**Revised Pathophysiology of Pregnancy-induced hypertension(Pre-eclampsia):A Multisystemic Spectrum of the Maternal Complications.**

**ABSTRACT**

Pregnancy-induced hypertension(PIH) , also referred to as Toxemia of pregnancy(obsolete) is a spectrum of multi-systemic dysfunction in pregnancy, usually seen in the third trimester in approximately 6–8% of pregnancies in the United States, according to the National High Blood Pressure Education Program (NHBPEP). The World Health Organization reported that this multisystem disorder accounts for 16% of maternal deaths in developed countries and 1.8%-16.7% in most developing countries.

PIH includes a progression of disorders ranging from gestational hypertension to preeclampsia, eclampsia, and in some cases, HELLP syndrome (Hemolysis, Elevated Liver enzymes, and Low Platelet count). Among these, preeclampsia is the most extensively studied and clinically significant due to its potential to evolve into life-threatening eclampsia, leading to seizures, stroke, multi-organ failure, maternal and fetal death. The spectrum can progress with short and long-term complications that may impact significantly on the quality of life of both the fetus and the mother.

Though the pathogenetic mechanisms remain unclear, evidence supporting the roles of genetic, immunologic, and environmental factors is rapidly evolving.The disorder is now recognized as a multifactorial condition, with genetic predisposition, immune maladaptation, and environmental factors (such as diet, obesity, and stress) playing contributory roles. There is also increasing evidence that insulin resistance, preexisting metabolic syndrome, and abnormal immune tolerance to paternal antigens may predispose women to developing PIH. Preeclampsia, an initial spectrum of the disorder, begins with abnormal placentation with failure of adaption, inflammatory changes, permanent vascular and metabolic damages, and increasing risk of cardiovascular, renal, endocrine, neurological, hematological, and socioeconomic complications. Regardless of the initiating mechanism, oxidative stress, placenta ischemia hypoxia with release of toxic substances, and endothelial dysfunction play crucial roles. The stressors release antiangiogenic factors (such as soluble fms-like tyrosine kinase-1 or sFlt-1 and endoglin), oxidative stress, inflammatory cytokine leading to vasoconstriction, capillary leak, coagulation abnormalities, and the release of microparticles into the maternal circulation essentially cumulating to worsening multiple organ damage.

American College of Obstetrics and Gynecology (ACOG) recommends early recognition and regular antenatal screening with early treatment for preeclampsia when the diastolic blood pressure (DBP) is above 105–110 mm Hg. Treatment options include labetalol, nifedipine, and hydralazine as first-line agents. Delivery remains the definitive cure, particularly when severe features develop or gestational age exceeds 37 weeks. In cases of early-onset preeclampsia, expectant management under close monitoring may be considered to improve neonatal outcomes. This article elucidate the pathophysiological mechanism associated with the spectrum of maternal complications in Pregnancy-induced hypertension.

**Keywords:** Eclampsia, Endothelial dysfunction, Placenta ischemia, Preeclampsia, pregnancy-induced hypertension, Toxemia of Pregnancy.

**ABBREVIATIONS**

National High Blood Pressure Education Program :NHBPEP, American College of Obstetrics and Gynecology :ACOG, reactive oxygen species :R.O.S, interleukins :IL, angiotensin II type 1 receptor autoantibody :AT1-AA,placental growth factor : PlGF, matrix metalloproteinases :MMPs(1,2,9),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-α:TNF-α,Interferon-γ :IF-γ, T-helper cells: Th, Regulatory T -cell: TREG, Renin-Angiotensin-Aldosterone System :RAAS, chronic kidney disease :CKD, estimated Glomerular Filtration Rate :eGFR, End-Stage Renal Disease :ESRD, HELLP syndrome :Hemolysis, Elevated Liver enzymes, and Low Platelet, posterior reversible encephalopathy syndrome :PRES.

