Iran J Public Health, Vol. 53, No.11, Nov 2024, pp.2392-2403

Review article

Preeclampsia: Etiology, Pathophysiology, Risk Factors, Impact and Prevention: A Narrative Review

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(Received 08 Feb 2024; accepted 05 Apr 2024)

Abstract

Background: Preeclampsia (PE) caused 30%-40% of maternal and newborn deaths worldwide. Despite unclear exact cause, strategies exist to mitigate less severe PE effects. This review explores PE etiology, pathophysiology, risk factors, impact, and prevention.

Methods: Searching Scopus, PubMed, ProQuest, Google Scholar, and Science Direct for "preeclampsia and pregnancy" and "prevention" yielded 2012–2022 articles.

Results: Preeclampsia features abnormal placental changes, altered immunity response, trophoblast apoptosis, and reduced uterine perfusion. Risk factors include hypertension history, nulliparity, age over 40, BMI over 35 kg/m², family history, amniotic pregnancy, and long pregnancy interval. This condition risks cardiovascular and neonatal morbidity, straining health resources. Prevention involves aspirin, vitamin D, exercise, folic acid, diet, early screening, and antenatal care.

Conclusion: Findings emphasize enhancing health literacy and preeclampsia education in prenatal care to mitigate PE risk among women. Further research, novel therapies, and assessing prevention strategies with accessible educational materials and multidisciplinary approaches are warranted to enhance pregnant women's health literacy and decrease PE risk.

Keywords: Preeclampsia; Etiology; Risk factor; Impact; Prevention

Introduction

Preeclampsia (PE) is a key public health problem. It happens after 20 wk of gestation. It causes high blood pressure and proteinuria (1, 2). PE is a multisystem disorder of pregnancy characterized by dysfunction of the placenta and maternal vasculature, and is significantly associated with

maternal and fetal morbidity and mortality, affecting more than 10 million women and annually contributing to more than 76,000 maternal deaths and 500,000 infant deaths (3,4). PE is significant in increasing infant and maternal mobility and mortality rates in the range of 30-40% worldwide (5-7). PE is often associated with complications involving other organs. These can arise in pregnancy and the postpartum period. PE occurs in about 4.6% of pregnancies worldwide (8). Preeclampsia affects 2.8% of live births on average in developing countries compared to 0.4% in developed countries, a seven-fold increase from previous incidence rates (9).

Research conducted by Rachael Fox et al. (10), along with the N. Stitterich et al. Another study (11), highlight knowledge gaps in the diagnosis, management and prevention of preeclampsia. Wainstock et al. and Stitterich et al. examined risk factors, including previous pregnancy complications and provided insights into the prevention of preeclampsia.

These studies contribute to comprehending the risk, impact, and prevention strategies of preeclampsia, advocating interventions like antenatal care, lifestyle adjustments, and nutritional supplementation to lessen preeclampsia incidence and enhance pregnancy outcomes.

Search Method

This study systematically reviewed preeclampsia's causes, occurrence, risk factors, impact, and prevention. It searched multiple databases including Scopus, PubMed, ProQuest, Google Scholar, and Science Direct using keywords "preeclampsia and pregnancy" and "preeclampsia prevention" from 2012 to 2022.

Inclusion criteria included articles on preeclampsia etiology, pathophysiology, risk factors, impact, and prevention, published in English and available in full text. Exclusion criteria involved articles single case studies, and editorial reviews or commentaries. Study selection included screening titles and abstracts.

