Medical Laboratory Journal
Online ISSN: 2538-4449
Golestan University of Medical Sciences

The pathophysiological spectrum of maternal complications of pregnancy-induced hypertension: Review Article

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Abstract

Background: Pregnancy-induced hypertension (PIH) is a multi-system disorder affecting 6-8% of pregnancies in the U.S. and contributing significantly to maternal mortality, accounting for 16% in developed countries. It progresses from preeclampsia to eclampsia, leading to multi-organ damage through mechanisms such as oxidative stress, placental ischemia, and endothelial dysfunction. While the exact pathogenesis remains unclear, genetic, immunologic, and environmental factors are implicated. The American College of Obstetricians and Gynecology (ACOG) recommends initiating treatment when diastolic blood pressure exceeds 105-110 mmHg.

Methods: This narrative review examines existing literature on PIH, including epidemiological data, pathophysiological mechanisms, clinical management guidelines, and associated complications such as abnormal placentation, oxidative stress, and endothelial dysfunction.

Results: This study demonstrates that hypertensive disorders of pregnancy (HDP) significantly impact maternal and fetal health, particularly in developing countries with limited healthcare access. Early detection and continuous monitoring play a key role in reducing complications. Additionally, HDP is associated with increased long-term cardiovascular and metabolic risks, highlighting the importance of postpartum follow-up.

Conclusion: HDP poses a serious threat to maternal and fetal health, with potential long-term consequences. Effective management requires early diagnosis, close monitoring, and postpartum follow-up. Global implementation of risk assessment and targeted care strategies can help reduce the burden of this condition. Strengthening healthcare systems and increasing awareness among healthcare providers and patients are essential steps toward improving outcomes.

Article Type: Review Article

Article History

Received: 8 May 2024
Received in revised form: 3 July 2024
Accepted: 11 June 2025
Available online: 16 June 2025
DOI: 10.29252/mlj.19.3.9

Keywords

Eclampsia
Placenta
Pre-Eclampsia
Hypertension, Pregnancy-Induced

Introduction

Hypertensive disorders in pregnancy encompass a spectrum of conditions, including chronic hypertension, gestational hypertension, preeclampsia, eclampsia, and chronic hypertension with superimposed preeclampsia. Preeclampsia is defined by new-onset hypertension (Systolic blood pressure ≥140 mmHg or diastolic ≥90 mmHg) after the 20th week of gestation, often accompanied by proteinuria or end-organ dysfunction. Clinical manifestations may include headaches, visual disturbances (Including blindness), dyspnea, peripheral edema, and epigastric or right upper quadrant pain, which are signs of imminent eclampsia. Eclampsia, a rare but life-threatening complication, involves tonic-clonic seizures in a patient with preeclampsia and represents a medical emergency (1).

The risk of preeclampsia is significantly elevated in women with preexisting conditions such as diabetes, obesity, chronic hypertension, or advanced maternal age below 20 or above 40 years. Additional risk factors include primiparity, multiple gestations, family history of gestational hypertension, assisted reproductive technologies (e.g., *in vitro* fertilization), and genetic predisposition. Other contributing factors may include nutritional deficiencies, anemia, urinary tract infections, thrombophilia, high-altitude residence, placental abnormalities (e.g., molar pregnancy, hydrops), and psychological stress (2).

The exact pathogenesis of preeclampsia remains unclear; however, current evidence suggests that placental dysfunction plays a central role. Inadequate remodeling of spiral arteries leads to reduced uteroplacental blood flow, triggering the release of pro-inflammatory cytokines, chemokines, and anti-angiogenic factors into maternal circulation (1,2).

The mechanism behind eclampsia -especially, the development of generalized tonic-clonic seizures- is not fully understood. However, it is hypothesized that cerebral autoregulation failure, similar to hypertensive encephalopathy, causes blood-brain barrier (BBB) disruption, resulting in cerebral edema and neuronal hyperexcitability (3).

If not promptly diagnosed and managed, hypertensive disorders in pregnancy can lead to severe maternal and fetal complications, including intrauterine growth restriction, placental abruption, preterm birth, and even death. Thus, early recognition and intervention are critical to improving outcomes.

Definitions and diagnostic criteria

I. **Gestational hypertension** is defined as systolic blood pressure greater than or equal to 140 mmHg and diastolic blood pressure greater than or equal to 90 mmHg, usually after 20 weeks of gestation, in the presence of proteinuria and edema, which typically resolve within weeks after delivery (4).

II. **Chronic hypertension** is defined as hypertension that develops before pregnancy or before 20 weeks of gestation. It might persist for more than 12 weeks after delivery (5).

III. **Preeclampsia** is defined as systolic blood pressure greater than or equal to 140 mmHg and diastolic blood pressure greater than or equal to 90 mmHg, and proteinuria (>0.3 g/day) developing after 20 weeks of gestation in women with normal blood pressure before pregnancy (6). However, some researchers have proven that Preeclampsia can occur without proteinuria in advanced disease stages (Table 1).

American College of Obstetricians and Gynecologists (ACOG) no longer considers proteinuria as a necessary criterion for diagnosing Preeclampsia while considering other factors listed in Table 1 as a possible diagnostic parameter (7,8).

IV. **Preeclampsia superimposed on chronic hypertension** is defined as the presence of maternal chronic hypertension with the development of Preeclampsia, which can progress to Eclampsia. This definition has been evolving in recent years.

