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From Epidemiology to Therapeutics: A Holistic Review of Preeclampsia's Burden, Mechanisms, Risks, and Innovations

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Abstract

Preeclampsia remains a leading cause of maternal and perinatal morbidity and mortality worldwide, yet its complex pathophysiology and heterogeneous clinical presentation continue to challenge early diagnosis and effective management. Despite decades of research, significant gaps persist in translating mechanistic insights into universally effective therapies, particularly for high-risk populations in resource-limited settings. This review addresses the urgent need to consolidate recent advances in preeclampsia research, bridging fundamental science with clinical applications to improve outcomes. The review synthesizes critical insights into the multifactorial origins of preeclampsia, emphasizing the central role of placental dysfunction, angiogenic imbalance, and systemic inflammation. It evaluates current diagnostic tools, including the soluble Fms-like tyrosine kinase-1/placental growth factor (sFlt-1/PlGF) ratio, alongside evidence-based interventions such as low-dose aspirin, statins, and optimized antihypertensive regimens. Regional disparities in prevalence and outcomes are analyzed, highlighting the disproportionate burden in low- and middle-income countries. Emerging therapeutic strategies targeting oxidative stress, immune dysregulation, and genetic susceptibility are critically appraised. The review also explores innovative approaches like personalized risk assessment, while underscoring the limitations of existing treatments. Clinical studies comparing drug efficacy (e.g., nicardipine vs labetalol) and preventive measures (e.g., 150 mg aspirin) are systematically reviewed to guide practice. Finally, the interplay between preeclampsia and long-term maternal cardiovascular health is examined, reinforcing the need for postpartum surveillance. Future research must prioritize large-scale trials to validate novel biomarkers and therapies across diverse populations, with particular attention to implementation in resource-constrained settings. Investigations into fetal microchimerism and epigenetic modifiers could unlock new preventive strategies, while artificial intelligence integration may revolutionize early-risk prediction models. Multidisciplinary collaborations are essential to develop standardized protocols for screening, management, and postpartum follow-up. By addressing these priorities, the field can mitigate the global burden of preeclampsia and its lifelong health consequences.

Keywords: Angiogenic factors, Biomarkers, Hypertensive disorders of pregnancy, Maternal-fetal outcomes, Pathophysiology, Prevention strategies, Therapeutic innovations

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Introduction

Preeclampsia is a complex pregnancy-related disorder characterized by hypertension and often accompanied by proteinuria [1-3]. It poses significant risks to both maternal and fetal health, contributing to a considerable burden of morbidity and mortality worldwide. It is characterized by new-onset hypertension and proteinuria after 20 weeks of gestation, often leading to severe complications if untreated [4-6]. The pathogenesis of preeclampsia involves a multifaceted interplay of genetic, molecular, and environmental factors, with the placenta playing a central role [7-9]. Despite its prevalence, the only definitive treatment remains the delivery of the fetus and placenta, which can result in preterm birth and associated neonatal complications. Recent research has focused on understanding the underlying mechanisms, risk factors, and potential therapeutic innovations to improve outcomes for affected women and their infants [10-12]. This article aims to provide a comprehensive overview of epidemiology, mechanisms, risk factors, and recent innovations in the management of preeclampsia.

The epidemiology of preeclampsia underscores its significant contribution to maternal and perinatal morbidity and mortality worldwide, positioning it as a critical public health concern [13]. Its prevalence is influenced by a complex interplay of risk factors, including socioeconomic determinants, which have been explored to better understand the etiology and potential avenues for prevention [10]. The condition's burden extends beyond pregnancy, with evidence linking preeclampsia to increased long-term cardiovascular risks, highlighting the importance of understanding its pathophysiology for

effective management [14]. Mechanistically, preeclampsia involves intricate pathophysiological processes. The comprehensive reviews emphasize the role of abnormal placental development, endothelial dysfunction, and immune maladaptation as central to its onset [15]. These mechanisms contribute to the clinical manifestations observed, such as hypertension and organ damage, by disrupting normal vascular and placental functions [15]. Additionally, the condition shares common pathways with other vascular and metabolic disorders, including insulin resistance, which may exacerbate disease severity and influence therapeutic strategies [16].

The risk factors associated with preeclampsia are multifaceted, encompassing both maternal and environmental components. Factors such as chronic kidney disease and metabolic disturbances have been identified as significant contributors, further complicating the clinical picture and emphasizing the need for holistic risk assessment [10, 17]. The association between preeclampsia and subsequent cardiovascular disease suggests shared pathogenic pathways, including vascular remodeling impairments and chronic inflammation [14]. Recent advances in predicting and preventing preeclampsia focus on identifying biomarkers and understanding underlying mechanisms to enable early intervention [10]. Innovations in therapeutics are increasingly targeting the molecular pathways involved in endothelial dysfunction and immune regulation, aiming to mitigate disease progression and improve outcomes [15]. The integration of mechanistic insights with clinical strategies holds promise for reducing the global burden of preeclampsia and its long-term sequelae.

In summary, the literature highlights preeclampsia as a multifactorial disorder with significant epidemiological impact, driven by complex pathophysiological mechanisms involving placental, vascular, and metabolic factors [18-20]. Advances in understanding these mechanisms are paving the way for improved predictive tools and targeted therapies, ultimately aiming to lessen their burden on maternal and fetal health [10, 14, 15].

Epidemiology of Preeclampsia

The prevalence of preeclampsia is estimated to be between 3% and 5% of pregnancies, but this burden is not uniformly distributed across populations [21-23]. It is a leading cause of maternal and perinatal morbidity and mortality, with a complex etiology involving genetic, environmental, and lifestyle factors. The disorder is not only a pregnancy-specific condition but also a predictor of future cardiovascular and metabolic diseases in affected women [24-26]. Understanding the epidemiology of preeclampsia is crucial for developing effective prevention and management strategies. Racial and ethnic minority groups, particularly non-Hispanic Black women and American Indian or Alaskan Native women, are disproportionately affected by preeclampsia [27]. This disparity highlights the need for further research to understand the underlying causes of these differences, as existing studies often focus on comparisons between White and non-Hispanic Black women, leaving gaps in knowledge regarding other racial and ethnic groups.