**INTRODUCTION**

Pregnancy-induced hypertension or hypertensive disorders in pregnancy include chronic hypertension, gestational hypertension, preeclampsia, Eclampsia, and chronic hypertension superimposed on preeclampsia. Preeclampsia is characterized by high blood pressure and protein in the urine, while Eclampsia is a rare but fatal complication of Preeclampsia with tonic-clonic seizure [1]. Preeclampsia is the new onset of hypertension after the 20th week of pregnancy, with a systolic blood pressure of 140 mmHg or higher or diastolic blood pressure of 90 mmHg or higher. It may also present with proteinuria and end-organ damage, such as headache, visual disturbances leading to blindness, dyspnea, edema, and epigastric or right upper quadrant abdominal pain (Imminent Eclampsia). The risk of Preeclampsia increases exponentially in the presence of comorbidities like diabetes, obesity, maternal age below 20 or over the age of 40, family history of gestational hypertension, history of diabetes or gestational diabetes, primiparity, genetics, and multiple gestations [2]. Other possible risk factors are preexisting urinary tract infection, anemia, nutritional deficiency, molar pregnancy, limited exposure to partner’s sperm, in vitro fertilization, thrombophilia, high altitude, large placenta, smoking, placenta hydrops, genetic and chromosomal anomaly, and mental stress [2].

The etiopathogenesis remains debatable, but there are studies supporting the presence of stressors activating syncytiotrophoblast to release pro-inflammatory cytokines, chemokines, and anti-angiogenic factors into the maternal circulation, leading to a decrease in uteroplacental blood flow with concomitant lack of remodeling of the spiral arteries [1][2]. The pathogenesis of new-onset generalized tonic-clonic seizures in a woman with untreated or poorly treated Preeclampsia is not well understood. However, it is hypothesized that irregularities in cerebral perfusion, similar to hypertensive encephalopathy, lead to blood-brain barrier damage [3]. This damage allows the passage of fluid, ions, and plasma proteins into the brain. Hypertension in pregnancy is associated with a spectrum of complications, both intrapartum and postpartum. It can eventually lead to the morbidity and mortality of the mother and fetus if not properly and timely diagnosed and treated.

**Definitions and Diagnostic criteria**

1. **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 gestation, in the absence of proteinuria and edema that normalizes within a few weeks after delivery [4].
2. **Chronic hypertension** is defined ashypertension that was present before pregnancy or diagnosed before 20 weeks gestation. It might persist for more than 12 weeks after delivery [5].
3. **Preeclampsia** is definedas Systolic blood pressure greater than or equal to 140 mmHg and diastolic blood pressure greater than or equal to 90 mmHg, with proteinuria (> 0.3 g/day) developing after 20 weeks of gestation in women with normal blood pressure prior to pregnancy [6]. However, studies have demonstrated that there is a possibility of having Preeclampsia without the presence of proteinuria due to advanced disease (see Table 1 for diagnostic criteria). American College of Obstetricians and Gynecologists (**ACOG**) no longer considers proteinuria as a necessary or mandatory criterion for diagnosing Preeclampsia while considering other factors listed in Table 1 as an alternative diagnostic criterion [7][8].
4. **Preeclampsia superimposed on chronic hypertension** is characterized by new-onset proteinuria or sudden worsening of BP in previously hypertensive patient, it is considered a precursor to eclampsia.” This definition has been evolving in recent years.
5. **Eclampsia** is a term used to define a pre-eclamptic patient who develops generalized tonic-clonic seizures after 20 weeks gestation within the intrapartum period and a few days postpartum [9]. It occurs in 2-3% of women with severe manifestations who are poorly managed for preeclampsia.

**PATHOPHYSIOLOGY**

***Placental ischemia***

Evidence supports the crucial roles of genetic, immunologic, and environmental factors with abnormal placentation, leading to ischemic changes of the placenta and subsequent remodeling. The increased demand in pregnancy causes 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].

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| In preeclampsia, inadequate trophoblastic invasion leads to failed spiral artery remodeling into high capacitant, low- resistant vessels, typically occurring between 8 and 16 weeks of gestation. |

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Due to the absence of vascular remodeling of the high resistance spiral arteries 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 process of 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, endothelin system upregulation, increased sympathetic nerve activity, and vasoconstriction causing hypertension (**Fig 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 promotes vasodilation and supports angiogenesis via VEGF mediated pathways while also reducing leukocyte adhesion, and placenta trophoblastic invasion. Likewise, the human system requires tetrahydrobiopterin (BH4) for optimal eNOS activity, which facilitates NADPH-derived electron transfer from eNOS reductase to the oxygenase domain to convert L-arginine to 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 (**Fig 1**). Factors such as 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 nitric oxide 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 hypertension[2].