V. **Eclampsia** is a term used to define a pre-eclamptic patient who develops generalized tonic-clonic seizures after 20 weeks of gestation during the intrapartum period, or within a few days postpartum (9). It occurs in 2-3% of women with severe manifestations who are poorly managed for Preeclampsia.

Table 1. Diagnostic criteria for preeclampsia based on American College of Obstetricians and Gynecology Guidelines (ACOG)

Hypertension	mmHg on two occasions at least four hours 140،90 ≤ apart or mmHg on two occasions within minutes 160،110≤ The new onset of hypertension and one of the following can be used for diagnosis
Proteinuria	mg/24 h (or this amount extrapolated from a timed 300≤ (collection or Protein/creatinine ratio ≥0.3 (each mL/4L) Dipstick reading of 1+ used only if other measures are) (unavailable
Thrombocytopenia	Platelet count < 100,000/μL
Renal insufficiency	Serum creatinine ≥1.1 mg/dL of Doubling of serum creatinine in the absence of otherrenal diseases
Impaired liver function	Twice the normal blood concentrations of liver transaminases (AST and ALT)
Pulmonary edema	-
Cerebral or visual symptoms	-

Pathophysiology

Placental ischemia

Evidence supports the crucial roles of genetic, immunological, and environmental factors with abnormal placentation in the ischemic changes of the placenta and subsequent remodeling. The increased demand in pregnancy allows the spiral arteries to undergo changes that increase blood flow, enhancing their capacity to enable adequate oxygen and nutrient delivery to the growing fetus (10).

In Preeclampsia, immunologic damage, fetal hypoxia, and trophoblastic invasion of these spiral arteries, typically occur around 8 to 16 weeks of gestation. This invasion of the trophoblast leads to a failure in remodeling. Due to the absence of vascular remodeling of the resistant vessels into high-capacitance vessels, there is a decrease in blood flow to the growing fetus. This ultimately results in ischemia, inflammation, cell death, and damage (11). The ischemia and inflammatory process involves the release of pro-inflammatory and anti-angiogenic factors, such as cytokines, chemokines, reactive oxygen species (ROS), and the angiotensin II type 1 receptor autoantibody (AT1-AA) into the maternal circulation, leading to widespread endothelial activation, upregulation of the endothelin system, failure of vascular remodeling and increased sympathetic nerve activity, and vasoconstriction causing hypertension (Figure 1).

Imbalance in angiogenic factors

In normotensive pregnancies, a decrease in placental oxygen and an increase in progesterone triggers the release of various chemokines and cytokines, including placental growth factor (PlGF), matrix metalloproteinases (MMP-1, MMP-2, MMP-9), and vascular endothelial growth factors (VEGF**).** These substances are proangiogenic and stimulate the release and action of prostaglandins and nitric oxide (NO), ultimately inducing vasodilation (11). NO induces vasodilation, angiogenesis, and vasculogenesis by promoting VEGF activity, leukocyte adhesion, and placental trophoblastic invasion. The human system requires tetrahydrobiopterin (BH4) for optimal endothelial nitric oxide synthase (eNOS) activity, facilitating NADPH-derived electron transfer from eNOS reductase to the oxygenase domain for converting L-arginine into NO and L-citrulline (2).

However, several imbalances in these cytokines and chemokines are observed in pre-eclamptic patients. For instance, soluble Fms-like tyrosine kinase (sFlt-1) opposes the action of vascular endothelial growth factors (VEGF) and PlGF (Figure 1). Factors such as transforming growth factor-β (TGF-β) also counteract nitric oxide, contributing to an altered balance between pro and anti-angiogenic factors. This eventually leads to endothelial dysfunction and impaired vasodilation in Preeclampsia via decreased NO production and endothelin (ET-1) release (12,13).

The decrease in vasodilators such as NO and prostacyclin and the upregulation of endothelin, thromboxane, superoxide, and increased vascular sensitivity to angiotensin II have been constantly shown to play a role in the development of hypertension by impairing renal function and increasing total peripheral resistance and decreasing renal natriuresis leading to high blood pressure (14,15)

