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Review Article

A Comprehensive Review of Preeclampsia: Risk Factors, Diagnosis, Pathogenesis and Treatment Strategies

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ABSTRACT

Preeclampsia is a pregnant hypertension condition. It has a significant negative impact on maternal and perinatal health and affects 2–8% of pregnancies worldwide. The disease's main features are hypertension and proteinuria, though systemic organ damage could follow. The aberrant placentation that precedes the release of antiangiogenic markers, which is predominantly mediated by soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin, is the first sign of the clinical condition.(sEng). Every maternal organ system, including the fetus, may be adversely affected by high levels of sFlt-1 and sEng due to endothelial dysfunction, vasoconstriction, and immunological dysregulation. With an emphasis on the mechanisms underlying the clinical symptoms, this article thoroughly investigates the pathogenesis of preeclampsia. The only permanent remedy is delivery. In high-risk populations, low-dose aspirin is advised for prophylaxis. There are few other therapy alternatives. The pathophysiology of this common disease has to be clarified in order to find possible therapeutic targets for better treatment and, ultimately, outcomes. The three most common causes of maternal morbidity and mortality worldwide are preeclampsia and eclampsia. Rates of eclampsia, maternal mortality, and maternal morbidity in wealthy nations have significantly decreased during the past 50 years. In contrast, maternal mortality, problems during pregnancy, and eclampsia rates are still high in developing nations. In industrialised nations, preeclampsia-eclampsia patients are properly managed, and prenatal care is widely accessible. These discrepancies are mostly attributable to these factors.

Keywords: Preeclampsia; Maternal mortality; pathogenesis; Diagnosis; Risk factors; Management.

INTRODUCTION

Preeclampsia is the new beginning of pregnancy-related hypertension with accompanying proteinuria, maternal organ failure, or constrained foetal development. It is a significant global cause of maternal death and morbidity**.** According to the gestational age upon diagnosis, preeclampsia is frequently subclassified as an early-onset or late-onset condition. Preeclampsia that manifests before 34 weeks of pregnancy is more severe for the mother, typically accompanied with foetal development restriction, and more likely to repeat in a subsequent pregnancy. Preeclampsia's exact cause is unknown, although the most widely accepted view suggests that it arises as a result of defective or insufficient placentation in the first trimester of pregnancy.[1]To fulfil the dietary and metabolic demands of the developing foetus, normal pregnancy is linked with significant uteroplacental and hemodynamic alterations. The uteroplacental perfusion pressure is kept at an acceptable level by placental growth and trophoblast invasion of the uterine spiral arteries. Blood pressure (BP) only slightly decreases as a result of increases in maternal plasma volume and cardiac output, which are accompanied with systemic vasodilation and lower vascular resistance.[2]Large observational studies have demonstrated a striking rise in the long-term risk of cardiovascular disease (CVD) among women who suffered various gestational hypertensive illnesses, which has sparked an interest in CVD in obstetrics in recent years.1–3

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Preeclampsia and pregnancy-induced hypertension (PIH), which affect 2% to 7% of all pregnancies globally, are two examples of this.[3] The disparities in risk among racial and ethnic groups point to a significant contribution of genetic factors to the pathophysiology of preeclampsia. The majority of ideas about the aetiology of preeclampsia contend that the condition is caused by a cascade of events that include inappropriate maternal inflammatory response, endothelial cell activation/damage with altered hemodynamic milieu, and abnormal immunity. It is still unknown exactly what sets off the aberrant vascular, immunological, and inflammatory responses. We evaluate treatment alternatives in this work and present new theories on the pathophysiology of preeclampsia.[4]Most signs and symptoms can be relieved by birth; however, preeclampsia can continue after delivery and, in rare instances, can develop de novo throughout the postpartum period. Preeclampsia following delivery, whether de novo or chronic, has become a significant risk factor for peripartum morbidity in the US. Long-term cardiovascular disease (CVD) and cerebrovascular disease are both significantly increased by hypertensive disorders of pregnancy, particularly preterm preeclampsia.[5]At this time, screening for preeclampsia involves evaluating clinical risk factors such age, body mass index (BMI), and family history in addition to an ultrasound examination at 20 weeks. However, a global cohort experiment found that clinical risk variables had only a limited ability to predict outcomes. The potential for predicting preeclampsia has recently been evaluated for a number of maternal serum indicators. Pregnancy-associated plasma protein A (PAPP-A), first trimester placental protein, and soluble fms-like tyrosine kinase-1 (sFlt-1) are a few examples of possible biomarkers for spotting the onset of pre-eclampsia. Treatment for individuals who have preeclampsia or eclampsia usually entails enhanced care, magnesium sulphate for eclampsia prevention and convulsion prevention, and, at a certain point, labour induction. Naturally, hospital admission is required for labour induction, and intensified treatment may occasionally entail inpatient monitoring as well.[6]