The World Health Organization reports an incidence range of 3% to 10% of pregnancies, with higher prevalence in developing countries [28]. In developed countries, preeclampsia is less common, affecting about 1 in every 2,000 labors [29]. In Latin America, preeclampsia is the leading cause of maternal death, with Peru reporting a prevalence of 13% in 2022 and a high percentage of perinatal mortality due to severe complications [28]. The International Federation of Gynecology and Obstetrics estimated that over 76,000 women died from hypertension complications in 2018 [28]. In Mexico, hypertension during pregnancy affects 250,000 to 300,000 pregnant women annually, leading to more than 1,000 deaths [28]. A study comparing Sweden and China found similar prevalence rates of 2.9% and 2.3%, respectively, but with more severe cases in China [23]. In the Middle East, the prevalence ranges from 0.17% to 5%, with a noted scarcity of research in some areas like the United Arab Emirates [30].

A study conducted in India found a prevalence of 6.2% among pregnant women, with a significant number of cases associated with severe features leading to adverse fetal outcomes such as low birth weight and preterm delivery [31]. In Addis Ababa, Ethiopia, the prevalence was reported at 5.5% among women attending antenatal care, with significant associations found with factors like maternal age and history of hypertension [32]. In the Central Region of Ghana, the prevalence was 8.8%, with a higher incidence among younger women and those with certain educational and occupational backgrounds [33]. Another study in Ghana reported a prevalence of 5.6% at the Ho Teaching Hospital, with a rising trend over the years [34]. In a rural hospital in Karu, Abuja, Nigeria, the prevalence was notably higher at 13.0%, with a significant number of cases resulting in preterm births [35]. A systematic review in Iran found a prevalence of 5.3%, with an increasing trend since 2015, highlighting the need for further investigation into risk factors [36]. In Bangladesh, the prevalence varied, with one study reporting 3.21% in the Rajshahi region, showing a decreasing trend over time [37]. Another study found a higher prevalence of 14.4%, indicating significant regional variability within the country [38].

While preeclampsia is a global issue, its prevalence and impact are disproportionately higher in low- and middle-income countries due to limited healthcare resources and higher rates of risk factors like obesity and metabolic syndrome. Efforts to improve healthcare access and address modifiable risk factors are essential in reducing the burden of preeclampsia worldwide. Additionally, more research is needed to understand regional differences and develop targeted interventions.

Pathophysiological Mechanisms

The pathophysiology of preeclampsia is multifactorial, involving abnormalities in placental development, immunologic factors, vascular changes, and inflammation (Figure 1) [15, 39, 40]. The disorder is primarily initiated by abnormal placentation, which results in placental hypoxia and the release of anti-angiogenic factors, contributing to widespread endothelial dysfunction and systemic inflammation [41-43]. Despite extensive research, a definitive genetic basis for preeclampsia remains elusive, although certain genetic variants, such as apolipoprotein L1, have been identified as potential risk modifiers [27]. The role of uteroplacental ischemia is also critical, as it leads to inadequate remodeling of maternal uterine spiral arteries, contributing to the development of preeclampsia and related complications [44]. This overview will delve into the key pathophysiological mechanisms of preeclampsia, highlighting abnormal placentation, oxidative stress, immune dysregulation, and genetic factors (Table 1).

Abnormal placentation

- Preeclampsia is initiated by poor placentation due to inadequate trophoblast invasion and improper remodeling of the uterine spiral arteries, leading to placental hypoxia [45, 46].
- This hypoxic environment triggers the release of anti-angiogenic factors such as sFlt-1 and soluble endoglin, which contribute to endothelial dysfunction and systemic inflammation [45, 47].

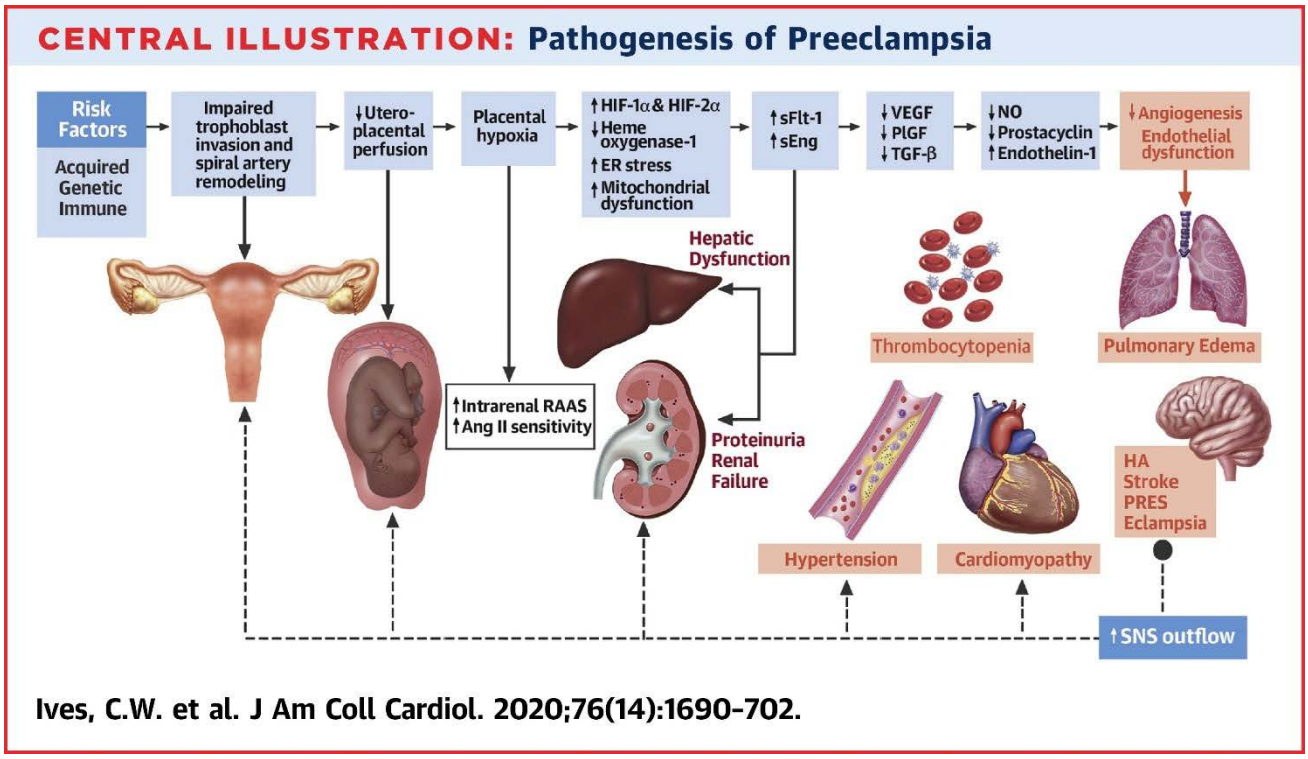

Figure 1: Pathogenesis of preeclampsia [15].

