World Journal of Advanced Pharmaceutical and Medical Research

Journal homepage: https://zealjournals.com/wjapmr/

ISSN: 2799-0656 (Online)

(REVIEW ARTICLE)

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Pre-eclampsia: A comprehensive review of pathophysiology, clinical features, prevention and management

Livinus Nnanyereugo Onah [1,*], Malachy Nwaeze Ezenwaeze [1] and Chibugo Ndidiamaka Nwankwo [2]

[1] *Department of Obstetrics and Gynaecology Enugu State University Teaching Hospital, Parklane, Enugu, Nigeria.*
[2] *Department of Paediatrics, University of Nigeria Teaching Hospital Ituku-Ozala, Enugu, Nigeria.*

World Journal of Advanced Pharmaceutical and Medical Research, 2025, 09(01), 012-019

Publication history: Received on 06 June 2025; revised on 16 July 2025; accepted on 19 July 2025

Article DOI: https://doi.org/10.53346/wjapmr.2025.9.1.0030

Abstract

Background: Preeclampsia is a hypertensive disorder of pregnancy characterized by new-onset hypertension and proteinuria or end-organ dysfunction after 20 weeks of gestation. It remains a leading cause of maternal and perinatal morbidity and mortality worldwide.

Objective: To provide a concise overview of the pathophysiology, clinical features, prevention, and current management strategies for preeclampsia.

Methods: A narrative review of recent literature on preeclampsia was conducted, focusing on diagnostic criteria, risk factors, and therapeutic approaches.

Results: Abnormal placentation, systemic endothelial dysfunction, and exaggerated inflammatory responses contribute to preeclampsia's pathogenesis. Clinically, it manifests with hypertension, proteinuria, and potentially severe complications such as eclampsia, HELLP syndrome, and multi-organ involvement. Management centers on blood pressure control, seizure prophylaxis, and timely delivery, balancing maternal and fetal risks. Aspirin prophylaxis in high-risk women has shown efficacy in reducing incidence.

Conclusion: Early identification and individualized management of preeclampsia are critical to improving outcomes. Ongoing research is exploring predictive biomarkers and novel therapeutic targets to prevent or mitigate this complex disorder.

Keywords: Pre-eclampsia; Pathophysiology; Clinical features; Management

1. Introduction

Preeclampsia is a multifaceted hypertensive disorder of pregnancy characterized by new-onset hypertension and proteinuria or end-organ dysfunction after 20 weeks of gestation.[1] It represents a major cause of maternal and perinatal morbidity and mortality globally. preeclampsia poses significant clinical and public health challenges, especially in low- and middle-income countries.[1,2] It is estimated to complicate approximately 2–8% of pregnancies worldwide [3,4] making it one of the most common medical disorders specific to pregnancy. Historically, the understanding of preeclampsia has evolved considerably. Previously considered a "toxemia of pregnancy," it was largely misunderstood until advances in vascular biology and immunology began elucidating its complex pathogenesis.[5] The current consensus recognizes preeclampsia as a disease of placental origin with systemic maternal consequences, driven by abnormal placental implantation and impaired remodeling of the spiral arteries.[6,7] Inadequate trophoblastic invasion leads to reduced

* Corresponding author: Onah Livinus Nnanyelugo

placental perfusion and ischemia, releasing antiangiogenic factors into the maternal circulation, which disrupt endothelial function and trigger widespread systemic effects.[8]

The condition's risk factors are diverse, encompassing maternal, paternal, and environmental contributors. Established maternal risk factors include nulliparity, advanced maternal age, obesity, chronic hypertension, diabetes mellitus, renal disease, multiple gestations, and a personal or family history of preeclampsia.[8] Additionally, immunological maladaptation between maternal and fetal tissues, genetic predisposition, and inflammatory pathways are implicated in its pathophysiology.[7]

2. Pathophysiology of preeclampsia

Pathophysiology of preeclampsia is highly complex and incompletely understood. It involves abnormal placentation, systemic endothelial dysfunction, and an exaggerated inflammatory response.