Risk Factors for Preeclampsia

Although Preeclampsia is a prevalent illness, its cause is yet unclear. The aetiology and pathophysiology of preeclampsia remain unknown despite countless scientific, clinical, and epidemiologic investigations that have been carried out during the past 50 years. Preeclampsia is most likely the prevalent last condition brought on by many factors. In addition to having a placental origin, preeclampsia can also be impacted by maternal conditions including diabetes and obesity. Both the father and the mother may have a role in preeclampsia's genetic basis. Epidemiologic indicators are now used to identify women who are more susceptible to preeclampsia. The known risk factors include advanced age, low socioeconomic status, smoking, high body mass index, preeclampsia in previous pregnancies, parity, type of pregnancy (single or multiple), family history of diabetes mellitus, and hypertension. The recognised risk factors for the disease include a first pregnancy, diabetes mellitus, preexisting hypertension or past preeclampsia, repeated gestations, and a higher body mass index, however they are not sensitive or specific enough. The greatest indicator of preeclampsia risk is parity.[7]

Complications of Preeclampsia

Significant maternal complications, both short-term and long-term, are linked to preeclampsia. Eclampsia, uncontrolled hypertension, or systemic inflammation are the leading causes of mortality that follow preeclampsia. Intracerebral haemorrhage is the primary cause of most of these maternal fatalities. Within 7 years of a preeclamptic pregnancy, 20% of preeclamptic women get hypertension or microalbuminuria, compared to 2% of women who had straightforward pregnancies. According to a recent meta-analysis by Bellamy et al., women were more likely to develop hypertension, ischemic heart disease, stroke, and venous thromboembolism following a preeclampsia-complicated pregnancy. These women are also more likely to die from cardiovascular disease and other causes. The biggest risk group appears to be women with early-onset severe preeclampsia. Preeclampsia therefore raises a warning sign for the possibility of developing cardiovascular and neurological disorders later in life.[9]

Pathogenesis

As one of the key beginning events in PE, the shallow cytotrophoblast migration towards the uterine spiral arterioles has been described as leading to incorrect vascular remodelling and a hypo perfused placenta. It becomes ischemic in the placenta, which causes the production of substances linked to maternal vascular endothelial dysfunction. Vasoconstriction and decreased blood flow to organs are the hallmarks of endothelial dysfunction, a PE characteristic that has been observed frequently. Aside from that, preexisting illnesses like diabetes and obesity influence the substances the ischemic placenta releases.[11] Endothelial dysfunction during PE is additionally correlated with an increase in immune cells and inflammatory cytokines. Importantly, it has been demonstrated that markers such endothelin-1 (ET-1), anti-angiogenic factor sFlt-

1, agonistic autoantibodies to the angiotensin II type I receptor (AT1-AA), and reduced nitric oxide (NO) play a significant role in the development of PE. [12]