Table 1: Pathophysiological mechanisms of preeclampsia.

Mechanism	Key components	Clinical consequences	Ref.
Abnormal placentation	• Inadequate trophoblast invasion • Failed spiral artery remodeling • Placental hypoxia	• Reduced uteroplacental blood flow • Fetal growth restriction	[45, 46]
Anti-angiogenic factors	• Elevated sFlt-1 • Soluble endoglin	• Endothelial dysfunction • Systemic vasoconstriction • Proteinuria	[45, 47]
Oxidative stress	• Ischemia-reperfusion injury • Reactive oxygen species overproduction	• Placental damage • Pro-inflammatory cytokine release	[48]
Immune dysregulation	• Altered maternal-fetal tolerance • Pro-inflammatory cytokines (TNF-α and IL-6)	• Systemic inflammation • Multi-organ dysfunction (liver and kidneys)	[8, 50]
Genetic/Epigenetic	• Polymorphisms (e.g., FLT1, and APOL1) • Dysregulated miRNAs (e.g., miR-519d)	• Impaired trophoblast function • Angiogenic imbalance	[8, 45]
Systemic impact	• Renin-angiotensin system activation • AT1 receptor autoantibodies	• Hypertension • Renal failure • Neurological complications	[47, 51]

- The two-stage model of preeclampsia development emphasizes the role of placental ischemia in the first stage, followed by systemic inflammation and endothelial dysfunction in the second stage [48, 49].

Oxidative stress and inflammation

- Oxidative stress is a significant contributor to the pathophysiology of preeclampsia, exacerbated by recurrent ischemia-reperfusion injury in the placenta [48].

- The condition is characterized by excessive activation of the immune system, with increased levels of proinflammatory cytokines and antiangiogenic factors in the fetoplacental unit and maternal circulation [50].

- Inflammatory processes are further driven by dysregulated immune responses, including altered levels of cytokines and complements, contributing to endothelial dysfunction [8, 50].

Genetic and epigenetic factors

- Genetic and epigenetic modifications play critical roles in preeclampsia, with polymorphisms in genes such as FLT1 and altered microRNA (miRNA) expression being implicated [45].

- Specific miRNAs, such as miR-519d and miR-517-5p, affect trophoblast function, while lncRNAs like IGFBP1 and EGFR-AS1 influence trophoblast regulation and angiogenesis [8].

- Fetal microchimerism, where fetal cells persist within maternal tissues, acts as a mechanistic link between placental dysfunction and maternal complications [8].

Systemic and multiorgan impact

- Preeclampsia affects multiple organ systems, with potential complications including renal failure, liver dysfunction, and neurological abnormalities [50].

- The disorder's systemic nature is underscored by the involvement of the renin-angiotensin system and the presence of antiangiotensin II type 1 receptor autoantibodies, which are associated with hypertension and endothelial dysfunction [47].

- Chronic kidney disease is a known risk factor for preeclampsia, highlighting the interplay between renal function and angiogenic homeostasis [51].

While the pathophysiology of preeclampsia is complex and multifactorial, understanding these mechanisms is crucial for developing targeted therapies and improving maternal and fetal outcomes. Despite advances in research, effective prevention and treatment strategies remain limited, necessitating continued investigation into the molecular pathways and potential therapeutic targets associated with preeclampsia [52-54]. This ongoing research is essential for translating findings into clinical practice and enhancing care for at-risk women.

Pharmacological Interventions

Pharmacological interventions for preeclampsia focus on managing symptoms and preventing disease progression, given the condition's significant impact on maternal and fetal health [55-57]. Current treatments primarily aim to control hypertension and prevent seizures, while emerging therapies target the underlying pathophysiological mechanisms. Despite advances, the definitive treatment remains delivery, highlighting the need for effective pharmacological strategies to manage preeclampsia until delivery is feasible [58-60]. This answer explores various pharmacological approaches, including established treatments and novel therapies under investigation.

Established pharmacological treatments

- Antihypertensive medications: Labetalol and nifedipine are commonly used to manage hypertension in preeclampsia. Labetalol is preferred due to its ability to lower blood pressure without causing reflex tachycardia or hypotension [61]. Methyldopa is another option for managing chronic or mild hypertension on an outpatient basis [61].

- Magnesium sulfate: This remains the drug of choice for preventing and controlling seizures in severe preeclampsia and eclampsia. It works by causing cerebral vasodilation, which helps reverse ischemia caused by cerebral vasospasm [61].

- Low-dose aspirin and calcium: These are used for secondary prevention, particularly effective when started before 16 weeks of pregnancy. Aspirin reduces the occurrence of early-onset preeclampsia (Figure 2), while calcium (Figure 3) supplementation is beneficial for women with low dietary calcium intake [62].

Emerging pharmacological interventions

- Statins and proton pump inhibitors: Statins like pravastatin have shown promise in reducing preterm preeclampsia and improving maternal and fetal outcomes. Proton pump inhibitors may lower sFlt-1levels, enhancing endothelial function, although clinical trials have been inconsistent [62].

- Metformin: Known for improving insulin sensitivity, metformin also has anti-inflammatory and vascular properties, potentially reducing preeclampsia incidence, especially in obese women [62].

- Nitric oxide donors and L-arginine: These agents can reduce vascular resistance and improve placental blood flow, potentially lowering preeclampsia risk [62].

- Antithrombin concentrate: This treatment corrects hypercoagulability and may improve fetal status and perinatal outcomes, allowing for a significant prolongation of pregnancy [63].