Etiology of Preeclampsia

The etiology of PE typically entails placental abnormalities and suboptimal maternal-placental interactions (12). The placenta contributes to maternal pregnancy adaptation and fetal development (13). The precise cause of PE remains uncertain (14, 15) . Epidemiological and experimental evidence shows placental angiogenic factor imbalance contributes to maternal preeclampsia symptoms (16, 17). PE and intrauterine growth restriction (IUGR) are frequent pregnancy complications linked to abnormal placental development (18-20). In preeclampsia, chronic stresses such as renal, metabolic, or autoimmune diseases appear prevalent (21). Maternal vascular and endothelial responses may be particularly sensitive to placental factors (22). Sequence variants associated with preeclampsia in the maternal genome at ZNF831/20q13 and FTO/16q12 have been identified in European and Central Asian mothers (23). Key immune checkpoint receptors like T-cell immunoglobulin mucin-3 (Tim-3) and Programmed cell death-1 (PD-1) regulate maternal antibodies response to infant antigens in pregnancy, where disrupted immune regulatory mechanisms contribute to adverse outcomes like preeclampsia (24). Pro- and anti-inflammatory cytokines influence placental development and function, potentially contributing to various pregnancy-related disorders like preeclampsia (25). Several studies have reported using biochemical markers, like pregnancy-associated protein and placental growth factor, in PE screening (26). In the third trimester, PE correlates with altered gut microbiota, hypertension, liver dysfunction, and lower birth weight compared to uncomplicated pregnancies (27). PE and gestational diabetes correlate with elevated neutrophil to lymphocyte ratio (NLR), but the direct causal link remains unclear (28). These findings the importance of understanding biological interactions to advance preeclampsia prevention and treatment strategies.

Pathophysiology of Preeclampsia

PE develops in two stages: placental abnormalities in the first trimester, followed by "mother

syndrome" in the second and third trimesters characterized by an excess of anti-angiogenic factors (29). PE involves heightened immune response, trophoblast apoptosis, reduced trophoblast infiltration, altered placental morphology like spiral artery remodeling, decreased uterine perfusion pressure (RUPP) (30) and placental ischemia or hypoxia. The RUPP condition can result from an imbalance in anti-angiogenic factors (such as fms-like tyrosekinase-1/SFlit-1 and soluble endoglin/SEng) and pro-angiogenic factors (such as vascular endothelial growth factor/VEGF and placental growth factor/PlGF). The stimulates the release of bioactive factors circulating in the blood, such as cytokines, hypoxia-inducible factor-1/HIF-1, reactive oxygen species/ROS, and angiotensin receptor agonist/AT1 AA autoantibodies (31, 32). Abnormal placenta in early pregnancy is considered an important early event in the development of PE, it causes the release of anti-angiogenic factors [mainly tyrosine kinase-1 (sFlt-1)] and soluble cytokines, leading to widespread vascular dysfunction (33). Systematic morphologic studies indicate that preeclampsia is associates with incomplete transformation of spiral arteries and the presence of endothelial and myogenic cells in endometrial segments (34). Angiotensin peptide imbalance might contribute to PE pathophysiology and fetal growth issues (35). Decidual macrophage dysfunction is pivotal in PE pathogenesis (36). These findings underscore the need for deeper understanding to develop more effective therapeutic approaches in managing PE. Figure 1 provides a simplified overview of the complex processes involved in the pathogenesis of preeclampsia.

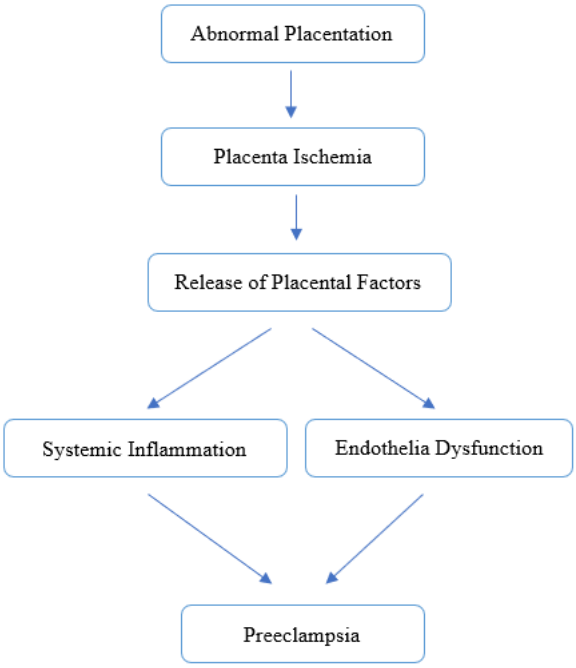

Fig. 1: Pathophysiology of Preeclampsia

Risk Factors for Preeclampsia

According to the 2019 NICE Guidelines, women at high risk of preeclampsia include those with a history of hypertensive disease in prior pregnancies or maternal conditions like chronic kidney disease, autoimmune disease, diabetes, or chronic hypertension. Moderate-risk women include nulliparous, aged ≥ 40, BMI ≥ 35 kg/m², with family history of preeclampsia, amniotic pregnancy, or pregnancy interval > 10 years (37,