2.1. Abnormal Placentation and Spiral Artery Remodeling

A central pathophysiologic feature of preeclampsia is abnormal trophoblast invasion of the maternal spiral arteries during early placentation. In normal pregnancy, cytotrophoblasts invade the spiral arteries, transforming them from high-resistance, narrow vessels into wide, low-resistance channels that ensure sufficient uteroplacental blood flow.[9, 10] In preeclampsia, this remodeling is shallow and incomplete. The spiral arteries remain narrow and musculoelastic, resulting in reduced uteroplacental perfusion and a hypoxic or ischemic placenta.[11]

2.2. Placental Hypoxia and Oxidative Stress

The insufficient transformation of spiral arteries causes relative placental ischemia, leading to fluctuating oxygen levels (so-called ischemia-reperfusion injury), which generates excessive reactive oxygen species (ROS) and oxidative stress.[12] Oxidative stress damages the syncytiotrophoblast, prompting the release of antiangiogenic factors and debris into maternal circulation.

2.3. Release of Antiangiogenic Factors

Two essential antiangiogenic factors in preeclampsia are: Soluble fms-like tyrosine kinase-1 (sFlt-1), which binds and neutralizes vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), impairing their angiogenic effects and causing endothelial dysfunction.[13] Soluble endoglin (sEng), which inhibits transforming growth factor-beta (TGF-β) signaling, contributing further to endothelial dysfunction and vascular permeability.[14] These factors are elevated weeks before clinical symptoms, suggesting their role in disease onset.[13]

2.4. Systemic Endothelial Dysfunction

The maternal systemic endothelial dysfunction in preeclampsia manifests as widespread vasoconstriction, increased vascular permeability, and a prothrombotic state.[15] Dysfunctional endothelium produces less nitric oxide (NO) and prostacyclin, while increasing thromboxane A2 and endothelin-1, promoting vasoconstriction and platelet aggregation.[16] The resultant effect of theendothelial dysfunction will include hypertension from increased systemic vascular resistance, Proteinuria from glomerular endotheliosis and increased vascular permeability, edema due to leaky capillaries, organ ischemia including in the brain, liver, kidneys, and placenta.[15]

2.5. Inflammatory and Immune Dysregulation

Preeclampsia involves a heightened systemic inflammatory response. Women with preeclampsia exhibit elevated levels of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-17 (IL-17).[16] There's also an imbalance between Th1 (pro-inflammatory) and Th2 (anti-inflammatory) immune responses, favoring a pro-inflammatory milieu.[17] Moreover, immune maladaptation to paternal antigens in the placenta is suspected, possibly contributing to abnormal placentation and systemic inflammation.[6]

2.6. Coagulation Abnormalities

Endothelial injury exposes subendothelial collagen, triggering platelet activation and the coagulation cascade, leading to a hypercoagulable state. This can result in microthrombi in various organs, contributing to organ dysfunction.[18] In severe cases, this process escalates to disseminated intravascular coagulation (DIC).

2.7. Genetic and Epigenetic Factors

Several genetic polymorphisms are linked to increased preeclampsia risk, including variations in genes for angiotensinogen, VEGF, and endothelial nitric oxide synthase (eNOS).[19] Epigenetic changes, like DNA methylation patterns in placental tissue, are increasingly recognized as contributors to abnormal trophoblast behavior and angiogenic imbalance.[20]

2.8. Maternal Risk Factors and Comorbidities

While the underlying placental pathology drives preeclampsia, maternal susceptibility influences disease expression. Women with chronic hypertension, obesity, diabetes, or pre-existing renal disease have heightened risk, possibly due to pre-existing endothelial dysfunction.[21]

In summary, pathogenesis of preeclampsia revolves around a complex interplay of abnormal placentation, placental ischemia, oxidative stress, antiangiogenic factors, systemic endothelial dysfunction, and immune dysregulation. While our understanding has advanced considerably, the precise triggers and mechanisms remain incompletely elucidated, and research continues into predictive biomarkers and preventive therapies.[15, 22]