Novel approaches

- Pathogenesis-target-drug strategy: This approach focuses on targeting specific pathophysiological pathways involved in

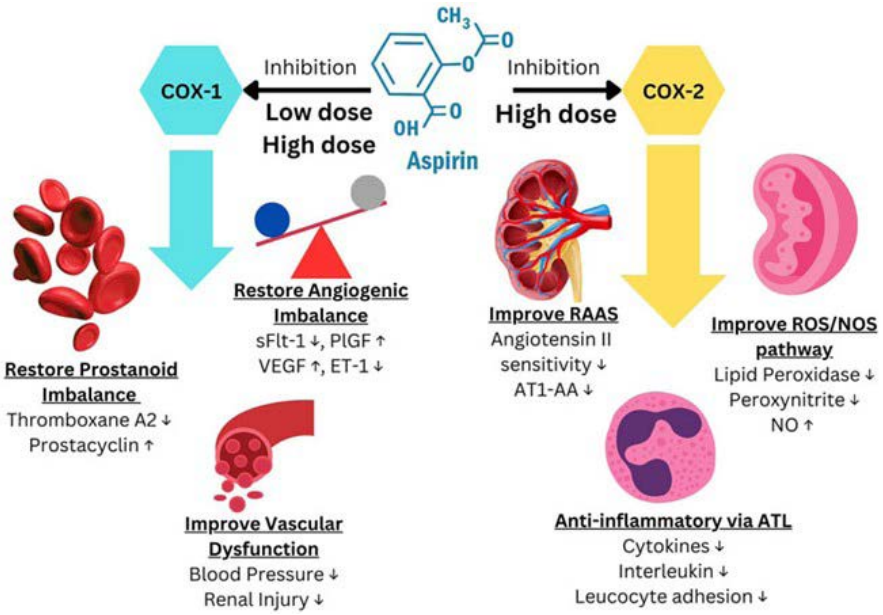

Figure 2: Aspirin mechanism of action to prevent preeclampsia [62].

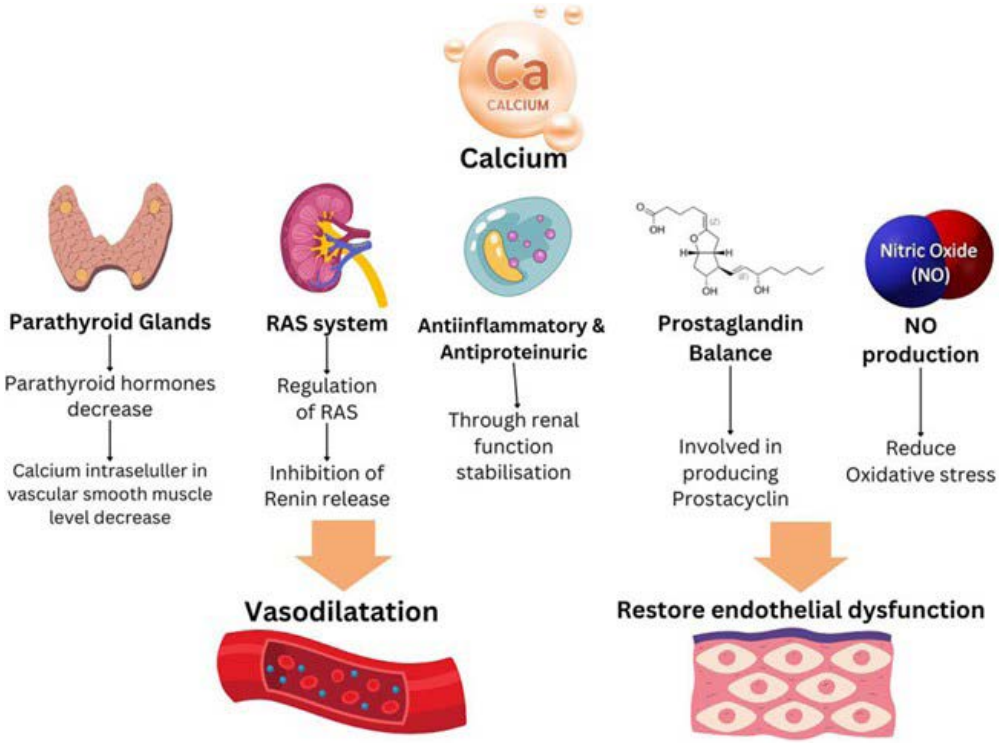

Figure 3: Mechanism of action of calcium in preeclampsia prevention [62].

preeclampsia. It includes the use of nanotechnologies to improve drug delivery and efficacy by targeting the placenta specifically [52].

- Remote monitoring and lifestyle interventions: While not strictly pharmacological, integrating remote blood pressure monitoring and dietary interventions like the DASH diet can complement pharmacological treatments, although their impact on preeclampsia prevention remains inconclusive.

Despite these advancements, preeclampsia remains a complex condition with no single effective treatment. The multifactorial nature of the disease necessitates a comprehensive approach that combines pharmacological and non-pharmacological strategies. Continued research into the pathogenesis of preeclampsia and the development of targeted therapies is crucial for improving maternal and fetal outcomes. Additionally, early screening and preventive measures, such as low-dose aspirin, play a vital role in managing high-risk pregnancies [62, 64].

Clinical Studies

The treatment of preeclampsia, a significant hypertensive disorder during pregnancy, remains a critical area of research due to its impact on maternal and neonatal health. Various clinical studies have explored both pharmacological and non-pharmacological interventions to manage and prevent preeclampsia.

