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Review Article

A Review on Pre-Eclampsia in Pregnancy

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ABSTRACT

Pre-eclampsia, a systemic condition that affects roughly 5-7% pregnancies, is the most prevalent but least understood pregnancy aliment. It is linked to higher mother and newborn mortality and morbidity because to its high prevalence. Pre-eclampsia in particular has been linked to cardiovascular consequence in the off spring, including as hypertension and changes in vascular function. Reduction in serum levels of calcium, magnesium, and zinc during pregnancy might be possible contributors in etiology of pre-eclampsia, and supplementation of these elements to diet maybe of value to prevent pre-eclampsia. The most crucial aspect of prevention is still receiving proper prenatal care. Prenatal surveillance can be focused on women who are most at risk of developing pre-eclampsia by estimating each womens unique risk. In terms of foetal or maternal monitoring and birth timing, this type of care results in early diagnosis and intervention.

INTRODUCTION

Pre-eclampsia is a progressive, multisystemic disorder characterized by triad of high-blood pressure to the extent of 140/90 mm Hg or more, edema, and proteinuria, developing after 20 weeks of gestation. It is one of the most common medical complications during pregnancy and the leading cause of both maternal and perinatal morbidity and mortality worldwide.1 The clinical spectrum of pre-eclampsia ranges from mild to severe. Pre-eclampsia occurs in 5-8% of pregnancies worldwide, and is the second leading cause of direct maternal and fetal deaths. The etiology of preeclampsia is still obscure, despite many attempts to identify possible causes.2 Globally, over half a million women die each year of pregnancy related causes and 99% of these deaths occur in developing countries. Put another way, women in developed countries have an average life time risk of dying from pregnancy related causes of between 1 in 4000 and 1 in 10000, whereas women in developing countries have a risk that is between 1 in 15 and 1 in 50. Although rare, eclampsia which is a complication of pre-eclampsia accounts for 50,000 maternal deaths a year.

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India is among those countries which have a very high maternal mortality rate i.e. 301 per 100,000 live births. The major causes of maternal deaths in India are haemmorrhage, sepsis, hypertension, obstructed labour, abortion and other conditions. Hypertension which can be a sign of pre-eclampsia accounts for 5% of maternal deaths in India. 3

Pre-eclampsia has been called a "Disease of theories" While management of pre-eclampsia involves the use of antihypertensive therapy to control blood pressure and steroids to accelerate fetal pulmonary maturity at gestational ages before 34 weeks, the only effective cure is delivery of the placenta. Even then, the disease can worsen, or appear for the first time, postpartum. Although the disease can affect almost any organ in the body, involvement of the brain with seizures, known as eclampsia, poses particular risk for mother and baby.4

Review:

Etiology: -

Although there is an extensive understanding of the clinical presentation, diagnostic criteria, and management of preeclampsia currently routinely utilized, the underlying etiology of preeclampsia is poorly understood. The principal mechanism of disease implicated in the etiology of preeclampsia and eclampsia is uteroplacental ischemia. This theory was based on the observation of placental infarctions in patients with eclampsia and on animal studies showing that subcutaneous injections of autolyzed human placental extracts into guinea pigs elicited convulsions, hepatic focal necrosis, and renal lesions, similar to those observed in women who died of eclampsia. The pathophysiology of preeclampsia, therefore, can be likened to the release and progression of a particular toxin, leading to a diffuse vasculopathy, which, if sustained, ultimately leads to severe complications such as the development of seizures seen in eclampsia.

While there are numerous supporting research investigations, the following evidence supports, and is the most widely accepted to support, a causal link between placental ischemia and the development of preeclampsia:

- experimentally induced ischemia in several animal models leads to hypertension and proteinuria.
- uterine blood flow is lower in patients with preeclampsia than in pregnant women without preeclampsia.
- placental histopathologic lesions indicative of ischemia are frequent and consistent findings in preeclampsia and eclampsia
- failure of physiologic transformation of the spiral arteries and atherosis are typical features of preeclampsia
- the pulsatility index of the uterine artery (a parameter to assess resistance to flow) is higher in patients with preeclampsia than in women with unaffected pregnancies.5