3. Clinical presentation of preeclampsia

- Hypertension: Hypertension has been identified as the hallmark feature of preeclampsia, defined as blood pressure ≥140/90 mmHg on two occasions at least four hours apart, or ≥160/110 mmHg on one occasion requiring urgent treatment.[23,24]
- Proteinuria: Proteinuria is classically present, defined as ≥300 mg of protein in a 24-hour urine collection, a protein/creatinine ratio ≥0.3, or a urine dipstick reading of at least 1+ if other methods are unavailable.[23] However, preeclampsia can occur without proteinuria, provided there is evidence of significant end-organ dysfunction.[18]
- Edema: edema, particularly of the hands and face, was previously considered diagnostic but is now recognized as a nonspecific finding and not required for diagnosis.[23] Nonetheless, women may report sudden swelling as a symptom.
- Neurological Symptoms: neurological symptoms include persistent headaches, visual disturbances (such as scotomata or blurred vision), hyperreflexia, and, in severe cases, seizures.[24]
- Hepatic Manifestations: liver involvement may cause right upper quadrant or epigastric pain, elevated liver transaminases, and, rarely, hepatic rupture.[18]
- Hematologic Manifestations: thrombocytopenia (platelets <100,000/μL) and hemolysis are features of severe disease and may occur in the context of HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets).[23]
- Renal Dysfunction: Women may develop renal insufficiency, evidenced by serum creatinine >1.1 mg/dL or a doubling of creatinine levels without other renal disease.[24]
- Pulmonary Edema: in severe cases, pulmonary edema can develop, leading to respiratory distress.[23]
- Fetal Manifestations: The fetus may experience fetal growth restriction (FGR) due to impaired uteroplacental perfusion.[18] Decreased fetal movements or abnormal fetal heart rate patterns may be observed.

Overall, the clinical presentation ranges from mild hypertension with minimal symptoms to severe multi-organ involvement, making vigilant monitoring essential.[23,24]

4. Complications of preeclampsia

Preeclampsia poses significant risks not only to maternal health but also to fetal and neonatal outcomes. The complications can be broadly divided into maternal complications and fetal/neonatal complications.

4.1. Maternal Complications

- Eclampsia: Eclampsia is the occurrence of generalized tonic-clonic seizures in a woman with preeclampsia, unrelated to other neurologic causes.[18] It can lead to maternal hypoxia, aspiration pneumonia, cerebral hemorrhage, and even death.
- HELLP Syndrome: HELLP syndrome (Hemolysis, Elevated Liver enzymes, and Low Platelets) occurs in about 10-20% of women with severe preeclampsia.[1] It is associated with significant morbidity, including liver rupture, disseminated intravascular coagulation (DIC), acute renal failure, and maternal mortality. Women often present with right upper quadrant pain, nausea, vomiting, and malaise.[18]

- Stroke: Severe hypertension and endothelial dysfunction increase the risk of cerebrovascular accidents. Intracerebral hemorrhage is among the leading causes of maternal mortality in preeclampsia.[24] Prompt control of severe blood pressure is crucial to reduce this risk.[1]
- Acute Renal Injury: Preeclampsia may cause reduced renal perfusion, glomerular endotheliosis, and acute tubular necrosis, leading to acute kidney injury (AKI). Severe cases may necessitate dialysis.[24]
- Pulmonary Edema: Increased vascular permeability and decreased oncotic pressure, combined with hypertension-related cardiac dysfunction, predispose women to pulmonary edema, manifesting as dyspnea, hypoxia, and potential respiratory failure.[24]
- Liver Hemorrhage or Rupture: Severe preeclampsia and HELLP syndrome can cause subcapsular hematoma and liver rupture, presenting as sudden severe abdominal pain, hypotension, and hypovolemic shock. Mortality rates are high unless diagnosed promptly.[18]
- Disseminated Intravascular Coagulation (DIC): DIC may complicate severe preeclampsia, particularly in cases of placental abruption or HELLP syndrome. It leads to widespread microthrombi formation and bleeding diathesis.[24]
- Placental Abruption: Preeclampsia increases the risk of placental abruption, where the placenta prematurely detaches from the uterine wall. This causes vaginal bleeding, abdominal pain, fetal distress, and significant maternal blood loss.[1]
- Cardiovascular Disease Later in Life: Women with a history of preeclampsia have an approximately twofold increased risk of developing chronic hypertension, ischemic heart disease, stroke, and heart failure in later life.[24]