Vascular Development of the Placenta

Studies have concentrated on the link between aberrant placental vascular development and the onset of preeclampsia since the placenta is essential to the disease's pathogenesis. Extravillouscytotrophoblasts from the foetus enter the decidua and myometrium's spiral arteries during the early stages of normal placental development. The maternal spiral arteries' endothelial layer is replaced by these invasive cytotrophoblasts, which cause the arteries to change from small, high-resistance vessels to large-caliber capacitance vessels that can supply enough placental perfusion to sustain the foetus. This change isn't complete in preeclampsia. The myometrial segments continue to be thin, and cytotrophoblast invasion of the spiral arteries is restricted to the superficial decidua. Because preeclamptic placentas had aberrant cytotrophoblast expression of adhesion molecules, one group of researchers was able to demonstrate the significance of adhesion molecules for the cytotrophoblast invasion process. The process of pseudo-vasculogenesis, also known as vascular mimicry, causes cytotrophoblasts to develop an endothelial phenotype during normal placental development. Pseudovasculogenesis takes place when adhesion molecules are downregulated and endothelial cell-surface adhesion phenotype is adopted. Cytotrophoblasts are unable to effectively penetrate the myometrial spiral arterioles in preeclampsia because they do not undergo this flipping of cell-surface chemicals.[11]

Hemodynamic Changes and Maternal Endothelial Dysfunction

Preeclampsia seems to start in the placenta, although the maternal endothelium is the actual target organ. Following the release of vasopressin substances from the afflicted placenta, generalised cellular damage to the endothelium of the mother's kidneys, liver, and brain most likely takes place. Women with preeclampsia have abnormal levels of von Willebrand antigen, cellular fibronectin, soluble tissue factor, soluble E-selectin, platelet-derived growth factor, and endothelin in their serum. Endothelial dysfunction is produced when preeclamptic women's serum is incubated with endothelial cells. [13]

Liver, Renal, and Cerebral Pathological Changes

Organ alterations observed during a pathologic examination of preeclamptic and eclamptic women's organs are consistent with extensive organ hypoperfusion. Infarction, necrosis, and intraparenchymal bleeding are frequently seen in the liver and adrenals. When hypovolemic shock occurs, endocardial necrosis identical to that brought on by hypoperfusion may be visible in the heart. The kidney best illustrates the pathologic alterations typical of preeclampsia as a result of damage to the maternal endothelium.[13]

DIAGNOSIS

Preeclampsia has pathophysiologic abnormalities that might present as single- or multi-organ dysfunction. As a result, the signs and symptoms will show which organs are affected. Proteinuria in preeclampsia is a sign of renal involvement brought on by glomerular endothelial damage (altered protein permeability) and improper tubular processing of filtered proteins. Because it typically appears after the development of hypertension and/or symptoms, proteinuria has historically been used to diagnose preeclampsia. Because prenatal proteinuria alone may signal the early manifestation of an imminent preeclampsia, women who have only recently developed gestational proteinuria should be thoroughly watched for the early diagnosis of preeclampsia. There are no prospective studies that have assessed the possibility of preeclampsia in those with gestational proteinuria. Additionally, these ladies need to be checked for any possible previous renal disease (such chronic pyelonephritis, lupus nephritis, immunoglobulin A nephropathy, and other nephropathies). Due to its potential as a treatable cause of proteinuria during pregnancy, lupus nephritis needs to be thoroughly ruled out. Women should be examined for underlying renal disease if proteinuria lasts longer than 8 weeks following delivery. There may be a need for renal biopsy in some of these patients. In addition, women with proteinuria and cardiorespiratory symptoms, ascites, or pulmonary edoema ought to be examined for possible cardiac conditions such congestive heart failure or peripartum cardiomyopathy.[8]