Risk Factor: -

The 2019 National Institute for Health and Care Excellence (NICE) guidelines classify a woman at high risk of preeclampsia if there is a history of hypertensive disease during a previous pregnancy or a maternal disease including chronic kidney disease, autoimmune diseases, diabetes, or chronic hypertension. Women are at moderate risk if they are nulliparous, ≥40 years of age, have a body mass index (BMI) ≥ 35 kg/m, a family history of preeclampsia, a multifoetal pregnancy, or a pregnancy interval of more than 10 years There are additional clinical factors that significantly increase preeclampsia risk, including raised mean arterial blood pressure before 15 weeks' gestation, polycystic ovarian syndrome , sleep disordered breathing , and various infections such as periodontal disease, urinary tract infections, and helicobacter pylori.In terms of obstetric history, vaginal bleeding for at least five days during pregnancy increases preeclampsia risk, as does the

use of oocyte donation, which has a higher risk of preeclampsia in comparison to in vitro fertilization (IVF) without oocyte donation or natural conception. Studies have reported that vitamin D deficiency can increase the risk of preeclampsia, and that vitamin D supplementation may offer some benefit in reducing preeclampsia risk.6 Extremes of maternal age have been associated with an increased risk of pre-eclampsia in some, but not all studies. In a review of risk factors for pre-eclampsia at ante-natal booking, including 52 cohort and case-control studies, women older than 40 years of age had almost twice the risk of developing pre-eclampsia compared with younger women. The increased risk was similar in primiparous and multiparous women. Young maternal age was not associated with an increased risk of pre-eclampsia.

Pathophisiology: -

During normal pregnancy, the villous cytotrophoblast invades into the inner third of the myometrium, and spiral arteries lose their endothelium and most of their muscle fibers. These structural modifications are associated with functional alterations, such that spiral arteries become low-resistance vessels, and thus less sensitive, or even insensitive, to vasoconstrictive substances. Pre-eclampsia has a complex pathophysiology, the primary cause being abnormal placentation. Defective invasion of the spiral arteries by cytotrophoblast cells is observed during pre-eclampsia. Recent studies have shown that cytotrophoblast invasion of the uterus is actually a unique differentiation pathway in which the fetal cells adopt certain attributes of the maternal endothelium they normally replace. In pre-eclampsia, this differentiation process goes awry. The abnormalities may be related to the nitric oxide pathway, which contributes substantially to the control of vascular tone. Moreover, inhibition of maternal synthesis of nitric oxide prevents embryo implantation. Increased uterine arterial resistance induces higher sensitivity to vasoconstriction and thus chronic placental ischemia and oxidative stress. This chronic placental ischemia causes fetal complications, including intrauterine growth retardation and intrauterine death. In parallel, oxidative stress induces release into the maternal circulation of substances such as free radicals, oxidized lipids, cytokines, and serum soluble vascular endothelial growth factor 1. These abnormalities are responsible for endothelial dysfunction with vascular hyperpermeability, thrombophilia, and hypertension, so as to compensate for the decreased flow in the uterine arteries due to peripheral vasoconstriction. Endothelial dysfunction is responsible for the clinical signs observed in the mother, ie, impairment of the hepatic endothelium contributing to onset of the HELLP (Hemolysis, Elevated Liver enzymes and Low Platelet count) syndrome, impairment of the cerebral endothelium inducing refractory neurological disorders, or even eclampsia. Depletion of vascular endothelial growth factor in the podocytes makes the endotheliosis more able to block the slit diaphragms in the basement membrane, adding to decreased glomerular filtration and causing proteinuria. Finally, endothelial dysfunction promotes microangiopathic hemolytic anemia, and vascular hyperpermeability associated with low serum albumin causes edema, particularly in the lower limbs or lungs. The crucial issue to understand is that the prime mover of pre-eclampsia is abnormal placentation. Two common theories appear to be interlinked, ie, a genetic theory and an immunological theory. Several susceptibility genes may exist for pre-eclampsia. These genes probably interact in the hemostatic and cardiovascular systems, as well as in the inflammatory response. Pre-eclampsia can be perceived as an impairment of the maternal immune system that prevents it from recognizing

the fetoplacental unit. Excessive production of immune cells causes secretion of tumor necrosis factor alpha which induces apoptosis of the extravillous cytotrophoblast. The human leukocyte antigen (HLA) system also appears to play a role in the defective invasion of the spiral arteries, in that women with pre-eclampsia show reduced levels of HLA-G and HLA-E. During normal pregnancies, the interaction between these cells and the trophoblast is due to secretion of vascular endothelial growth factor and placental growth factor by natural killer cells. High levels of soluble fms-like tyrosine kinase 1 (sFlt-1), an antagonist of vascular endothelial growth factor and placental growth factor, have been found in women with pre-eclampsia.[7]