A study by Easterling et al. [65] (NCT01912677) compared the efficacy and safety of nifedipine retard, labetalol, and methyldopa for managing severe hypertension in pregnancy, revealing key differences and similarities among the treatments. The primary outcome was blood pressure control within 6 h without adverse events. All three oral antihypertensive drugs-nifedipine retard, labetalol, and methyldopa-successfully reduced blood pressure to the target range (systolic 120 to 150 mm Hg and diastolic 70 to 100 mm Hg) in most women. Nifedipine retard was significantly more effective in achieving the primary outcome (blood pressure control without adverse events) compared to methyldopa (84% vs 76%, $p = 0.03$). When considering the attainment of the primary outcome without needing additional antihypertensive therapy, nifedipine and labetalol were significantly more effective than methyldopa. The primary outcome did not differ significantly between the nifedipine and labetalol groups (84% vs 77%, $p = 0.05$). Similarly, there was no significant difference in the primary outcome between the labetalol and methyldopa groups ($p = 0.80$). Nifedipine was more likely to achieve the blood pressure target at 6 h compared to both labetalol ($p = 0.03$) and methyldopa ($p = 0.01$). The median time from randomization to the start of oral antihypertensive therapy was consistently 10 min across all groups. Slightly less than half of women in the nifedipine and labetalol groups received a second dose of their allocated medication. Women assigned to methyldopa were more likely to require an additional or second hypertensive drug during the study period compared to those receiving nifedipine or labetalol. Maternal adverse events were infrequent across all three treatment groups. Only one serious adverse event (an intrapartum seizure) was reported in the labetalol group. No maternal deaths, adverse central nervous system outcomes, or need for dialysis were observed. The incidence of stillbirth, neonatal death, and neonatal morbidities did not significantly vary between the groups. However, neonatal admission to an intensive care unit was significantly higher for babies born to women in the nifedipine group compared to those in the labetalol ($p = 0.009$) and methyldopa ($p = 0.004$) groups. This was primarily attributed to low or very low birthweight in the nifedipine group. Despite this, no differences were found in intubation, survival rates, or lengths of stay among admitted neonates. Labor and delivery outcomes, including the rate of caesarean sections, did not vary significantly between the groups. In summary, while all three oral antihypertensives proved viable for managing

severe hypertension in pregnancy, nifedipine retard demonstrated superior efficacy in achieving blood pressure control compared to methyldopa, and comparable efficacy to labetalol. Although nifedipine was associated with higher rates of neonatal intensive care unit admissions due to lower birthweight, overall maternal and neonatal outcomes were favorable across all treatment groups, supporting their use as initial options in low-resource settings.

A study by Arias-Hernández et al. [66] (NCT04222855) compared the efficacy of diltiazem and nifedipine in controlling blood pressure in puerperal patients with severe preeclampsia, revealing several key findings regarding treatment effects on blood pressure, heart rate, adverse events, and length of intensive care unit stay. A total of 42 puerperal patients with severe preeclampsia were randomized and completed the study, with 21 patients in each group (diltiazem and nifedipine). Five patients were excluded for not meeting inclusion criteria. Both treatment groups were homogeneous at baseline across various characteristics, including maternal age, gestational age, childbirth method, pregnancy type (primiparous/multiparous), baseline blood pressure parameters (systolic, diastolic, and mean), heart rate, and liver and kidney functions. There were no statistically significant differences in baseline systolic (156.2 mmHg for diltiazem vs 158.3 mmHg for nifedipine) or diastolic (112.6 mmHg for diltiazem vs 111.2 mmHg for nifedipine) blood pressure between the groups. Mean arterial pressure was also not statistically significant at baseline. From 6 to 48 h post-treatment, significant statistical differences were observed between the diltiazem and nifedipine groups for systolic, diastolic, and mean blood pressures. At 6 h, the diltiazem group showed a significantly lower systolic blood pressure (133.4 mmHg) compared to the nifedipine group (147.9 mmHg) ($p < 0.001$). This trend of lower blood pressure in the diltiazem group continued throughout the 48 h observation period. Similarly, at 6 h, diastolic blood pressure was significantly lower in the diltiazem group (78.5 mmHg) compared to the nifedipine group (90.6 mmHg) ($p < 0.001$). This difference was maintained over 48 h. The average mean arterial pressure was also statistically significant between treatments from 6 to 48 h. Diltiazem controlled arterial hypertension more effectively and uniformly than nifedipine in the patients studied. The average basal heart rate was not statistically different between the diltiazem (103.4 beats/min) and nifedipine (96.4 beats/min) groups ($p = 0.13$). At all other time points (excluding baseline and 6 h), the difference in heart rate recordings between the groups was statistically significant, with diltiazem generally leading to lower heart rates. The number of hypotension episodes was statistically significant between groups ($p < 0.001$). Only 3 (14.3%) patients in the diltiazem group experienced hypotension, compared to 15 (71.4%) patients in the nifedipine group. The incident rate ratio for hypotension episodes in the diltiazem group was 0.114 compared to the control group, indicating a significantly lower rate. No hypertension episodes were observed in the diltiazem group, whereas 7 (33.3%) patients in the nifedipine group experienced hypertension episodes ($p = 0.01$). Patients treated with diltiazem had fewer collateral effects. Patients in the diltiazem group spent an average of 2.47 days in the intensive care unit, significantly less than the 4.57 days spent by patients in the nifedipine group ($p < 0.001$). This suggests potential cost savings with diltiazem. In summary, diltiazem demonstrated superior efficacy in controlling blood pressure, reducing both hypotension and hypertension episodes, and shortening intensive care unit stay compared to nifedipine in puerperal patients with severe preeclampsia. These findings suggest diltiazem as a more favorable treatment option due to its more uniform blood pressure control and fewer adverse effects.

A study by Bijvank et al. [67] compared the effectiveness and safety of ketanserin vs dihydralazine for treating severe hypertension in early-onset preeclampsia, ultimately concluding that neither drug is well-suited for this purpose nor highlighting the successful use of nicardipine as a rescue medication. Dihydralazine was found to be significantly more effective than ketanserin in lowering blood pressure. Specifically, 73.3% of patients treated with ketanserin experienced persistent severe hypertension, compared to only 13.3% in the dihydralazine group. There was no significant difference observed between the ketanserin and dihydralazine groups regarding the prolongation of pregnancy. Dihydralazine was associated with a significantly higher rate of severe maternal side effects compared to ketanserin. These included increased heart rate (>20/min), tachycardia (>120/min), nausea, and vomiting. Hypotension was a major reason for discontinuing dihydralazine, leading to fetal distress and emergency caesarean sections in some cases. Ketanserin, while safer in terms of maternal side effects, showed inadequate efficacy. No significant difference was found between ketanserin and dihydralazine in the development of hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome. The study's results do not suggest a beneficial effect of ketanserin in preventing HELLP syndrome. The study found no statistically significant differences in fetal and neonatal morbidity or safety between the two groups. Fetal demise occurred in two patients, and two neonates died within one month after birth due to necrotizing enterocolitis and sepsis. The study was stopped prematurely after 30 inclusions due to the high rate of persistent hypertension with ketanserin and the high rate of maternal side effects with dihydralazine. The apparent successful use of the rescue drug, nicardipine, without severe side effects also contributed to this decision. Nicardipine was used as a rescue medication when study medication failed or caused severe side effects. All 14 patients who received nicardipine successfully reached their target blood pressure, and their pregnancies were prolonged. The need for rescue medication was significantly higher in the ketanserin group compared to dihydralazine. Nicardipine has since become the first-line treatment for severe hypertension in pregnancy at the Erasmus Medical Centre and Isala Clinic. In summary, the study's findings do not support the use of either dihydralazine or ketanserin for treating severe hypertension in pregnancy due to dihydralazine's high rate of maternal side effects and ketanserin's insufficient efficacy. The successful application of nicardipine as a rescue medication suggests its potential as a more effective and safer alternative, warranting further research to compare it with other current antihypertensive drugs.