The oxidative stress in P.E. increases Reactive oxygen species (ROS) by TNF-α, IL-6, activated neutrophils, and antithrombin-1 and vice versa. ROS causes lipid peroxidation with endothelial damage, proliferation, migration, and angiogenesis. In addition, ROS prevents insulin from facilitating cellular glucose uptake, contributing to further tissue damage.[2] In PE, there is depletion of BH4 by oxidative stress, followed by eNOS instability and uncoupling, leading to reduce NO production and more superoxide generation. The overwhelming presence of inherent antioxidants in the body caused by stressors generated by Preeclampsia may also play an important role [2]. 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 [2].

***Immunological dysregulation***

Evidence in many genetic studies of Preeclampsia 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 (**Fig 1**).

In pre-eclamptic patients, Tumor Necrosis Factor (TNF-α) and Interferon (IFN-γ) produced by T-helper cells (Th-1) in pregnancy cause trophoblastic invasion into the uterine spiral arteries, subsequently leading to a decrease in the production of IL-4 and IL-10 (anti-inflammatory cytokines). The 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 [14]. In a similar pattern to the cytokine imbalances seen in autoimmunity, Preeclampsia is also associated with irregularities in the secretion of pro-inflammatory cytokine-producing cells such as Th1 and Th17 and reduced anti-inflammatory cytokines like IL-10 and IL-4 from Treg and Th2 cells.[14][15].

Brewer et al. discovered that 46 out of 47 patients diagnosed with Eclampsia developed PRES (posterior reversible encephalopathy 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 [16][17][18]. The pathogenesis of Eclampsia may involve TNF-alfa and AT1-AA, resulting in endothelial injury, edema, and vascular narrowing, leading to a decrease in blood flow to the brain [8]. Also, there is damage to the blood-brain barrier (BBB), leading to hypertensive encephalopathy and cerebral edema. Several other research has shown that PRES is present in most patients diagnosed with Eclampsia [16][17].Lowering blood pressure in these women might slow down cerebral edema and limit potential brain damage. The exact association of this condition with Eclampsia or severe Preeclampsia is not well-known, and further research is needed to understand this association [19]. PRES is characterized by confusion, headache, loss of consciousness, seizure, visual impairment including potential 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 [20]. It is still 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. There is a need for immediate infusion of antihypertensive via the venous route because of its rapid effect on 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 [21]. It is also worth mentioning that the urge to decrease 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 mean arterial pressure 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 [22][23]. 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. It is cautioned against reducing blood pressure by more than 10–15% of the baseline value within one hour.

**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 [24]. 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 harm (**Fig 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 [25].

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 imperative to acknowledge that as this study relied on registry data, patients with preexisting renal disease were not excluded, and this will affect the overall risk [26][27].

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 [28]. The goal of understanding the renal complication of Preeclampsia led Geisinger Health System 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<60mL/min/1.73m2 (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, U.S.A., from 1976 to 2010 revealed a 4-fold increase in End-Stage Renal Disease (ESRD) and a median duration from pregnancy to the time of diagnosis of ESRD of 17.7 years [20].

**Pulmonary complications**

Pulmonary edema could develop because of multiple factors, such as hypervolemia, left ventricular failure, and pulmonary capillary leakage [29][30]. 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, there is direct airway compromise, thereby causing significant changes in pressure, and when this happens, fluids can leak into the alveoli, subsequently causing edema [31].

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 [32]. Likewise, the emergence of pulmonary edema may stem from combining these elements. The occurrence of pulmonary edema is one of the most severe complications of Preeclampsia, and this should be considered in cases of dyspnea in pregnant individuals. Although it has 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 [33]. A cohort study of pre-eclamptic women found 5.6% with pulmonary edema. It was recorded that they had higher postpartum rates and increased the 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 [29].

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, necessitating the need for heightened awareness of peripartum cardiomyopathy diagnosis and adequate follow-up of pregnant women diagnosed with Preeclampsia by healthcare professionals [33][31].

**Cardiovascular Complications**

Cardiovascular disease is one of the significant complications of Preeclampsia, and several studies have shown that pregnant women diagnosed with hypertensive disorders of pregnancy have an increased risk of developing cardiovascular disease later in life [34]. According to the European Society of Cardiology (ES C), 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. It was found out that women aged between 30 and 39 years with preeclampsia history 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 [35].