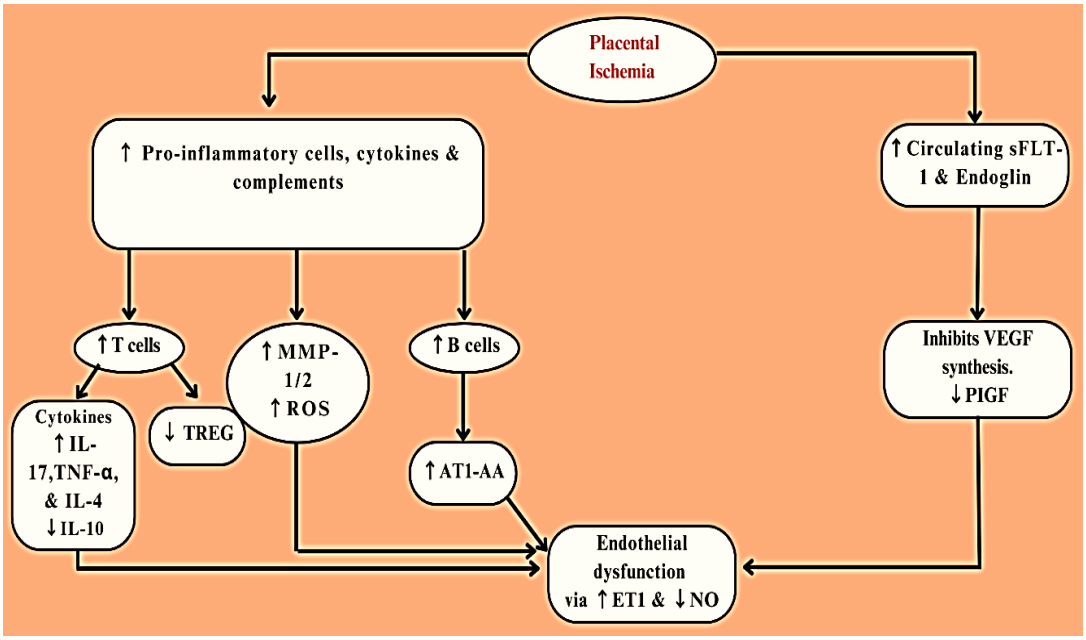

Figure 1. The pathology of placenta ischemia

The oxidative stress in Preeclampsia increases ROS by tumor necrosis factor-alpha (TNF-*α), interleukin (IL-6), activated neutrophils, and antithrombin-1 and vice versa.* ROS causes lipid peroxidation, leading to endothelial damage, proliferation, migration, and angiogenesis. In addition, ROS prevents insulin from facilitating cellular glucose uptake, contributing to further tissue damage (16,17).

In Preeclampsia, there is depletion of BH4 by oxidative stress, followed by eNOS instability and uncoupling, leading to reduced NO production and increased superoxide generation. The overwhelming presence of inherent antioxidants in the body caused by stressors generated by Preeclampsia may also play an important role (18,19). A study documented that the urinary oxidative stress marker, known as urinary 8-oxoGuo excretion, is associated with albuminuria, and the excretion can be linked to cardiovascular mortality risk in patients with diabetes mellitus. Preeclampsia is strongly linked to albuminuria, diabetes mellitus, and cardiovascular mortality risk (20,21).

Immunological dysregulation

Many genetic studies on Preeclampsia have demonstrated the activation of innate and adaptive immune systems. The resultant effects of this are the production of the unique complex with the maternal killer cell Ig-like receptor (KIR) MHC by fetal extravillous trophoblasts that challenge the mother's immune system, cause inappropriate secretion of chemokines and cytokines by Natural killer cells, and ultimately impact trophoblast invasion (Figure 1). In pre-eclamptic patients, TNF-α and interferon (IFN-γ) produced by T helper cells (Th1) in pregnancy causes trophoblastic invasion into the uterine spiral arteries, subsequently leading to a decrease in the production of IL-4 and IL-10 (Anti-inflammatory cytokines). Decreased production of anti-inflammatory cytokines may stimulate an increased secretion of inflammatory cytokines, making the patients susceptible to the development of maternal intravascular disease (22). In a similar pattern to the cytokine imbalances seen in autoimmunity, Preeclampsia is also associated with irregularities in the secretion of pro-inflammatory cytokines such as Th1 and Th17 and a decline in anti-inflammatory cytokines such as Treg and Th2 (22,23).

Brewer et al. reported that 46 out of 47 patients diagnosed with Eclampsia developed PRES syndrome; the first case was in 1996, while another study recorded about 92.3% and 19.2% cases of confirmed Eclampsia and Preeclampsia, respectively demonstrated **posterior reversible encephalopathy syndrome** (PRES) using imaging studies (24-26). The pathogenesis of Eclampsia may involve TNF-α and AT1-AA, resulting in endothelial injury, edema, and vascular narrowing, leading to a decrease in blood flow to the brain (8). Additionally, damage to the BBB leads to hypertensive encephalopathy and cerebral edema. Several other studies have proven that PRES is present in most patients diagnosed with Eclampsia (24,25). Lowering blood pressure in these women might slow down cerebral edema and limit potential brain damage. The exact relationship between PRES and Eclampsia or severe Preeclampsia is not fully understood, and further research is needed to understand this association (27). PRES is characterized by confusion, headache, loss of consciousness, seizure, visual impairment, and blindness, with other signs of vascular edema.

Maternal complications

In recent years, some researchers have indicated that women diagnosed with hypertensive disorders of pregnancy face elevated risks of both immediate and long-term complications. However, the current guidelines for managing hypertension during pregnancy have not evolved in line with those for the general population, mainly because studies addressing the safety and benefits of lowering blood pressure in pregnancy are lacking (28). It remains an underestimated risk factor for future cardiovascular, cerebrovascular, and kidney disease, developing often in the perimenopausal period of a woman's life. The benefits of antihypertensive medication in patients with Preeclampsia cannot be over-emphasized. Immediate intravenous infusion of antihypertensive medication is necessary due to its rapid effect in eclamptic patients. Poor control of blood pressure can lead to several complications, such as increased intracranial pressure, renal failure, heart attack, pulmonary edema, and a high risk of mortality for both mother and fetus (29). It is also worth mentioning that the urge to decrease the blood pressure too quickly should be avoided due to the increased risk of hypotension leading to decreased organ perfusion in the mother and placental circulation, which may lead to fetal hypoxia, distress, and demise.