Complications: -

Preeclampsia and eclampsia are major causes of maternal mortality in the Unites States and worldwide. Women who have preeclampsia are at risk of placental abruption in the current pregnancy, possibly because both disorders are related to uteroplacental insufficiency. Pregnant women may develop pulmonary edema, acute kidney injury, liver rupture, or cerebrovascular hemorrhage, with or without seizures.

Fetal complications may include growth restriction, oligohydramnios, or stillbirth (3). Diffuse or multifocal vasospasm can result in maternal ischemia, eventually damaging multiple organs, particularly the brain, kidneys, and liver. Factors that may contribute to vasospasm include decreased prostacyclin (an endothelium-derived vasodilator), increased endothelin (an endothelium-derived vasoconstrictor), and increased soluble Flt-1 (a circulating receptor for vascular endothelial growth factor). The HELLP syndrome (hemolysis, elevated liver function tests, and low platelet count) develops in 0.2 to 0.6% of pregnancies. Most pregnant women with HELLP syndrome have hypertension and proteinuria, but some have neither.

Diagnosis: -

- Preeclampsia: New onset after 20 weeks gestation of hypertension plus new unexplained proteinuria (> 300 mg/24 hours or a urine protein/creatinine ratio of ≥ 0.3) and/or signs of end-organ damage.

Blood pressure (BP) criteria for preeclampsia are one of the following:

- Systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg (at least 2 measurements taken at least 4 hours apart)
- Systolic BP ≥ 160 mm Hg and/or diastolic BP ≥ 110 mm Hg (at least 2 measurements)

Proteinuria is defined as > 300 mg/24 hours. Alternatively, proteinuria is diagnosed based on a protein/creatinine ratio ≥ 0.3 or a dipstick reading of 2+; the dipstick test is used only if other quantitative methods are not available. Absence of proteinuria on less accurate tests (eg, urine dipstick testing, routine urinalysis) does not rule out preeclampsia.

In the absence of proteinuria, preeclampsia may be diagnosed if pregnant women meet diagnostic criteria for new-onset hypertension and also have new-onset signs of end-organ damage.

- Preeclampsia with severe features is diagnosed in patients with new onset of persistent severe hypertension and/or signs or symptoms of end-organ damage. The blood pressure criterion is systolic BP ≥ 160 mm Hg and/or diastolic BP ≥ 110 mm Hg on at least 2 measurements taken at least 4 hours apart.

Signs or symptoms of end-organ damage may include one or more of the following:

- Thrombocytopenia (platelets < 100 x 109 L)
- Impaired liver function (aminotransferases > 2 times normal) not accounted for by alternative diagnoses
- Severe persistent right upper quadrant or epigastric pain unresponsive to medications

- Renal insufficiency (serum creatinine > 1.1 mg/dL or doubling of serum creatinine in the absence of renal disease)
- Pulmonary edema
- New-onset headache unresponsive to medication and not accounted for by alternative diagnoses
- Visual disturbances

Additional diagnostic categories of preeclampsia are as follows:

- HELLP syndrome is classified as a severe form of preeclampsia and is diagnosed when all of the following are present: lactate dehydrogenase (LDH) ≥ 600 IU/L; aminotransferases > 2 times normal; and platelets < 100 × 109 L. HELLP syndrome may have an atypical clinical presentation, with the absence of hypertension or proteinuria in up to 15% of patients.
- Preeclampsia superimposed on chronic hypertension is diagnosed when a patient known to have chronic hypertension develops one of the following after 20 weeks: new unexplained proteinuria or worsening proteinuria; BP elevations above baseline; or signs of end-organ damage. Women with chronic hypertension are at high risk of preeclampsia and should be monitored closely. An elevated uric acid level suggests a diagnosis of superimposed preeclampsia rather than solely chronic hypertension.