A study by Hanff et al. [68] reported use of nicardipine treatment in severe, early-onset preeclampsia. All patients in the study successfully reached the target diastolic intra-arterial blood pressure. This was achieved within a median of 23 min, with a range of 5 to 60 min, after initiating nicardipine treatment. Nicardipine treatment was effective in postponing delivery for a median duration of 4.7 days, with a range extending from 1 to 26 days. The maximum dosage of nicardipine used during treatment ranged from 3 to 9 mg/h. Detailed hemodynamic parameters corresponding to nicardipine dosages were collected for nine of the patients. Unwanted hypotensive periods were observed in one-fifth of the patients during treatment, but these were manageable through dosage adjustments. Fetal well-being did not appear to be adversely affected by the treatment. In summary, the study demonstrated that intravenous nicardipine is a potent antihypertensive agent capable of rapidly achieving target blood pressure and prolonging pregnancy in severe, early-onset preeclamptic patients who had not responded to other standard antihypertensive drugs. While some

hypotensive episodes occurred, they were manageable, and fetal well-being was not negatively impacted.

A study by Cornette et al. [69] reported the hemodynamic effects of intravenous nicardipine, impact on blood pressure and vascular resistance. Administration of nicardipine led to a significant reduction in mean arterial blood pressure, with a median difference of 26 mmHg ($p = 0.002$). Concurrently, total vascular resistance also significantly decreased by a median difference of 791 dynes x s/cm^5 ($p = 0.002$) in all women included in the study. This reduction in blood pressure and vascular resistance induced a reflex tachycardia, resulting in a consequent increase in cardiac output by 1.55 L/min ($p = 0.004$). Importantly, there were no significant changes observed in other measured maternal or fetal hemodynamic parameters, including maternal diastolic function, microcirculatory perfusion, uteroplacental perfusion, or fetal perfusion. In summary, the study found that nicardipine effectively lowers blood pressure by reducing afterload, which in turn increases cardiac output due to a reflex increase in heart rate, without adversely affecting other crucial maternal or fetal circulatory functions.

The Indonesia pravastatin to prevent preeclampsia (INOVASIA) study by Akbar et al. [70] investigated the effectiveness of pravastatin in preventing preeclampsia in high-risk pregnant patients. A total of 173 individuals participated in the study. The control group consisted of 86 participants, while the pravastatin group included 87 participants. The pravastatin group showed a significantly lower rate of preterm preeclampsia (13.8%) compared to the control group (26.7%). This difference was statistically significant ($p = 0.034$) with an odds ratio (OR) of 0.034 (95% confidence interval (CI): 0.202 to 0.905). Preeclampsia occurred later in the pravastatin group (36.39 ± 2.32 weeks) than in the control group (34.89 ± 3.38 weeks), with a p-value of 0.048. The rate of preterm birth was significantly lower in the pravastatin group (16.1%) compared to the control group (36%). This was also statistically significant ($p = 0.003$) with an OR of 0.340 (95% CI: 0.165 to 0.7), primarily due to indicated preterm birth. Overall, the pravastatin group exhibited better perinatal outcomes. Neonates in the pravastatin group had significantly lower rates of low Apgar scores (<7) at both 1 min (5.7% vs 25.6%, $p = 0.000$) and 5 min (2.3% vs 25.6%, $p = 0.028$) compared to the control group. The rate of low birthweight babies (< 2500 g) was lower in the pravastatin group (27.6%) compared to the control group (40.7%), though this difference was not statistically significant ($p = 0.069$). In conclusion, the study found that pravastatin (20 mg twice daily) significantly reduced the risk of preterm preeclampsia and preterm birth in high-risk pregnant women, and was associated with improved perinatal outcomes, including better Apgar scores.

The innovation in science pursuit for inspired research (INSPIRE) study by Cerdeira et al. [71] investigated the use of the sFlt-1/PlGF ratio in predicting preeclampsia in women with suspected cases. The study recruited a total of 370 women, with 186 assigned to the 'reveal' arm (clinicians knew the sFlt-1/PlGF result) and 184 to the 'nonreveal' arm (result unknown to clinicians). Preeclampsia developed in 85 of these women, accounting for 23% of the total participants. The number of admissions within 24 h of the test, which was the primary end point, did not significantly differ between the two groups. Specifically, there were 48 admissions in the nonreveal group compared to 60 in the reveal group, with a p-value of 0.192, indicating no statistical significance. The 'reveal' trial arm admitted 100% of the cases that developed preeclampsia within 7 days. In contrast, the 'nonreveal' arm admitted 83% of such cases ($p = 0.038$). The use of the sFlt-1/PlGF ratio test demonstrated a sensitivity of 100% (95% CI: 85.8 to 100). It also showed a negative predictive value of 100% (95% CI: 97.1 to 100). For comparison, clinical practice alone had a sensitivity of 83.3% (95% CI: 58.6 to 96.4) and a negative predictive value of 97.8% (95% CI: 93.7 to 99.5). The study concluded that using the sFlt-1/PlGF ratio significantly improved clinical precision in managing suspected preeclampsia cases without altering the overall admission rate. In summary, while the sFlt-1/PlGF ratio test did not change the total hospitalization rate, it significantly improved the identification and admission of women who would subsequently develop preeclampsia within a week, demonstrating high sensitivity and negative predictive value.