38) . Additionally, primigravida status and alcohol consumption correlate with risk of PE. Alternatively, consuming vegetables protects against PE development (39) and there is an association of ABO blood group in pregnant women with pregnancy complications including preeclampsia (40).

Other risk factors, encompassing socio-demographic and clinical aspects, contribute to PE occurrence (41). Preeclamptic mothers face elevated lead exposure risks both at work and home, correlating with higher blood lead levels and increased preeclampsia risk (42). Preeclampsia prevalence is higher in couples using condoms, shorter cohabitation, first pregnancy in multiparous women with partner change, and pregnancy post-assisted reproduction with gamete donation. In most developed countries with a "Western lifestyle," 80-90% of preeclampsia cases are strongly linked to maternal metabolic syndrome variables (43). Identifying risks and implementing preventive strategies, such as lifestyle modifications and close medical monitoring, is crucial for reducing preeclampsia.

Impact of Preeclampsia

Preeclampsia and Cardiovascular Disease

Cardiovascular disease (CVD) is the leading cause of pregnancy-related mortality (44, 45). Women with prior hypertensive pregnancy disorders face a 5%-10% increased risk of cardiovascular disease (46-50). First-pregnancy hypertension correlates with a 63% higher incidence of cardiovascular disease later in life. Over 80% of this risk is attributed to developing chronic hypertension post-delivery, suggesting that preeclampsia may heighten cardiovascular risk (50, 51). Epidemiologic studies support these findings, indicating that gestational hypertension and preeclampsia elevate the risk of future cardiovascular disease compared to women without pregnancy-related hypertension (48). Besides short-term impacts, preeclampsia has long-term repercussions for both mothers and offspring, as indicated by abundant epidemiological evidence. Studies demonstrate heightened susceptibility to cardiovascular, metabolic, and neurologic disorders, and other maladies among offspring affected by preeclampsia (49). The occurrence of cardiometabolic conditions in pregnancy, like gestational diabetes and hypertension, elevates the likelihood of subsequent cardiovascular events (50). Preeclampsia and small-for-gestational-age infants correlate with CVD (51).

Preeclampsia and neonatal Outcomes

PE is linked to higher long-term maternal and child morbidity risks related to prematurity (52). PE is linked to immune-based pregnancy issues and atopic abnormalities in newborns (53). PE significantly affects fetal growth restriction by impairing spiral artery remodeling and trophoblast invasion, thereby reducing nutrient supply to the fetus (54). Preeclampsia triggers placental vascular insufficiency, leading to epigenetic and pathological alterations in both maternal and fetal systems. Infants exposed to preeclampsia exhibited diminished weight, height, and BMI compared to controls with normotensive pregnancies at 2 years. Accelerated weight gain in controls potentially supports growth to age 2, influencing long-term cardiometabolic health. Yet, disparities exist regarding the impact of preeclampsia on infant motor and cognitive development or vice versa (55). The intrauterine environment in PE adversely affects fetal lung development, altering gene profiles and postnatal alveolar and bronchial structures (56). Evidence indicates hypertension, gestational diabetes, and preeclampsia are associated with intrauterine growth restriction (IUGR) and potentially small for gestational age (SGA) (57).

Preeclampsia and economic impact

Managing PE incurs substantial costs, imposing a significant burden on healthcare systems, especially regarding hospitalization and addressing maternal and obstetric complications (62, 63). Preeclampsia costs $1.03 billion for moms and $1.15 billion for babies over the first 12 months following delivery. The cost burden per baby varies with gestational age, starting at 26 wk and going up to 36 wk, or $1311, respectively (60).