The aim of antihypertensive drug treatment is the gradual reduction in blood pressure. Hypertensive medications are employed to facilitate a gradual reduction in blood pressure, aiming for a systolic pressure below the range of 150-140 mmHg and a diastolic pressure between 90-105 mmHg, along with a MAP II ranging from 126-105 mmHg. Continuous monitoring of the fetus's heart rate is conducted through cardiotocography (CTG) recording. According to Sibai, maintaining systolic blood pressure values lower than 160 mmHg, yet not dipping below 140 mmHg, is recommended (30,31). Similarly, keeping diastolic blood pressure below 110 mmHg but not below 90 mmHg is advised to uphold proper maternal cerebral perfusion pressure and ensure uteroplacental blood flow. Reducing blood pressure by more than 10-15% of the initial value within one hour is discouraged.

Renal complications

Several studies have indicated a heightened occurrence of microalbuminuria up to five years post-delivery in individuals with a history of Preeclampsia. Numerous mechanisms are postulated to elucidate the correlation between Preeclampsia and subsequent kidney disease (32). One potential explanation is that Preeclampsia induces direct injury to the endothelial cells in the kidneys, increasing vascular resistance, loss of podocytes, persistent proteinuria, and hypertension that perpetuates subsequent damage (Figure 2). Several studies reveal that about 20% to 40% of women who experienced Preeclampsia exhibit microalbuminuria three to five years after childbirth, a prevalence significantly higher than the 2% observed in women without a history of Preeclampsia. The dysregulation of the Renin-Angiotensin-Aldosterone System (RAAS) and the imbalance between angiogenic and anti-angiogenic factors, shared characteristics of both Preeclampsia and chronic kidney disease (CKD), may contribute to why a history of Preeclampsia predisposes women to CKD (33).

An investigation showed that when Preeclampsia occurs during the first pregnancy, it increases the risk of end-stage renal disease (ESRD) shortly, characterized by a reduced Glomerular Filtration Rate, Proteinuria, and Cortical Necrosis. While the absolute risk of ESRD after any pre-eclamptic pregnancy was low (14.5/100,000 person-years), the adjusted relative risk was elevated at 4.3 (95% CI 3.3-5.6). Notably, in women with more than two pre-eclamptic pregnancies, the adjusted relative risk surged to 10.9 (95% CI 5.0-23.8). It is important to note that, as this study relied on registry data, patients with preexisting renal disease were not excluded, and this will affect the overall risk (34,35).

It remains unclear whether it is the hypertensive pregnancy itself that elevates the risk of these complications or if there is some damage to the endothelium in the mother's blood vessels that manifests at various life stages. This calls for close follow-up and adequate lifestyle modification to decrease the risk of these long-term complications (36). To better understand the renal complication of Preeclampsia, Geisinger Health System was used to compare pregnancy complications with Preeclampsia with those without Preeclampsia. The findings reveal an elevated risk among pregnant individuals with Preeclampsia for subsequent hypertension, diminished estimated Glomerular Filtration Rate (eGFR), and albuminuria. In the meticulous matching of multiple characteristics, individuals with Preeclampsia exhibited an increased risk in the development of chronic hypertension (H.R., 1.77 [95% CI, 1.45-2.16]), eGFR<60 mL/min/1.73 m2 (H.R., 3.23 [95% CI, 1.64-6.36]), albuminuria (H.R., 3.60 [95% CI, 2.38-5.44]), and subsequent preeclampsia episodes (H.R., 24.76 [95% CI, 12.47-48.36]) in comparison to matched controls devoid of Preeclampsia. A cohort study of 34,581 women who have been pregnant in Olmsted County, Minnesota, USA, from 1976 to 2010 revealed a 4-fold increase in ESRD and a median duration from pregnancy to the time of diagnosis of ESRD of 17.7 years (28).

Pulmonary complications

Pulmonary edema can develop because of multiple factors, such as hypervolemia, left ventricular failure, and pulmonary capillary leakage (37,38). Pulmonary edema, broadly categorized as either cardiogenic or non-cardiogenic, presents challenges in pregnant women due to physiological adaptations. In pregnancy, cardiac output peaks postpartum, while plasma volume increases from sodium and water retention, enhancing preload. Simultaneously, vasodilation leads to decreased afterload. Normal pregnancy sees a massive decline in pulmonary vascular resistance akin to systemic vascular resistance. The

reduced colloid osmotic pressure/pulmonary capillary wedge pressure gradient, by approximately 30%, heightens vulnerability to pulmonary edema. Preeclampsia, with increased pulmonary vascular permeability, further exacerbates this risk, emphasizing the importance of monitoring cardiac preload and pulmonary capillary permeability in pregnant individuals. In cases of vascular damage, direct airway compromise alters pressures, leading to fluid leakage into the alveoli and subsequent edema (39).

Another theory is that a rise in systemic vascular resistance triggers significant alterations in ventricular myocardium loading conditions, contributing to diastolic filling irregularities, and fostering an ischemic substrate. This, in turn, creates the potential for heart failure, pulmonary edema, and eventually death (40). Likewise, the emergence of pulmonary edema may stem from combining these elements. Pulmonary edema is one of the most severe complications of Preeclampsia, and this should be considered in cases of dyspnea in pregnant individuals. Although pulmonary edema may have a favorable prognosis, it can serve as an indicator of underlying and undetected dilated cardiomyopathy. Some studies have indicated a few cases of atypical toxemia of pregnancy without an increase in blood pressure and proteinuria. In these unique cases, pulmonary edema was the major presentation typified by conventional supportive treatment, which included diuretics, oxygen, and respiratory support. However, the final decision remains on placental and fetal delivery (41). A cohort study of pre-eclamptic women found 5.6% with pulmonary edema. It was recorded that they had higher postpartum rates and increased risk of cesarean section deliveries. Also, among these pregnancies, 81% needed intensive care, and 60% required mechanical ventilation. Mechanical ventilation was associated with Eclampsia ($p = .04$), and the scoring model used in the study predicted a 46%–99% likelihood of requiring mechanical ventilation (37).