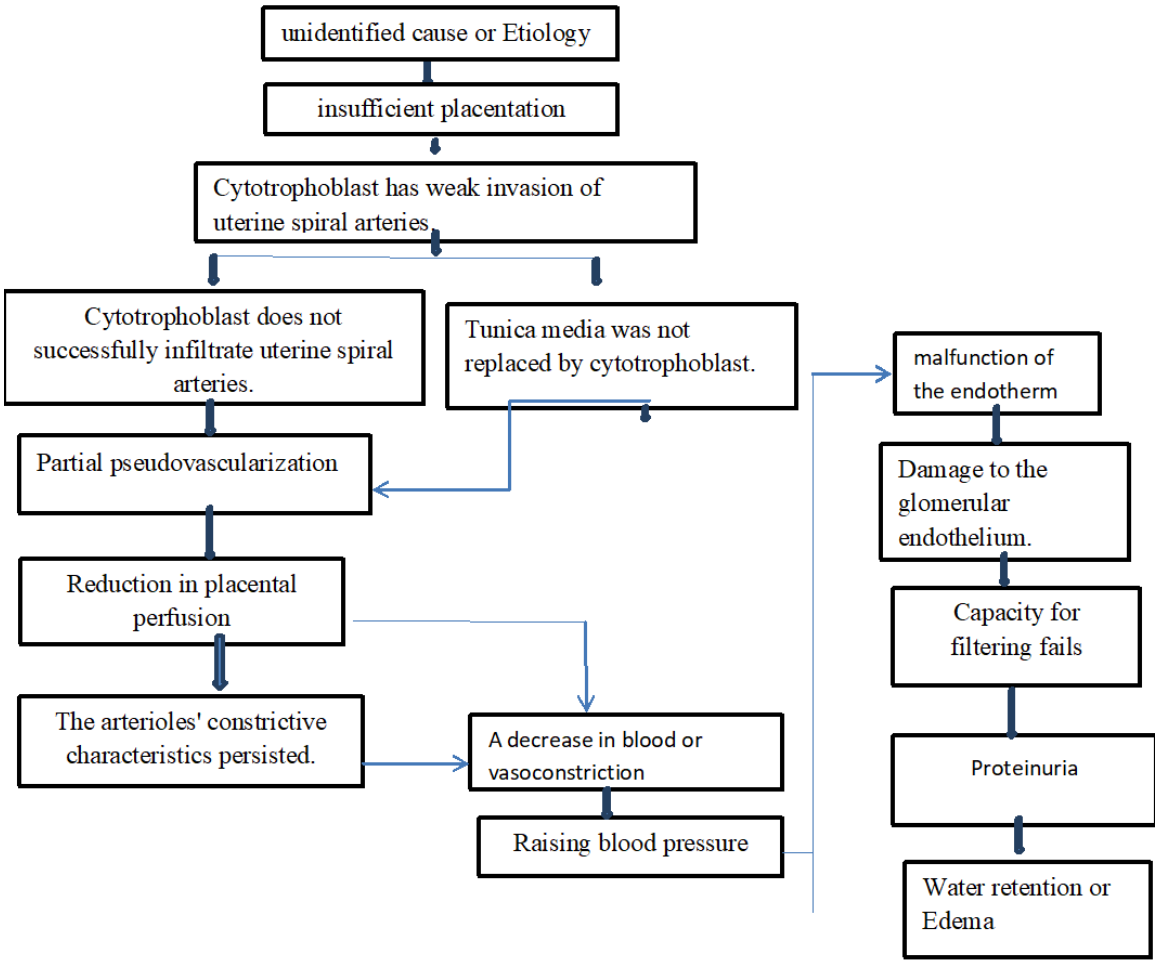

Figure 1: Schematic Diagram on Pathogenesis of Preeclampsia

Management

Preventing the development of complications like eclampsia is the main objective of controlling preeclampsia, which involves keeping the blood pressure of the affected woman within the normal range. Preeclampsia can only be successfully treated by delivering the foetus and placenta, but tragically, most patients who are diagnosed before the baby is fully developed do not have this alternative. The majority of treatment focuses on symptom management while problems are being watched for. Once blood pressure rises above a particular point, it may cause direct vascular damage, which then causes complications that pose a serious risk of death, like renal failure, stroke, and foetal distress. There is no one specific medication that should be used to treat pregnancy-related hypertension problems. Magnesium sulphate is the medication of choice for both preventing eclampsia in cases of severe preeclampsia and treating eclampsia. It can be administered fully intravenously or intramuscularly. Magnesium sulphate use is regarded to have played a large role in the United Kingdom's decrease in eclampsia incidence. Most patients consult a clinician in LMICs at the stage of severe preeclampsia or eclampsia because routine antenatal coverage is either not ubiquitous or of poor quality and there is insufficient access to healthcare. The imminent danger to the mother and the unborn child in such situations makes them an obstetric emergency. When compared to a placebo or no anti-convulsant, studies have shown that the use of magnesium sulphate is helpful in that the risks of eclampsia and placental abruption are greatly reduced (approximately half and more than half, respectively). However, due to concerns among medical professionals about its safety, magnesium sulphate use in the community is restricted. This is true even though it is a drug that almost all nations consider to be a need due to its proven efficacy, low cost, and availability.

