigravida.
- Pregnant women who are older than 40 and younger than 20 years.
- Insulin resistance and obesity.
- Triplets, twins, or more.
- Long periods of time between pregnancies.
- Diabetes during pregnancy.
- A history of specific illnesses, including: rheumatoid arthritis, renal disease, diabetes, migraine headache, chronic hypertension, urinary tract infections, and periodontal disease during pregnancy.

## 8. Laboratory evaluation of preeclampsia

Currently, there is no singular, cost-effective, and precise screening test for preeclampsia. Women at high risk for preeclampsia should get a baseline laboratory evaluation early in pregnancy [32].

Preeclampsia biomarkers might be used to diagnose the illness early since biochemical changes in expecting women' serum happen before the disorder's clinical symptoms appear [33].

Numerous biomarkers have been investigated as possible markers for the diagnosis and screening of preeclampsia; however, combinations of two or three biomarkers are being investigated because of the frequency of inconsistent and poorly reproducible results [33].

- A. Hematocrit: The diagnosis of preeclampsia is supported by hemoconcentration [34].
- B. Platelet count: Thrombocytopenia is a sign of a serious illness [35].
- C. Quantification of protein excretion: Proteinuria is defined as the excretion of 300 mg or more in a 24-hour period or the presence of at least a positive protein result on the dipstick of two urine samples taken at least four hours apart [36].
- D. Serum creatinine concentration: Slightly increased [37].
- E. Activities of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT): Increased or elevated ALT and AST values [38].
- F. Lactate dehydrogenase (LDH): Increased LDH activity on a peripheral blood smear are indicators of microangiopathic hemolysis. In HELLPs syndrome, microangiopathic hemolysis is evident [39].
- G. Serum uric acid: Which is often raised in Preeclampsia and one of the indicators of disease severity [40].
- H. Coagulation function assessments: In the absence of thrombocytopenia or hepatic failure, prothrombin time, activated partial thromboplastin time, and fibrinogen levels are typically within normal ranges. [41].

Oxidative stress, syncytiotrophoblast stress, and inflammation Increased ROS and lipid peroxidation products are indicators of oxidative stress brought on by placental ischemia. Systemic inflammation is exacerbated by the production of syncytiotrophoblast Microparticles (STBM) and inflammatory cytokines (TNF- $\alpha$ , IL-6) into the maternal bloodstream. By stimulating endothelial Toll-like receptors (TLRs) and functioning as damage-associated molecular patterns (DAMPs), these STBM exacerbate endothelial injury [42].

## 9. Complications

Significant repercussions of postponed fetal delivery in preeclamptic patients during the late preterm phase encompass eclampsia, a condition called HELLP syndrome, pulmonary oedema,

coronary artery disease, acute respiratory distress syndrome, stroke, kidney and retinal impairment, as well as foetal complications including fetal growth restriction, placental abruption, or fetal or maternal mortality [43].

There are frequent issues when starting medical treatment to achieve proper blood pressure regulation. These include fetal cardiac tracing anomalies, headaches, hypotension, and tachycardia while using nifedipine, labetalol, or hydralazine. There are also dangers and side effects associated with using magnesium sulfate for seizure prevention, including cardiac arrest and respiratory depression. Patients on magnesium sulphate therapy should have blood magnesium levels tested and undergo physical assessments every four to six hours [44].

## 10. Management

Preeclampsia management depends on the stage of the disease [45]:

- **Mild Preeclampsia:** Monitoring, corticosteroids for fetal lung maturity if <34 weeks, and antihypertensives (methyldopa, labetalol).
- **Severe Preeclampsia:** Antihypertensives, magnesium sulfate for seizure prevention, hospitalization, and birth planning according to fetal health and gestational age.
- **Eclampsia:** magnesium sulfate and stabilization right away; when the mother is stabilized, an urgent delivery occurs.

The ultimate treatment is delivery. The progression of the sickness, maternal and fetal well-being, and gestational age all influence time.

New research and prospects current research investigates immune cell morphologies, angiogenic profiles, and genetic polymorphisms (e.g., HLA-G, VEGF). There is hope in trials looking at recombinant PlGF, metformin, and statins. Future studies should concentrate on immunotherapies, personalized risk-based care plans, and predictive biomarkers [46].

## 11. Prevention

- For high-risk women, low-dose aspirin (75–150 mg/day) should begin before 16 weeks [47].
- Supplementing with calcium (1–2 g/day) in populations with inadequate dietary intake [48].
- Lifestyle changes aimed at controlling blood sugar, weight, and quitting smoking [49].
- Biochemical indicators and uterine artery Doppler techniques are used in preliminary screenings to assess risk stratification [50, 51].

## 12. Conclusion

Preeclampsia has several different etiological paths and is a complicated, multisystemic illness. Comprehending how oxidative stress, immunological dysregulation, and placental disease interact is essential. Developments in preventative treatments and diagnostics with biochemical lab testing might lessen its worldwide burden. Improved maternal-fetal outcomes, efficient care, and early identification all depend on interdisciplinary cooperation.

## Ethical issue

Not applicable.

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## Conflicts of interest

The authors declare no conflict of interest.

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