Pulmonary edema in pre-eclamptic patients usually occurs in the third trimester. It is characterized by sudden shortness of breath, coughing up pink or frothy sputum, palpitation, lightheadedness, dizziness, and wheezing (34). Acute pulmonary edema is a rare but potentially fatal complication in Preeclampsia, requiring heightened awareness of peripartum cardiomyopathy diagnosis and adequate follow-up of pregnant women diagnosed with Preeclampsia by healthcare professionals (41,39).

Cardiovascular complications

Cardiovascular disease is one of the significant complications of Preeclampsia, and several studies have proven that pregnant women diagnosed with hypertensive disorders of pregnancy have an increased risk of developing cardiovascular disease later in life (42). According to the European Society of Cardiology (ESC), women with Preeclampsia have four times increased risk of heart attack within the first ten years of delivery than women without Preeclampsia. The risk was stratified according to age, and it was discovered that age also plays a significant role. They found out that women aged between 30 and 39 years with a history of preeclampsia have a three to five-fold higher risk of developing heart attack when compared with those of similar age with no history of Preeclampsia. A study that assessed about 1,157,666 women showed that about 2% of patients with Preeclampsia in their first pregnancy had a heart attack within 20 years after delivery (43).

It has been proposed that pregnancy acts as a stressor on the heart during pregnancy, thus making the heart undergo a few changes, such as increased cardiac output, heart rate, and stroke volume. This occurs in the third trimester to allow the growing fetus to support the growing fetus with adequate nutrients. Early in pregnancy, plasma volume and the mass of red blood cells begins to expand. When the intravascular volume exceeds the cell mass, dilutional anemia of pregnancy occurs due to expansion in volume due to sodium and water retention. Uteroplacental blood flow increases in normal pregnancy to allow for adequate blood supply of the intervillous spaces and promote fetal growth. There is a trophoblastic invasion of the spiral arteries, which are replaced by fibrinoid material, transforming them into large, dilated blood vessels to increase blood flow to the placenta and fetus. It has been observed that preeclampsia and cardiovascular diseases share similar risk factors, such as advanced maternal age, obesity, dyslipidemia, diabetes mellitus, and endothelial damage, leading to a pro-inflammatory state. Pregnancy serves as a trigger and cardiovascular stressor that stimulates the development of cardiovascular disease. Some researchers also claim that it helps to identify those who are at risk of developing cardiovascular disease later in life (44,45).

A research study conducted among 15,000 women with Preeclampsia noted that most women had other comorbidities such as chronic hypertension, increased body mass index, and hypercholesterolemia (45). In multigravida with elevated blood pressure and Preeclampsia, it was observed that these risk factors increased the occurrence of the disease. Another study conducted in the Netherlands showed that women with pregnancy complicated by Preeclampsia had an increased prevalence of metabolic syndrome (46). Some clinical evidence has shown that some of these changes that occur as a result of Preeclampsia can eventually lead to long-term complications. A study of hospital records was conducted in six different states, and it was found that 535 patients had Peripartum cardiomyopathy, 29.3% had Preeclampsia, and 46.9% had hypertension (47,48). The cardiovascular complication may be characterized by an S3 heart sound and dyspnea on exertion. An echocardiogram reveals decreased ejection fraction, usually less than 45%, and left ventricular systolic dysfunction. This should not be confused with heart failure induced by pulmonary edema, in which the ejection fraction is not affected despite sharing almost similar pathophysiology, which is diastolic dysfunction (49,50).