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. These changes typically begins in the second trimester to allow the growing fetus to adapt and deliver 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, this results in dilutional anemia of pregnancy 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 studies also claim that it helps to identify those who are at risk of developing cardiovascular disease later in life [36][37]

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 [37]. In multigravida with elevated blood pressure and Preeclampsia, it was observed that these risk factors increased the occurrence of disease. Another study conducted in the Netherlands showed that women with pregnancy complicated by Preeclampsia had an increased prevalence of metabolic syndrome [38]. 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 investigated in six different states, and it was found that 535 patients had Peripartum cardiomyopathy, 29.3% had Preeclampsia, and 46.9% had hypertension [39][40].

The cardiovascular complication may be characterized by 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 similar pathophysiology, which is diastolic dysfunction. [41][42]

**Central nervous system complications**

According to the European Society of Cardiology (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 [36]. 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 blood-brain barrier, interfering with cerebral perfusion and the development of brain edema (Fig 3). Individuals with previously normal blood pressure may exhibit encephalopathy symptoms at levels as low as 160/100 mm Hg. Although hypertensive emergencies are rare, hypertensive encephalopathy accounts for 15% of cases and has contributed to increased hospitalizations in the U.S. between 2000 and 2011. Fig 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 (Fig 3). Elevated blood pressure and peripheral resistance may be influenced by heightened sympathetic vasoconstrictor activity, contributing to various complications [44]. Patients with hypertensive encephalopathy may exhibit severe headaches, altered mental status, visual disturbances, and seizures. In the absence of adequate management, coma and death may occur. Immunosuppressive medications like steroids, seizures, infection, shock, and metabolic abnormalities have the potential to further complicate the condition by damaging the blood-brain barrier 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 posterior reversible encephalopathy syndrome (PRES) [45]. 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 were similar, which included 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 comprised almost half of both hemorrhagic and ischemic strokes. The observed manifestations included cerebral hemorrhage, headache, cortical blindness, posterior reversible encephalopathy syndrome (PRES), and seizures [46]. 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 mm Hg just prior to the occurrence of cerebrovascular events [47]. Notably, less than six patients reached a diastolic blood pressure of 105 mm Hg, 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 mm Hg in severe pre-eclamptic and eclamptic patients [48]. 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 [49]. This was 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 [50][51]. 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 [51]. 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 [52][53].

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 [54]. 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, considering 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 [55].

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 [56]. The risk of mortality in a pre-eclamptic patient in a developing country is seven times more than that in a developed 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 [57].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 [58].

**Hematologic and Digestive system complications**

Pregnancy is associated with exaggerated 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, 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 still need to be better understood, but it is believed to be from multiple pathways like genetic abnormalities, hormonal abnormalities, and unspecified idiopathic routes [59]. 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 [59]. The basolateral membrane of the hepatocyte's permeability to bile can be decreased by estrogen, 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 [59][60].

In Preeclampsia, most unique hematological and G.I. complications share the exact 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[59][60]. HELLP syndrome is defined by the presence of **H**emolysis, **El**evated **L**iver enzymes, and **L**ow **P**latelets, occurring in 0.17-0.85% of all pregnancies, more frequently in older multiparous Caucasian women (>34 years) and spectrally progressing into Disseminated consumptive coagulopathy (DIC) [59][60]. In general, the pathway favors a pro-coagulation state in pregnancy, constituting the development of a thromboembolic crisis. Cortical blindness, placenta abruption, cerebral hemorrhage, splenomegaly(rupture), renal insufficiency, intestinal infarction ,cardiomegaly and pancreatitis are sequels of the thromboembolic complication [59][60].

**Empirical evidence based on clinical studies**

There are documented evolutionary studies of preeclampsia dated back to the 18th century. John C. W. Lever at Guy’s Hospital in London, England in 1843 identified the association of convulsions, proteinuria and edema[61]. John William Ballantyne at the University of Edinburgh in 1885 identified hypertension as an important component of eclampsia[61].Though, by 1897 reports credited Louis Henri Vaquez and Pierre Nobécourt with the discovery of eclamptic hypertension[61].Between 1850–1700 BC medical text from late Middle Kingdom(The Kahun Gynecological Papyrus) addressing women’s health mentioned the characteristics features of eclampsia, and this was found near the modern-day Egyptian town of Lehun in 1889 by Flinders Petrie[61]. In 1914, James Young observed an increased frequency of placental infarcts in women when compared with pregnant women without albuminuria[61].