4.2. Fetal and Neonatal Complications

- Intrauterine Growth Restriction (IUGR): Preeclampsia is associated with abnormal placentation and uteroplacental insufficiency, leading to reduced oxygen and nutrient delivery to the fetus. IUGR affects up to 30% of pregnancies with preeclampsia.[25]
- Preterm Birth: The only definitive cure for preeclampsia is delivery. Severe disease often necessitates preterm delivery to prevent maternal or fetal compromise. Approximately 15% of preterm births are attributable to preeclampsia.[24]
- Fetal Hypoxia and Stillbirth: Placental dysfunction can result in chronic fetal hypoxia, acidemia, and stillbirth. Fetal monitoring is critical in managing pregnancies complicated by preeclampsia.[1]
- Neonatal Complications of Prematurity: Prematurity leads to risks including respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and long-term neurodevelopmental impairments.[18]
- Neonatal Thrombocytopenia: Newborns of mothers with preeclampsia or HELLP syndrome may develop thrombocytopenia due to immune-mediated destruction or placental dysfunction.[24]

5. Psychological and Economic Implications

Beyond physical morbidity, preeclampsia has substantial psychological and economic impacts. Women may experience postpartum anxiety, depression, or post-traumatic stress related to a complicated pregnancy.[25] The economic burden is significant, with increased healthcare utilization during pregnancy and in the neonatal period.[27]

5.1. Long-Term Outcomes

Both mothers and children face long-term health risks following pregnancies complicated by preeclampsia. Offspring have increased risks of hypertension, cardiovascular disease, and metabolic syndrome later in life.[28]

5.2. Management of preeclampsia

Management of Preeclampsia aims to balance maternal stabilization and minimizing prematurity risks. General Principles of management depends on severity assessment, distinguishing mild (without severe features) from severe preeclampsia. Severe features include: BP ≥160/110 mmHg, Platelet count <100,000/μL, elevated liver transaminases with severe right upper quadrant pain, Progressive renal insufficiency, Pulmonary edema, neurological symptoms. Women with severe features require close monitoring and often prompt delivery.[24] Management of mild Preeclampsia (Without Severe Features) involves expectant management. Before 37 weeks, patients with mild disease may be managed expectantly if maternal and fetal conditions are stable, close surveillance is possible. This involves frequent BP checks, weekly laboratory assessments (CBC, liver enzymes, renal function) [1], Fetal monitoring via non-stress tests, ultrasound for growth and amniotic fluid.[29] Delivery is usually planned at 37 weeks.[1, 30]

- Management of Severe Preeclampsia: Women with severe features are hospitalized for blood pressure control, seizure prophylaxis, maternal and fetal monitoring. Indications for antihypertensive treatment include, persistent systolic BP ≥160 mmHg, diastolic BP ≥110 mmHg.[1] Preferred agents include Labetalol, IV bolus 20 mg, to repeat doses if needed, hydralazine: IV 5-10 mg, nifedipine (oral, immediate-release): 10-20 mg. The goal is to Lower BP below severe thresholds (e.g., <160/110 mmHg) but avoid hypotension that may reduce placental perfusion.[24]
- Seizure Prophylaxis: magnesium sulfate is the drug of choice to prevent eclampsia: 4-6 g IV loading dose over 15-20 minutes followed by 1-2 g/hour infusion. Therapeutic levels of 4.8-8.4 mg/dL is to be maintained.[1] Toxicity requires discontinuation and calcium gluconate administration as antidote.
- Timing of delivery: delivery is the definitive treatment for preeclampsia.[1,30] Recommendations: ≥34 weeks with severe preeclampsia → recommend delivery <34 weeks → consider expectant management if maternal and fetal status are stable, in specialized centers, with corticosteroids for fetal lung maturity.[29] Immediate delivery is indicated for Uncontrolled hypertension, eclampsia, pulmonary edema, deteriorating renal function, abnormal fetal testing.
- Special Considerations: corticosteroids for pregnancies <34 weeks, corticosteroids improve fetal lung maturity (e.g., betamethasone 12 mg IM every 24 hours × 2 doses).[1]
- Fluid Management: Fluid overload is to be avoided due to risk of pulmonary edema. Restrict fluids (~80 mL/hour) unless significant blood loss occurs. [24]
- Thromboprophylaxis: Women with reduced mobility or risk factors may require thromboprophylaxis with LMWH unless contraindicated.[30]
- Postpartum Management: BP may worsen postpartum, requiring continued monitoring.[1] antihypertensive therapy may be needed. magnesium sulfate may be continued for 24 hours postpartum in severe cases.[1] Counseling about long-term cardiovascular risk is essential as preeclampsia increases future hypertension, stroke, and ischemic heart disease risk.[24]
- Long-Term Follow-Up: women should be counseled about cardiovascular risk factors, annual BP checks, weight management and healthy lifestyle.[24]

6. Prevention of preeclampsia

preventing preeclampsia can be challenging because the exact etiology remains incompletely understood. However, several strategies, ranging from pre-pregnancy counseling and risk assessment to pharmacologic interventions have been studied and adopted to mitigate its incidence and severity.