Respiratory rate, urine output, and deep tendon reflexes are clinically useful indicators of toxicity. Magnesium sulphate is not used to its full potential due to a number of problems, including inadequate provider training and expertise, a lack of national guidelines and procedures, sociocultural factors, and other variables. WHO advises administering the loading dose of magnesium followed by referral to a higher level medical institution for primary care facilities where the complete schedule of magnesium sulphate cannot be administered or when the onset of subsequent problems is anticipated. So, a key component of the plan for tackling the preeclampsia prob5lem is educating healthcare professionals and taking steps to boost their self-assurance. Magnesium sulphate for preeclampsia is used clinically with caution because studies comparing different regimens of the drug are of poor quality, are too small, and lack the statistical power to draw any accurate conclusions.[10]

While other potential causes of the aforementioned symptoms are being ruled out, magnesium sulphate medication should be started right away in instances with hypertension, symptoms of headache or impaired vision, with or without seizures, at 48 hours following delivery. We advise a loading dosage of 6 g to be given over 30 minutes, followed by a maintenance dose of 2 g/hour for at least 24 hours after the last seizure, and that urine output, blood pressure, and maternal symptoms should be regularly watched after discontinuing magnesium sulphate. Antihypertensive therapy should be given to the patient if they only have severe hypertension in order to stabilise their blood pressure at 150/100 mm Hg. To rule out the presence of any additional cerebral diseases, brain imaging with magnetic resonance imaging and, if necessary, angiography should be done if the condition does not improve with such therapy, the patient continues to have seizures despite magnesium sulphate therapy, or the patient still experiences cerebral symptoms.[8]

CONCLUSION

The delivery of the foetus and placenta, the sole treatment for preeclampsia, entails severe morbidity and death for the newborn. Preeclampsia is a primary cause of maternal morbidity and mortality globally. Despite the fact that better antenatal surveillance and early therapies have considerably reduced preeclampsia-eclampsia mortality in the United States, postpartum and lifetime sequelae of preeclampsia have increased in number and significance. We now know that women with a history of preeclampsia are at an increased risk for dementia and CVD, in later life, including acutely fatal myocardial infarction without the progressive, warning symptoms of the acute coronary syndrome. It is unclear whether the risk precedes and confounds preeclampsia or is a result of it. Other opportunities exist in areas like better risk classification and medicines, where new developments are imminent. Even while research on maternal immune response and placental oxidative stress continues to offer fascinating insights, the maternal angiogenic factor imbalance and its implications on vascular function may be the most promising field of study. The ratios of proangiogenic and antiangiogenic factors, such as PlGF and sFLT1 and sENG, are being used in risk stratification techniques, and they have demonstrated high detection rates for preterm preeclampsia when combined with other predictive elements. They have also demonstrated high negative predictive value when used as an isolated assay. Preeclampsia symptoms are reduced and gestation is greatly prolonged when antiangiogenic proteins are removed using plasma apheresis compared to controls, Recombinant human PlGF and siRNA have produced encouraging effects in animal models, suggesting potential therapeutic alternatives to premature delivery, according to studies, and siRNA. Most crucially, risk-stratification techniques based on antiangiogenic factors have previously demonstrated to be reliable, effective, and affordable, opening the door to their use in nations with underdeveloped healthcare systems. preeclampsia has the highest fatality rate.

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