Preeclampsia impacts maternal and infant health, necessitating research and interventions to mitigate risks and economic burdens.

Prevention of Preeclampsia

Aspirin

Aspirin prevented early PE by 62% in pregnant women at high risk of preeclampsia (65, 66, 67). Aspirin™ (acetylsalicylic acid) stands out as the sole effective medication in lowering PE rates, boasting analgesic properties and anti-cardiovascular effects. It has remained indispensable for over 120 years due and is listed in the WHO Essential Medicines Catalog. Administering low-dose Aspirin (80-150 mg) once nightly is recommended. Evidence indicates increased efficacy with higher doses. While deemed safe for mother and fetus at low doses, usage exceeding 100 mg is uncommon. Furthermore, the safety of a preventive regimen with 150 mg daily remains incompletely validated. (64). Evidence-based studies indicate that administering 150 mg/day Aspirin before 16 wk of gestation, particularly at night, to high-risk individuals identified through combined first-trimester screening, can lower preterm preeclampsia by 62% (65). Low-dose aspirin prevents preeclampsia, with efficacy linked to dosage, reducing postpartum hemorrhage, fetal growth restriction, preterm birth, and cesarean section (66). Aspirin should be recommended pre-16 wk gestation to prevent preeclampsia and preterm birth (67). At all pregnancy ages, aspirin doses led to a 30% reduction in preeclampsia risk (68). The optimal dose of aspirin daily is 75 mg (69).

Vitamin D

Pregnant women with deficiency vitamin D have a higher preeclampsia risk (70). Vitamin D promise for its positive effects on placental attachment, the immune system, and angiogenesis (75). Vitamin D supplementation significantly protects against Preeclampsia incidence (76) (77) (78).

Structured Sports

Women with a preeclampsia history require accurate lifestyle guidance (79). Yoga, with its combination of aerobic, strength, and flexibility elements, offers superior risk reduction for hypertensive disorders of pregnancy (HDP) compared to standalone aerobic exercise. It serves as a low-impact physical activity, potentially providing a safer and more acceptable means for pregnant women to mitigate HDP risk (80). In addition, progressive muscle relaxation is an alternative for pregnancy complications, reducing muscle tension and promoting relaxation in pregnant women (81).

Folic Acid

High-dose folic acid supplements taken three months before conception until delivery can reduce the risk of preeclampsia in pregnant women (82).

Mushroom Diet

The Mushroom Diet aims to prevent gestational hypertension, preeclampsia, and associated comorbidities such as gestational diabetes and excessive pregnancy weight gain (83).

Consumption of Ajwa Dates

Pregnant women prone to preeclampsia may benefit from consuming seven Ajwa dates daily, reducing mean arterial pressure (MAP) and Roll-Over Test (ROT), potentially preventing preeclampsia (84).

Consume Extra Virgin Olive Oil

Preeclampsia induces trophoblast release into maternal circulation, impacting fetal health. Extra virgin olive oil (EVOO) harbors tocopherols (vitamin E) with antioxidant properties, while Haramonting, an Indonesian traditional remedy, prevents DNA damage and exhibits antioxidant activity. Co-administration of EVOO and nano herbal Haramonting augments trophoblast count and improves placental histology (85).

Preeclampsia Screening

The subsequent aspects necessitate meticulous consideration during preeclampsia screening:

1) Early detection of blood pressure changes is crucial for preventing preeclampsia (81). During early pregnancy, women ought to undergo screening for clinical risk indicators of preeclampsia (strong, moderate). When feasible, screening should occur between wk 11 and 14 of gestation utilizing a blend of clinical risk markers, uterine artery pulsatility index, and placental growth factor (PlGF) risk factors to assess pre-eclampsia risk (strong, moderate) (86).