A 1960s study of the pathogenesis of pre-eclampsia of >100 placental bed biopsy samples from women with various hypertensive disorders of pregnancy reported that samples from women with chronic hypertension demonstrated hyperplasia and arteriosclerosis with proliferation of the intima and media of both basal and spiral arteries with mural microthrombi of the spiral arteries in an attempt to distinguish from the pathological findings in normotensive gravid women[62]. Studies further affirmed that during normal placentation, cytotrophoblasts differentiate from an epithelial to an endothelial phenotype(‘pseudo-vasculogenesis’ or ‘vascular mimicry’)[62].Farger clinical studies emphasize the use of circulating 2-ME(2-methoxyoestradiol) and estrogen metabolites assays in understanding the the role of the Catechol-O-methyltransferase(COMT) pathway in the processes associated with pre-eclampsia[61].

In 2000, a study demonstrated the importance of heme oxygenase-1(HO1),an antioxidase enzyme as a valuable endogenous mediator of placental development and regulation and further reported that the level was substantially altered and decrease in pre-eclamptic patients when compared with the placentae of normotensive[62].

A study by Lynch.et.al in 2006 further documented the role of complements in the pathogenesis of preeclampsia[63].The study showed activation of complement(anaphylatoxin C5a) in an antibody-independent mouse model of spontaneous miscarriage and intrauterine growth restriction with both of conditions characterized by placentation abnormalities[62].

A clinical study of about 500 pregnant women with autoimmune diseases (lupus and/or antiphospholipid antibody syndrome) ended up with severe adverse outcomes, including early-onset pre-eclampsia, fetal demise and preterm delivery with higher-than-normal levels of sENG, PlGF and particularly sFLT1,while in a large cohort-study(*n* = 4,099) in the United Kingdom, the plasma sFLT1:PlGF ratio measured at mid-trimester (~28 weeks) had a positive predictive value of 32% for preterm pre-eclampsia in a cohort of unselected nulliparous women[62].Gong S et.al in 2025 hypothesis suggested elevated Leptin and Pappalysin2 cell-free RNAs should be the hallmark of the assessment of these patients [63].

Another study that used a decision-analytic model estimated the economic impact pf using angiogenic markers instead of standard diagnostic steps to have saved £945 per patient in the UK using 1,000 pregnant women receiving standard obstetric care[62].

There are several studies of therapeutic trials and management of toxemia in pregnancy in several literatures, such as clinical trials that reported the use of aspirin prophylaxis early in pregnancy. This was highly effective for prevention of pre-eclampsia using an algorithm containing biophysical and angiogenic risk factors to identify patients at risk of preterm pre-eclampsia for enrolment[62].Sildenafil therapy prolonged pregnancy duration by 4 days and lowered blood pressure as observed in a small cohort study[62]. However, in the case of the STRIDER multicenter study, a trial of sildenafil to treat early-onset growth restriction, was discontinued due high number of fetal lung disease and death among the intervention group[62].

There are several studies and clinical trials in several literatures that documented epidemiology, pathogenesis, diagnosis ,treatment trials and prognosis; few examples of the treatment findings in the study are[62][63][64][65] :

i.Biguanides like metformin, an insulin sensitizer that is approved for use in type 2 diabetes mellitus during pregnancy to be associated with a reduced incidence of pre-eclampsia.

ii. Proton pump inhibitors (PPIs) can be used to block sFLT1 production in cell culture studies and reverse hypertension in sFLT1-transgenic mice.

iii. Antioxidants(Vitamins E and C, oligoelements) nitric oxide and anticoagulants(heparin) have shown potential beneficial effects in pre-eclampsia without much success.

iv.Statins which stimulate HO-1 expression and inhibit sFlt-1 release, have been used in several animal models of early onset pre-eclampsia with promising results.

v.Antiplatelets therapy such as aspirin reduces the risk of pre-eclampsia by 10% in women, serving as secondary preventive therapy.

vi. Calcium supplementation at a dosage of 1.5 g/day( at 15 weeks to delivery) is recommended for prevention of pre- eclampsia in women with a daily calcium intake <600 mg/day.