Patients with any type of preeclampsia are at risk of developing eclampsia. Sometimes eclampsia occurs before a diagnosis of preeclampsia is made.

- **Eclampsia** is new onset of tonic-clonic, focal, or multifocal seizures with no other known causes (eg, epilepsy, cerebral arterial ischemia or infarction, intracranial hemorrhage, or drug use).

Management: -

Currently, prevention of preeclampsia relies on early screening and monitoring of high-risk patients, and pharmacologic prophylaxis.

Low-dose aspirin is the most rigorously studied and commonly used agent to prevent or delay the onset of preeclampsia, through its inhibition of placental thromboxane A2 synthesis with minimal effects on vascular prostacyclin levels . Preeclampsia is associated with inadequate prostacyclin (vasodilator) and elevated thromboxane.8 Delivery remains the ultimate treatment for preeclampsia .When possible, vaginal delivery is preferable to avoid the added physiologic stressors of cesarean delivery. If cesarean delivery must be used, regional anesthesia is preferred because it carries less maternal risk. In the presence of coagulopathy, use of regional anesthesia generally is contraindicated. Women with preeclampsia and preterm pregnancy can be observed on an outpatient basis, with frequent assessment of maternal and fetal well-being. Women who are noncompliant, who do not have ready access to medical care, or who have progressive or severe preeclampsia should be hospitalized. Women whose pregnancy is remote from term should be cared for in a tertiary care setting or in consultation with an obstetrician or family physician who is experienced in the management of high-risk pregnancies. During labor, the management goals are to prevent seizures and control hypertension. Magnesium sulfate is the medication of choice for the prevention of eclamptic seizures in women with severe preeclampsia and for the treatment of women with eclamptic seizures. One commonly used regimen is a 6-g loading dose of magnesium sulfate followed by a continuous infusion at a rate of 2 g per hour. Magnesium sulfate has been shown to be superior to phenytoin (Dilantin) and diazepam (Valium) for the treatment of eclamptic seizures. Although magnesium sulfate commonly is used in women with preeclampsia, studies to date have been inadequate to show that it prevents progression of the disorder. Antihypertensive drug therapy is recommended for pregnant women with systolic blood pressures of 160 to 180 mm Hg or higher and diastolic blood pressures of 105 to 110

mm Hg or higher The treatment goal is to lower systolic pressure to 140 to 155 mm Hg and diastolic pressure to 90 to 105 mm Hg. To avoid hypotension, blood pressure should be lowered gradually. Although evidence about the potential adverse effects of most antihypertensive drugs has been poorly quantified, use of many of these agents is contraindicated during pregnancy. Hydralazine (Apresoline) and labetalol (Normodyne, Trandate) are the antihypertensive drugs most commonly used in women with severe preeclampsia Nifedipine (Procardia) and sodium nitroprusside (Nitropress) are potential alternatives, but significant risks are associated with their use. Note that labetalol therapy should not be used in women with asthma or congestive heart failure. Use of angiotensin-converting enzyme inhibitors is contraindicated in pregnant women.9

Antihypertensive Management:

Blood pressure control includes both immediate antihypertensive management in cases of severe hypertension (ie, ≥160 mm Hg systolic and/or ≥110 mm Hg diastolic) as well as maintenance antihypertensive management either in the antepartum or postpartum periods depending on the particular diagnosis of preeclampsia.

Antihypertensive medications, which are efficacious and without adverse effects on the fetus, include the following medications:

- Beta-blockers, such as labetalol
- Calcium-channel blockers, such as nifedipine
- Alpha-2 agonists, such as clonidine
- Vasodilators, such as hydralazine

Medications commonly used in the treatment of severe hypertension include IV labetalol, IV hydralazine, or PO immediate-release nifedipine. While there is no evidence to suggest a benefit of either IV medications as an initial choice for antihypertensive management, the decision of medication is usually dictated by the presence of IV access at the time of diagnosis, with PO nifedipine being favored in cases where IV access is either unavailable or not possible. Medications commonly used to treat blood pressure maintenance include PO labetalol, extended-release nifedipine, and extended-release clonidine. As with the IV antihypertensive medications, there is no evidence to suggest a benefit of either PO medication as an initial choice in terms of efficacy. Nifedipine and clonidine offer less frequent dosing options, which may benefit noncompliant patients where extended-release nifedipine is a daily dosed medication and clonidine is usually administered as a weekly patch.