2) Personal History Screening and History Family for preeclampsia in men and women should be a priority. Mothers with a history of preeclampsia should be alerted to the heightened risk in subsequent pregnancies and commence prenatal monitoring promptly. Factors like blood pressure, multiple gestations, and familial hypertension history enhance the prenatal care link, aiding in early preeclampsia detection and complication prevention (87).

3) Screening for urinary tract infections (UTIs) links to maternal and infant complications like low birth weight, preterm birth, stillbirth, preeclampsia, maternal anemia, sepsis, and amnionitis, even when asymptomatic. UTI occurrence in pregnancy, notably in the third trimester, strongly associates with preeclampsia, hinting at heightened maternal inflammation elevating preeclampsia risk. Preventing UTIs could potentially and affordably curb preeclampsia development (47).

4) Monitoring urinary protein levels, while not diagnostic, correlates with severe preeclampsia symptoms, potentially leading to premature labor (88). Proteinuria, common in preeclampsia patients, predicts adverse outcomes. Monitoring urinary protein levels is advised for follow-up care (89).

Antenatal Care Visit

Enhancing pregnant women's health-seeking behavior in urban and rural areas offers an opportunity for early preeclampsia diagnosis and complication prevention (90).

Timely intervention and risk mitigation are vital in preventing preeclampsia in both mothers and infants. Table 1 was prepared based on provided information, covering preeclampsia's etiology, pathophysiology, risk factors, effects, and preventionants.

Table 1: Summary of preeclampsia: etiology, pathophysiology, risk factors, impact, and prevention and preventive measures

Summary	*Aspects*
Etiology	- Disorders in placental development. - Vascularization abnormalities in the placenta. - Inappropriate immune response
Pathophysiology	- Placental abnormalities in the first trimester. - Maternal syndrome in the second and third trimester. - Excess anti-angiogenic factors
Risk Factors	- Hypertension during previous pregnancy. - Chronic kidney disease, autoimmune disease, diabetes. - Nulliparous, age ≥ 40 years, BMI ≥ 35 kg/m². - Family history of preeclampsia, pregnancy loss. - Pregnancy interval more than 10 years
Impact	- Future cardiovascular disease. - Neonatal morbidity and mortality. - Long-term effects on mother and child, including cardiovascular, metabolic and neurological risks. - Prematurity, atopic disorders in newborns. - Fetal growth restriction, spiral artery remodelling. - Placental vascular insufficiency, epigenetic and pathological changes
Preventive measures	- Aspirin at low doses. - Vitamin D supplementation. - Regular exercise. - Folic acid consumption. - Special diets, such as mushroom diet. - Consumption of Ajwa dates. - Consumption of extra virgin olive oil. - Early screening and risk monitoring

Consider various interventions, including hypertension treatment, antenatal care, delivery services, postpartum care, and enhanced education and standardization of hypertension testing during pregnancy, to mitigate and prevent hypertensive disorders in pregnancy (91, 92).

Recommendations include conducting multicentric research to gather diverse data on preeclampsia dynamics, testing new therapies (both pharmacological and non-pharmacological), evaluating preventive strategies like low-dose aspirin and vitamin D supplementation. Intervention studies to enhance pregnant women's health literacy on preeclampsia .along with assessing its long-term impact on incidence and pregnancy outcomes.
This study was limited by the availability and access to recent literature, potentially overlooking new findings or recommendations in obstetrics and gynecology that emerged after the writing period.

Conclusion

This article elucidates preeclampsia's etiology, pathophysiology, risk factors, impact, and preventive measures, arising from compromised placental development, vascularization issues, and immune dysregulation.
The implications of this study emphasizes the necessity of enhancing health literacy and integrating preeclampsia education into prenatal care to empower pregnant women in mitigating preeclampsia risk.

Journalism Ethical considerations

Ethical issues (including plagiarism, informed consent, errors, falsification and/or fabrication of data, multiple publications and/or submissions, redundancy, etc.) have been fully addressed by the authors.

Funding

The authors revealed financial and personal conflicts of interest and received financial support but stressed no conflicts affecting manuscript objectivity.

Conflict of interest

The authors declare that there is no conflict of interests.

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