Combination of markers is one of the most likely ways to effectively predict the risk of pre-eclampsia in clinical setting, mostly using the combination of markers that assess elevated sFlt-1, placental growth factor, endoglin, and vascular endothelial growth factor(VEGF) in the first or second trimester[63][64].The outcome is better if combined with Doppler indices. In nested case-control study, second trimester maternal serum cystatin C, C-reactive protein, and uterine artery mean resistance index were observed to be independent predictors of pre-eclampsia[63][65].

Current research will in the near future be exploring the use of proteomic studies such as mass spectrometry, urinary proteomics and metabolomics and protein microarray, for the detection and prognostication of pre-eclampsia.

**CONCLUSION**

Hypertensive disorder in pregnancy is a fatal medical condition requiring adequate knowledge and rapid treatment responses with a high index of suspicion by medical professionals and patients. The mortality and morbidity of hypertensive spectrum in pregnancy is generally high in developing and underdeveloped countries but lower in the United States. The socioeconomic implication is high regardless of the geographical location.

Though multiple and varying pathogenetic mechanisms seem involved in developing various complications, the need for early detection and screening with proper monitoring remains a crucial methodology in controlling the disease and its progression. Likewise, the need to adequately understand the disease stems from later life complications like 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 strategy should be universally adopted with adequate monitoring of biophysical profile, lipid profile, metabolic profile, blood pressure, angiogenic biomarkers and blood glucose all through pregnancy and after delivery.

Preeclampsia is not only a pregnancy complication but also a marker for future health risk. Women with a history of preeclampsia are at higher risk for **chronic hypertension**, **ischemic heart disease**, **stroke**, **type 2 diabetes**, and **renal disease** later in life. Fetal consequences also include increased susceptibility to metabolic syndrome and neurodevelopmental delays.

Pregnancy-induced hypertension represents a complex and evolving clinical challenge with profound implications for maternal and fetal health. Clinicians must maintain high vigilance, especially in high-risk populations, to reduce morbidity and mortality associated with this multi-system disorder.

Despite advances in knowledge of pathophysiology, further research is essential to develop predictive markers, preventative strategies, and targeted therapies. There is a need for research funding of underserved areas to better understand the processes that intertwined complications and evaluate various possible therapeutic measures and trials that address the inequality in global healthcare in preventing, and treating hypertensive disorders in pregnancy and their various complications.

**Conflict of Interest**

This is an output of intra-faculty and international collaboration of medical educators and mentees as part of continuous medical education necessitating the need for republishing of this review. All authors declare no conflict of interest.

**Disclaimer (Artificial intelligence)**

Authors hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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**Table 1:**Diagnostic Criteria for Preeclampsia Based on **A**merican **C**ollege of **O**bstetrics and **G**ynecology Guidelines (**ACOG**).

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

**↑ Circulating sFLT-1 & Endoglin**

**Inhibits VEGF synthesis.**

**↓ PIGF**

**↑ Pro-inflammatory cells, cytokines & complements**

**Endothelial dysfunction**

**via ↑ ET1 & NO**

**Cytokines**

**↑IL-17, TNF-α,**

 **& IL-4**

**↓ IL-10**

**↓TREG**

**↑AT1-AA**

**Fig 1**: The pathology of placenta ischemia.

**Placental Ischemia**

**\*Endothelial dysfunction\***

**↑ Total peripheral resistance**

**Loss of podocyte integrity**

**↑ Renovascular resistance**

**↓ Renal blood flow**

**↓GFR**

**↓ Renal pressure**

**Natriuresis**

**Renal Failure**

**Fig 2**: Pathophysiology of renal failure in Preeclampsia.

**Placental Ischemia**

**Neuromuscular**

**↓ coupling**

**↑ Blood brain**

**barrier**

**permeability**

**↓ Myogenic tone**

**↓ Cerebral blood flow auto regulation**

**and**

**vascular resistance**

**↑ Capillary pressure**

**Cerebral vessel rupture**

**Hemorrhagic**

**Cerebrovascular accident**

**Cerebral edema**

**Fig 3:** Cerebrovascular complications of pregnancy-induced hypertension