Antiseizure Management:

The first choice for seizure prophylaxis in patients with preeclampsia with severe features is IV magnesium sulfate therapy. In cases where magnesium sulfate IV is contraindicated, leviteracetam can be used for prophylaxis.

Management of eclampsia (ie, development of seizure activity) is discussed in a separate article, but includes seizure treatment initially with an IV benzodiazepine medication.

For recurrent seizures despite magnesium sulfate IV (or if it is contraindicated), alternative medications include:

- Lorazepam: 2-4 mg IV x 1, may repeat x 1 after 10-15 min
- Diazepam: 5-10 mg IV every 5-10 min to max dose 30 mg
- Phenytoin: 15-20 mg/kg IV x 1, may repeat 10 mg/kg IV after 20 min if no response
- Levetiracetam: 500 mg IV or orally, may repeat in 12 hours

Antepartum Management and Delivery Timing:

Fetal evaluation should include ultrasonography of the amniotic fluid index, estimated fetal weight, and antenatal testing, such as non-stress tests and biophysical profiles. Fetal status may also play a major role in determining delivery versus expectant management in preeclamptic patients.

Ultimately, the definitive treatment of preeclampsia is the delivery of the fetus. While continued observation is permissible for preterm gestations in patients with either well-controlled gestational hypertension or preeclampsia without severe features in the setting of normal antepartum testing, risks of expectant management exist (see "Complications" section). If expectant management is undertaken in stable patients, serial ultrasonography, weekly antepartum testing, and close observation of symptoms, blood pressure, and laboratory values should be employed. As per ACOG, it is recommended that patients at 37 0/7 weeks gestation diagnosed with gestational hypertension or preeclampsia without severe features should undergo delivery rather than expectant management. It is also recommended that patients diagnosed with preeclampsia with severe features at or beyond 34 0/7 weeks gestation undergo delivery after maternal stabilization and should not be delayed to accommodate steroid administration. In cases where patients less than 34 0/7 weeks gestation are diagnosed with preeclampsia with severe features, proper stabilization of both maternal and fetal well-being should be initiated, with management usually continued in the inpatient or outpatient setting expectantly. However, there is little evidence to suggest a benefit to this practice, and this is mainly based upon expert opinion and individualized treatment plans between patient and provider. While neonatal and maternal outcomes may benefit from delivery or expectant management, informed decision-making regarding benefits and risks must be discussed with the patient. Antepartum admission with close monitoring of maternal and fetal conditions may be employed with a low threshold for delivery if maternal or fetal deterioration is suspected. Findings that indicate expeditious delivery after stabilization, regardless of gestational age, can be described as fetal and maternal factors. Fetal factors include abnormal antepartum testing and sustained reversed end-diastolic flow of the umbilical artery. Maternal factors include uncontrolled blood pressure, continued headaches/visual disturbance or right upper quadrant/epigastric pain despite repeated medical management, myocardial infarction, stroke, pulmonary edema, HELLP syndrome, eclampsia, or suspicion of placental abruption or bleeding with no other diagnosis. Delivery before 34 0/7 weeks gestation, if indicated, should prompt the administration of antenatal steroids for fetal lung maturation, but this should not delay delivery. This also applied to the late preterm period of 34 0/7 through 36 6/7 weeks gestation. 5

CONCLUSION: -

Understanding the pathophysiology and factors alter the orgin of the disease and its complication is essential for preventing preeclampsia. In this context calcium, magnesium and zinc may be crucial. Pregnant women with long term condition such as hypertension, should receive the best care treatment. Preeclampsia risk is lightly to be decreased by lowering body weight and engaging in physical activity both before and during pregnancy. To effectively implement research and porogrammatic activities to improve morbidity and mortality, there has to be more community education about preeclampsia. The two antihypertensive medications most frequently prescribed to women with preeclampsia are labetolol (Normodine, Trandate) and Hydralazine (Apresoline).

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