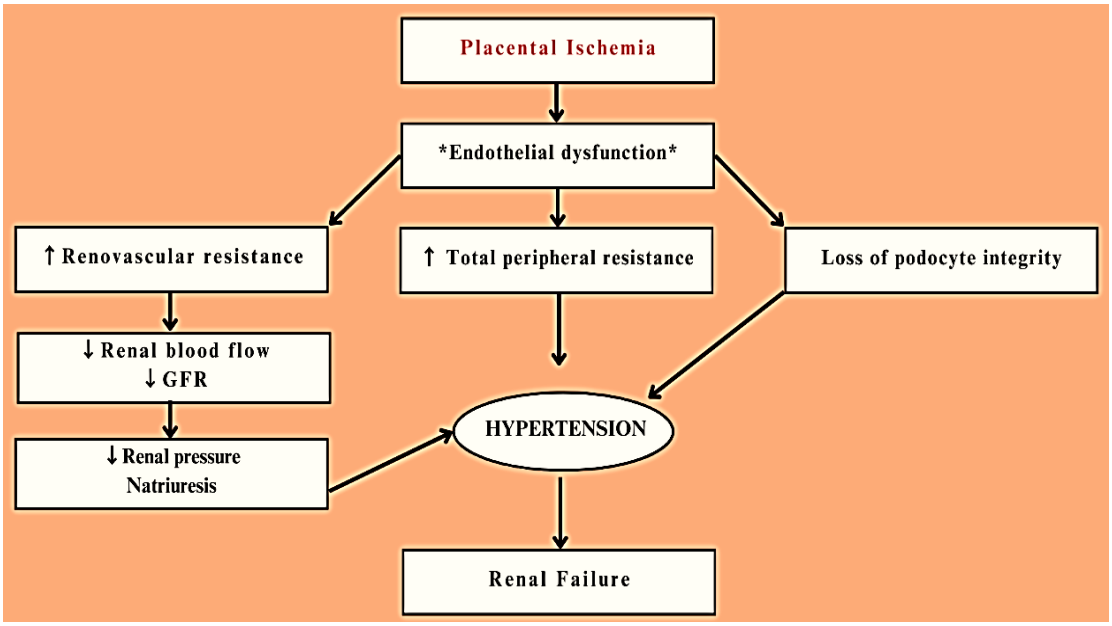

Figure 2. Pathophysiology of renal failure in preeclampsia

Central nervous system complications

According to the ESC, women diagnosed with Preeclampsia have an increased risk of developing stroke within ten years of delivery than those without Preeclampsia. The raised likelihood of neurologic disease in those with a history of Preeclampsia persisted throughout adulthood, with women over 50 years of age at double risk compared to their peers with no history (44). Hypertensive encephalopathy is caused by a sudden and sustained increase in blood pressure, often due to poorly controlled primary hypertension. This elevated blood pressure surpasses the brain's autoregulation capacity, leading to disruptions in the BBB, interfering with cerebral perfusion and the development of brain edema (Figure 3). Individuals with previously normal blood pressure may exhibit encephalopathy symptoms at levels as low as 160/100 mmHg. Although hypertensive emergencies are rare, hypertensive encephalopathy accounts for 15% of cases and has contributed to increased hospitalizations in the United States between 2000 and 2011. Figure 3 shows the initial pathogenetic pathways associated with the loss of cerebral autoregulation due to severely elevated blood pressure ("breakthrough theory") or intense vasoconstriction in response to acute hypertension ("overregulation theory") (4). Preeclampsia/eclampsia affects many systems and is linked to abnormal vascular responses during placentation: increased systemic vascular resistance, enhanced platelet aggregation, coagulation system activation, and endothelial cell dysfunction (Figure 3). Elevated blood pressure and peripheral resistance may be influenced by heightened sympathetic vasoconstrictor activity, contributing to various complications (51). Patients with hypertensive encephalopathy may exhibit severe headaches, altered mental status, visual disturbances, and seizures. In the absence of inadequate management, coma and death may occur. Immunosuppressive medications such as steroids, as well as seizures, infection, shock, and metabolic abnormalities, can further complicate the condition by damaging the BBB through various mechanisms, including direct toxic effects, endothelial dysfunction, vasoconstriction, and thromboxane and prostacyclin imbalances. Computed tomography (CT) scans in hypertensive encephalopathy patients may be normal or show signs of cerebral edema. Posterior leukoencephalopathy visible on Magnetic Resonance Imaging (MRI) scans parallels the clinical presentations. Hypertension may be a significant risk factor for PRES (52). Neurological manifestations of Preeclampsia can range from headaches, visual symptoms such as blindness, cerebral edema, seizures, or acute cerebrovascular disorders such as intracerebral hemorrhage. Researchers have found that patients with migraines were linked to a 1.8-fold increased risk of Preeclampsia. The most significant risk was observed in women aged 30 years or older with a diagnosis of migraines. Additionally, the association between migraines and Preeclampsia seemed to be influenced by pre-pregnancy overweight status. It was observed that women who were overweight and had migraines had a higher risk of Preeclampsia. The underlying pathophysiology of migraine and Preeclampsia is similar, including inflammation, endothelial dysfunction, and alterations in blood vessel responsiveness. Pregnant and postpartum women who complain of headaches should be evaluated appropriately; adequate clinical history, detailed physical examination, and imaging studies should be requested. A focused history of any form of headache should be elicited from patients as part of routine obstetrical care. This will help in early diagnosis and avoid hidden complications (46). One of the most dreaded complications of Eclampsia is cerebrovascular accident. In 1995, a study was carried out in France involving approximately 31 patients diagnosed with stroke during pregnancy. Eclampsia accounts for nearly half of both hemorrhagic and ischemic strokes. The observed manifestations included cerebral hemorrhage, headache, cortical blindness, PRES, and seizures (53). In another study by Martin et al., about 28 women who had severe preeclampsia/Eclampsia with stroke, it was observed that their systolic blood pressures were as high as 155 mmHg just prior to the occurrence of cerebrovascular events (54). Notably, less than six patients reached a diastolic blood pressure of 105 mmHg, thus suggesting that, according to the current NHBPEP and ACOG guidelines, they might not be considered candidates for treatment. The study reported a maternal death rate of 53.6%, and merely 3 out of the 28 patients showed no lingering impairments following the stroke. Consequently, the authors proposed a shift in the treatment to help address systolic blood pressure levels of 155-160 mmHg in severe pre-eclamptic and eclamptic patients (55). Therefore, this confirms that neurological complications are a significant contributor to maternal morbidity and mortality in pre-eclampsia-eclampsia.