6.1. Identification of High-Risk Women

A key strategy in prevention begins with identifying women at increased risk. The following are recognized risk factors for preeclampsia: Previous history of preeclampsia, chronic hypertension, diabetes mellitus, chronic kidney disease, autoimmune disorders (e.g., lupus, antiphospholipid syndrome), multiple gestation, obesity, advanced maternal age (>35 years), first pregnancy (nulliparity). Screening tools, such as uterine artery Doppler ultrasonography in the first or early second trimester, may help predict women at risk by assessing uteroplacental blood flow resistance.[31]

6.2. Lifestyle Modifications

Weight Management and Exercise: Obesity is a significant modifiable risk factor for preeclampsia. Pre-pregnancy weight loss and achieving a healthy BMI may reduce the risk.[1] During pregnancy, moderate exercise is generally safe and may confer benefits in reducing hypertensive disorders, though evidence specifically for preeclampsia prevention is limited (American College of Obstetricians and Gynecologists.[1]

6.3. Dietary Considerations

Calcium supplementation: Among women with low dietary calcium intake (<600 mg/day), calcium supplementation (1.5–2 g/day) has been shown to reduce the risk of preeclampsia, particularly in high-risk populations.[32]

Low-Dose Aspirin Prophylaxis: Low-dose aspirin (LDA) is one of the most evidence-supported interventions for preeclampsia prevention. Meta-analyses indicate that LDA (usually 81–150 mg daily) initiated before 16 weeks' gestation reduces the risk of preeclampsia, particularly preterm preeclampsia.[31]

The U.S. Preventive Services Task Force (USPSTF) recommends low-dose aspirin starting between 12 and 28 weeks (ideally before 16 weeks) for women at high risk.[33] Benefits are more significant in preventing early-onset disease than term preeclampsia.

Antioxidants and Vitamins: Despite earlier hypotheses, supplementation with vitamins C and E, selenium, or other antioxidants has not been shown to significantly reduce the incidence of preeclampsia and is not recommended for prevention.[34]

Pharmacologic Interventions Beyond Aspirin: several other pharmacologic measures have been studied: Low molecular weight heparin (LMWH): Limited evidence suggests potential benefit in women with antiphospholipid syndrome but not for routine prevention.[35]

Statins: Though theoretically promising due to anti-inflammatory effects, statins are not currently recommended during pregnancy for preeclampsia prevention outside research settings.[36]

6.4. Monitoring and early detection

Even with preventive strategies, some women will develop preeclampsia. Therefore, regular antenatal surveillance is critical. Monitoring blood pressure, urine protein levels, and symptoms like headaches, visual changes, and epigastric pain ensures early detection and intervention.[1]

6.5. Counseling and education

Educating women, particularly those at high risk, about the warning signs and symptoms of preeclampsia is vital. Early reporting of symptoms can prompt timely medical attention, improving outcomes for both mother and baby.

7. Conclusion

Preeclampsia is a multi-system disease with potentially devastating consequences for both mother and fetus. Early recognition, close monitoring, and timely intervention are crucial in reducing the risk of severe complications. Understanding the spectrum of possible complications allows clinicians to optimize outcomes and counsel affected women regarding future health risks.

Recommendations

To help prevent preeclampsia, women planning pregnancy or already pregnant should attend regular antenatal visits for early detection and management of risk factors. Maintaining a healthy weight, engaging in moderate physical activity, and controlling chronic conditions like hypertension and diabetes are crucial. Low-dose aspirin (75–150 mg daily) may be recommended from 12 weeks of gestation for women at high risk, as advised by a healthcare provider. Adequate calcium intake is also beneficial, especially in populations with low dietary calcium.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed

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