A study by Bozorgan et al. [72] investigated the effectiveness of adding furosemide to antihypertensive treatment for postpartum hypertension in women with preeclampsia. The key findings highlight the impact of furosemide on blood pressure reduction, the need for additional medication, and the time to achieve normal blood pressure. Systolic blood pressure, diastolic blood pressure, and mean arterial pressure were significantly reduced in all patients and in both treatment groups (nifedipine alone and nifedipine plus furosemide) from the first to the fifth day after delivery. On the second day, diastolic blood pressure was significantly lower in the nifedipine group ($p = 0.005$), but systolic blood pressure and mean arterial pressure did not show significant differences between the groups. From the third to the fifth day, systolic blood pressure was significantly lower in the nifedipine plus furosemide group ($p < 0.05$). However, diastolic blood pressure did not show a significant change during this period ($p > 0.05$). Mean arterial pressure was significantly lower in the nifedipine plus furosemide group on the third and fourth days ($p < 0.05$), but this difference was not significant on the fifth day ($p = 0.383$). The need for additional medication to control blood pressure was higher in the nifedipine-only group compared to the nifedipine plus furosemide group. Specifically, 22 patients (20%) overall required additional medication, with 17 patients (31%) in the nifedipine group and 5 patients (9%) in the nifedipine plus furosemide group ($p = 0.005$). The study found that adding furosemide reduced the need for further medication to control blood pressure. Blood pressure normalized (less than 120/80 mmHg) in 74 patients (68%) within five days after delivery. This normalization was more frequent in the nifedipine plus furosemide group ($p < 0.001$). The frequency of reaching normal blood pressure was significantly higher and faster in the nifedipine plus furosemide group. The majority of patients in this group reached normal blood pressure on the third and fourth days. The mean urinary output during the first five days after delivery was significantly higher in the nifedipine plus furosemide group (10603 ± 608 mL) compared to the nifedipine group alone (8507 ± 315 mL) ($p < 0.001$). The study concluded that the inclusion of furosemide in the nifedipine regimen for postpartum hypertension in women with preeclampsia led to a further reduction in systolic blood pressure and mean arterial pressure. It also decreased the need for additional medication and increased the speed and frequency of achieving normal blood pressure. Therefore, furosemide can be administered alongside other drugs to manage blood pressure in postpartum preeclampsia, though larger studies are recommended to confirm its efficacy and safety.

A study by Sinha et al. [73] compared the efficacy of 75 mg vs 150 mg aspirin for preventing preeclampsia in high-risk pregnant women, revealing significant differences in preeclampsia incidence between the two dosages, while fetomaternal outcomes remained largely similar. A significantly higher number of pregnant women receiving 75 mg aspirin developed preeclampsia (33.92%) compared to those receiving

150 mg aspirin (8.77%). The odds of developing preeclampsia were five times greater in the 75 mg aspirin group compared to the 150 mg aspirin group (OR = 5.341, 95% CI: 1.829 to 15.594, p = 0.001). After adjusting for other significant variables, the odds of preeclampsia were still significantly higher with 75 mg aspirin (adjusted OR = 9.060, 95% CI: 2.334 to 35.169). Women with chronic hypertension had a significantly higher incidence of preeclampsia (34.60%) compared to those without (9.80%), with an OR of 4.853 (95% CI: 1.753 to 13.432, p = 0.001). A baseline systolic blood pressure of ≥140 mmHg was associated with a higher incidence of preeclampsia (40.9%) compared to systolic blood pressure ≤140 mmHg (16.5%), with an OR of 3.508 (95% CI: 1.272 to 9.673, p = 0.012). Higher mean systolic blood pressure (≥140 mmHg) and mean diastolic blood pressure (≥90 mmHg) during the study period were also significantly associated with increased preeclampsia incidence. There was no statistically significant difference in fetomaternal outcomes between the 75 mg and 150 mg aspirin groups. These outcomes included neonatal intensive care unit admission, intrauterine growth restriction, neonatal death, stillbirth, eclampsia, HELLP syndrome, placental abruption, and pulmonary edema. A significantly greater increase in urine protein was observed in the 75 mg aspirin group (0.48 ± 0.78) compared to the 150 mg aspirin group (0.14 ± 0.48) at delivery (p = 0.006). This suggests a less favorable renal outcome with the lower dose. There was a statistically insignificant difference in the change of systolic blood pressure and diastolic blood pressure from enrollment to delivery between the two groups. Both groups showed a decreasing trend in mean systolic blood pressure and diastolic blood pressure over the study period, but this decrease was not statistically significant between the groups. In summary, the study concludes that 150 mg aspirin is more effective in preventing preeclampsia in high-risk pregnant women than 75 mg aspirin, while both dosages show similar fetomaternal outcomes. The higher dose also resulted in a lesser increase in urine protein, indicating better management of a key preeclampsia indicator.

A study by Saxena et al. [74] (CTRI/2023/12/060983) describes the study protocol for a randomized double-blind clinical trial, rather than presenting its results. The trial aims to compare the efficacy and safety of two different aspirin dosages (75 mg vs 150 mg) for preventing preterm pre-eclampsia in high-risk women. The study involves screen-positive women aged 18 to 45 years with singleton pregnancies between 12 and 16 weeks of gestational age. Participants will be randomized in a 1:1 ratio to receive either 75 mg or 150 mg of aspirin nightly until 37 weeks of pregnancy or until preterm preeclampsia develops. The primary objective is to assess fetomaternal outcomes, including the incidence of preterm preeclampsia and other neonatal and maternal complications. A total of 370 participants (185 per group) is planned, accounting for a 20% attrition rate, based on sample size calculations for expected proportions of preterm preeclampsia in both groups. In conclusion, this paper outlines the methodology and design of an ongoing clinical trial.

While these studies highlight promising interventions for preeclampsia, it is important to consider the broader context of treatment options. For instance, the use of novel drug therapies, such as dexmedetomidine and compound Danshen combinations, is being explored for severe preeclampsia and eclampsia, although these are currently off-label and require further research [75]. Additionally, the integration of biomarkers like PlGF into clinical algorithms has shown potential in reducing the time to diagnosis and improving maternal outcomes, although its implementation is limited by regional availability [76].