Socioeconomic complications

Hypertensive disorders were recorded to have caused the death of about 42,000 worldwide in the year 2015 (56). This was mainly linked to low socioeconomic status. This vast difference has enabled us to understand that inequality exists in the health care of women with Preeclampsia and other hypertensive disorders of pregnancy. Researchers are trying their best to increase awareness of the disease and improve the quality of care to limit the complications associated with the disease. Lindquist et al. demonstrated a connection between socioeconomic challenges and pregnancy complications in both the intrapartum and postpartum periods. Individuals with lower incomes are primarily at risk of fetal and maternal complications, such as preterm delivery and low birth weight, as compared to those with higher incomes (57,58). Another study proved that women with lower financial status have a higher likelihood of having a cesarean delivery when compared with those of higher status (58). Additional studies by different researchers have substantiated that lower socioeconomic groups exhibit a higher risk of pregnancy complications compared to their higher socioeconomic counterparts. Moreover, individuals in lower socioeconomic groups face an increased likelihood of experiencing severe complications, including mortality, in comparison to those who are professional (59,60).

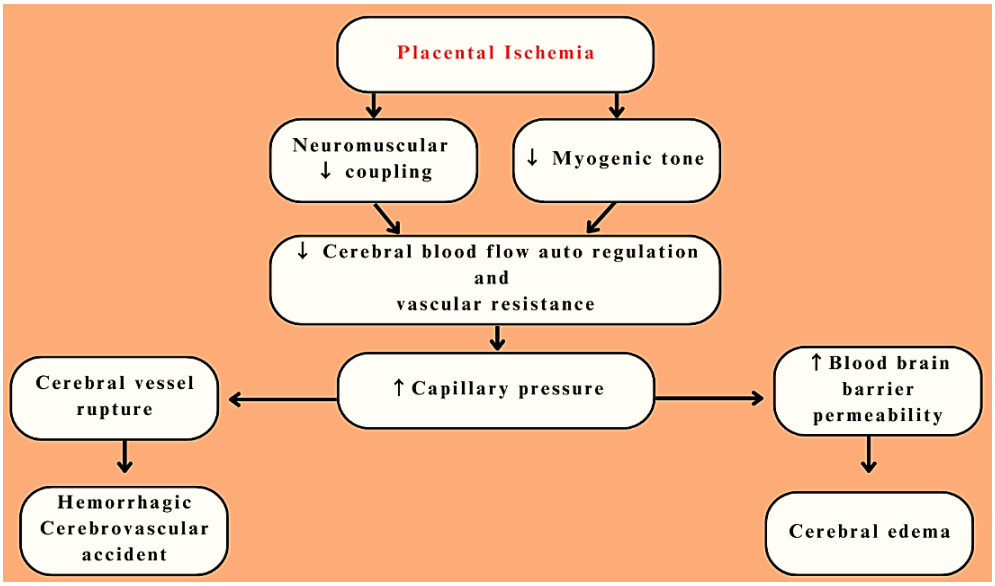

Figure 3. Cerebrovascular complications of pregnancy-induced hypertension

Economic recession worldwide has had a significant impact on maternal health and has led to some of the inequality that persists to date, thus a rise in Preeclampsia. Studies have shown that the expensive health cost of Preeclampsia is because of medical services needed to manage pregnant and postpartum women and their babies effectively, who will be born prematurely (61). A study was conducted to examine the immediate healthcare expenses linked to Preeclampsia using official documents to gather data and estimate the additional financial burden of medical care for women with Preeclampsia and their infants compared to those without the condition. Despite the widespread prevalence of Preeclampsia, it has not received adequate attention or investigation, despite its significant contribution to complications in maternal-fetal health during pregnancy and puerperium. There exist varying modalities and measures based on location to improve the quality of healthcare provided to women, particularly those with Preeclampsia, with a disastrous end fatality culminating in debilitation and death (62).

The average number of deaths related to pregnancy and childbirth is about 800 per day, while the vast majority occur in developing countries, and a smaller percentage occurs in developed countries. An annual report of maternal death and fetal death from Preeclampsia is over 70,000 and 500,000, respectively. Most of these deaths occurred because of inadequate antenatal care, unhealthy reproductive practices, lack of access to good health care, financial burden, and socioeconomic inequalities in healthcare (63). The risk of mortality in a pre-eclamptic patient in a developing country is seven times higher than in a developing country and about 10 to 25 percent maternal death.

It is essential to ensure adequate monitoring and care of women diagnosed with Preeclampsia to prevent Eclampsia and other health complications, primarily in women in remote areas inaccessible to health care. Factors such as decreased awareness and lack of understanding of presenting symptoms, distance, religious practices, poverty, and inadequate personnel are some of the factors that further increase mortality, which is an ultimate complication of Preeclampsia and Eclampsia (64). To lower the mortality risk and improve medical care amongst pregnant women, all these factors will have to be addressed one after the other at all levels of the healthcare system. This might include health education, increasing awareness of the signs and symptoms of Preeclampsia, sustainable monitoring, and improving the health care system (65).

Hematologic and digestive system complications

Pregnancy is generally associated with gastrointestinal and hematological symptoms. Nausea and vomiting, gastroesophageal reflux, and constipation are common manifestations of pregnancy. Hyperemesis gravidarum, intrahepatic cholestasis, Toxemia of Pregnancy (Preeclampsia, Eclampsia, and hemolysis, elevated liver enzymes, and low platelet [HELLP] syndrome), and acute fatty liver of pregnancy are distinct disease entities peculiar to pregnancy. All these manifestations, including gallstones, hematological manifestations, and any other systemic disorders, may worsen or precipitate in pregnancy.