Innovations in Prevention and Management

Recent advancements in the prevention and management of preeclampsia include the recommendation of low-dose aspirin for high-risk women, which has shown varying efficacy across different populations [77-79]. For instance, a population-based study indicated that while low-dose aspirin significantly reduced recurrent preeclampsia among Hispanic women, it did not yield similar benefits for non-Hispanic Black women [27]. This finding underscores the necessity for tailored approaches in clinical practice that consider the unique needs of diverse populations. Innovations in the prevention and management of preeclampsia have seen significant advancements, focusing on early detection, risk assessment, and novel therapeutic strategies. Preeclampsia, a complex pregnancy disorder characterized by hypertension and potential organ dysfunction, poses a substantial risk to maternal and fetal health. Recent research has emphasized the importance of early screening and preventive measures, alongside the development of new pharmacological interventions [80-82]. These innovations aim to mitigate the adverse outcomes associated with preeclampsia, which remains a leading cause of maternal and fetal morbidity and mortality (Table 2). The following sections detail key advancements in this field.

Table 2: Innovations in prevention and management of preeclampsia.

Category	Innovation	Mechanism/Target	Key findings	Ref.
Early screening	sFlt-1/PlGF ratio	Angiogenic imbalance detection	Predicts preeclampsia 5 to 8 weeks before symptoms (100% negative predictive value)	[71]
	AI/deep learning models	Multi-parameter risk assessment	30% higher detection rate for late-onset cases vs traditional methods	[85]
Pharmacological prevention	Low-dose aspirin (150 mg)	COX-1 inhibition → improved placental perfusion	5x lower preeclampsia risk vs 75 mg (OR = 0.2)	[73]
	Pravastatin (20 mg bid)	Upregulates VEGF, reduces sFlt-1	50% reduction in preterm preeclampsia (13.8% vs 26.7%)	[70]
	Metformin	Improves insulin sensitivity + anti-inflammatory effects	Promising for obese women (reduces incidence by 30 to 40%)	[62]
Acute management	Nicardipine IV	Calcium channel blockade → vasodilation	Achieves BP control in 23 min (median), prolongs pregnancy by 4.7 days	[68]
	Diltiazem vs nifedipine	Vascular smooth muscle relaxation	Superior BP control (133/78 vs 148/91 mmHg at 6 h), fewer side effects	[66]
Novel therapies	Furosemide add-on	Volume management + RAS modulation	Faster BP normalization (3 vs 5 days), 3x less rescue meds needed	[72]
	Antithrombin concentrate	Restores angiogenic balance	Prolongs pregnancy by 2 weeks in severe cases	[63]
Lifestyle interventions	DASH diet + stress reduction	Improves endothelial function	25% risk reduction when combined with aspirin	[80]

Early screening and risk assessment

- Biomarkers and screening models: Advances in screening methods include the use of biomarkers such as the sFlt-1/PlGF ratio, which can predict preeclampsia weeks before symptoms appear. This approach enhances early diagnosis and management, allowing for timely interventions [83, 84].

- Artificial intelligence and deep learning: Artificial intelligence and deep learning technologies have improved the predictive accuracy of preeclampsia, particularly for late-onset cases. Artificial intelligence models have shown higher detection rates compared to traditional methods, offering new opportunities for early screening and management [85].

- Risk factor identification: Comprehensive risk modeling, incorporating demographic, biophysical, and biochemical factors, has been developed to identify women at high risk of developing preeclampsia. This model aids in the early identification and monitoring of at-risk pregnancies [5].

Preventive strategies

- Low-dose aspirin: The administration of low-dose aspirin has been validated as an effective preventive measure, significantly reducing the risk of preterm preeclampsia when started early in pregnancy [83, 86].

- Lifestyle and dietary interventions: Stress reduction, dietary changes, and lifestyle modifications are being explored as preventive measures. These interventions aim to address underlying risk factors and improve overall maternal health [80].

- Pharmacological innovations: Emerging therapies include the use of statins, CoQ10, and nitric oxide donors, which target the pathophysiological mechanisms of preeclampsia. These therapies are in various stages of clinical trials and show promise in reducing the incidence and severity of the condition [86, 87].

Management approaches

- Pharmacological management: Antihypertensives and magnesium sulfate remain essential for managing acute symptoms of preeclampsia. New therapeutic approaches, such as antiangiogenic therapies and hypoxia-inducible factor suppression, are being investigated to improve outcomes [86, 88].

- Delivery timing: Expedited delivery in cases of late preterm preeclampsia has been shown to protect against maternal adverse outcomes, although it may increase neonatal unit admissions. This highlights the need for careful decision-making regarding delivery timing [84].

- Multidisciplinary care: A comprehensive, multidisciplinary approach is crucial for managing preeclampsia, involving obstetricians, neonatologists, and other healthcare professionals to optimize maternal and fetal outcomes [88].

To address the disproportionate burden of preeclampsia on minority populations, future research should adopt a multilevel framework that incorporates the influence of behavioral, environmental, and healthcare system factors, alongside individual risk factors [27]. This holistic approach may facilitate the development of effective strategies to mitigate the impact of preeclampsia and improve health outcomes for all women. While significant progress has been made in the prevention and management of preeclampsia, challenges remain. The exact pathophysiology of the condition is not fully understood, and current treatments are not universally effective. Continued research is necessary to uncover the molecular mechanisms underlying preeclampsia and to develop more targeted therapies. Additionally, addressing healthcare disparities and ensuring access to advanced screening and management options are critical for improving outcomes across diverse populations [11, 86].

Conclusion

Preeclampsia remains a multifaceted disorder with significant global health implications, characterized by complex interactions between placental, vascular, and immunological mechanisms. Despite advances in understanding its pathophysiology, delivery of the placenta remains the only definitive treatment, often necessitating preterm birth with associated neonatal risks. Current innovations-such as the sFlt-1/PlGF ratio for early prediction, pravastatin for prevention, and tailored antihypertensive regimens-demonstrate promising improvements in maternal and fetal outcomes. However, disparities in access to these advancements persist, particularly in low-resource settings where the burden of preeclampsia is highest. Addressing these inequities through scalable screening programs and cost-effective therapies must be prioritized to reduce global morbidity and mortality.

Looking ahead, the integration of artificial intelligence for risk stratification, alongside targeted therapies addressing angiogenic imbalance and oxidative stress, holds transformative potential. Future research should focus on personalized approaches that account for racial, ethnic, and socioeconomic factors influencing disease susceptibility and treatment response. Collaborative efforts among researchers, clinicians, and policymakers are essential to translating mechanistic insights into equitable clinical practices. By combining innovative diagnostics, pharmacotherapies, and community-based interventions, the field can move closer to eliminating preventable deaths and long-term complications associated with this pervasive pregnancy complication.

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Conflict of Interest

None.

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