The pathophysiology and exact mechanism are still not well understood, but it is believed to be from multiple pathways like genetic abnormalities, hormonal abnormalities, and unspecified idiopathic routes (66). Progesterone has an inhibitory effect on the smooth muscle of the pylorus and small bowel, decreasing gastrointestinal motility, delaying gastric emptying, and inhibiting hepatic glucuronosyltransferase, thereby causing nausea with vomiting and cholestasis, respectively (66). Estrogen can decrease the permeability of the hepatocyte basolateral membrane to bile, constituting decreased bile secretion in synergism with progesterone. Recent studies have investigated the mutation of hepatobiliary transporter genes (Hepatic phospholipid transporters (MDRD3, ABCB4)) and bile salt export pump (BSEP, ABCB11) in pregnant women as a possible cause of cholestasis in addition to the earlier stated mechanism. The other sequels linked to some of these pathways are acute liver failure, a rare complication with an incidence of 5/100,000, and spontaneous hepatic rupture, which occurs in less than 2% of cases (66,67). In Preeclampsia, most unique hematological and gastrointestinal complications share similar pathophysiological mechanisms like an abnormal vascular response to placenta growth associated, endothelial dysfunction, metabolic changes, increased inflammatory responses, generalized endothelial and microvascular injury resulting in microangiopathic anemia, hepatic artery vasospasm and vasoconstriction, periportal or portal fibrin deposits with necrosis of liver lobules and thrombocytopenia in addition to hemodilution anemia, marginal elevation of platelets and low albumin (66,67). HELLP syndrome is defined by the presence of hemolysis, elevated liver enzymes, and low platelets, occurring in 0.17-0.85% of all pregnancies, more frequently in older multiparous Caucasian women (>34 years) and potentially progressing into disseminated intravascular coagulation (DIC) (66,67). In general, the pathway favors a pro-coagulation state in pregnancy, constituting the development of a thromboembolic crisis. Cortical blindness, placenta abruption, cerebral hemorrhage, and pancreatitis are omplications of thromboembolism (66,67).

Abbreviations

National High Blood Pressure Education Program: NHBPEP; American College of Obstetricians and Gynecology: ACOG; Reactive Oxygen Species: ROS, Interleukin: IL; Angiotensin II Type 1 receptor Autoantibody: AT1-AA; Placental Growth Factor: PlGF; Matrix Metalloproteinases: MMPs; Vascular Endothelial Growth Factors: VEGF; Nitric Oxide: NO; Tetrahydrobiopterin: BH4; soluble Fms-like tyrosine kinase: sFlt-1; Transforming Growth Factor-β: TGF-β; Endothelin-1: ET-1; Tumor Necrosis Factor-alpha: TNF-α; Interferon-γ: IFN-γ; T helper cell: Th, regulatory T cell: Treg; Renin-Angiotensin-Aldosterone System: RAAS; Chronic Kidney Disease: CKD; estimated Glomerular Filtration Rate: eGFR; End-Stage Renal Disease: ESRD; Hemolysis, Elevated Liver enzymes, and Low Platelet: HELLP; Posterior Reversible Encephalopathy: PRES; Blood-Brain Barrier: BBB; Disseminated Intravascular Coagulation: DIC; endothelial Nitric Oxide Synthase: eNOS.

Conclusion

Hypertensive disorders in pregnancy are fatal medical conditions requiring adequate knowledge and rapid treatment responses with a high index of suspicion by medical professionals and patients. The mortality and morbidity associated with hypertensive disorders in pregnancy are high in developing and underdeveloped countries, but lower in the United States. The socioeconomic implication is high regardless of the geographical location. Although multiple pathogenetic mechanisms contribute to the development of various complications, the need for early detection and screening with proper monitoring remains a crucial methodology in controlling the disease and its progression. Furthermore, a thorough understanding of the disease is essential due to its long-term complications such as myocardial infarction, stroke, and metabolic disease. Follow-up of women with hypertensive disorders of pregnancy should never be overlooked to prevent or minimize long-term complications. Risk assessment and stratification strategies should be universally adopted, including regular monitoring of lipid profile, blood pressure, and blood glucose after delivery. There is a need for more research to better understand the pathophysiological process of the intertwined complications and evaluate various possible therapeutic measures and trials to address the inequality in global healthcare in preventing and treating hypertensive disorders in pregnancy.

Acknowledgement

Not applicable.

Funding sources

None.

Ethical statement

This review article is based on previously published studies, and no new human or animal data were collected. All sources have been properly cited, and the authors have adhered to ethical guidelines in academic writing, including avoiding plagiarism and ensuring transparency in reporting.

Conflicts of interest

The authors declare no conflict of interest.

Author contributions

All authors contributed to the article and unanimously approved the submitted version. CK created the diagrams and figures.

Data availability statement

Not applicable.

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How to Cite:

Okikiade A, Kanu C, Iyapo O, Omitogun O. The pathophysiological spectrum of maternal complications of pregnancy-induced hypertension: Review article. *Med Lab J.* 2025;19(3):9-16. http://dx.doi.org/10.29252/mlj.19.3.9