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Review Article

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Pregnancy induced hypertension & pre eclampsia: Pathophysiology & recent management trends: A review

Monalisa Jena[1]*, Swati Mishra[2], Swetalina Jena[3], Sarita Pradhan[4], Smita Das[5], Jyotirmoyee Jena[6], Sashi Bhusan Biswal[7] and Sudhansu Sekhar Mishra[8]

[1]MD (Assistant Professor) Department of Pharmacology, AIIMS, Bhubaneswar, Odisha, India
[2]MD (Associate Professor) Department of Pharmacology, IMS & SUM Hospital, SOA University, Bhubaneswar 751003, (Odisha), India
[3]MD (SR) Department of Microbiology, VSS Medical college & Hospital, Burla, Odisha, India
[4]MD (Assistant Professor) Department of Pathology, IMS & SUM Hospital, Siksha 'O' Anusandhan University, Khandagiri Square, BBSR, 751003, Odisha, India
[5]MD (Assistant Professor) Department of Pharmacology, IMS & SUM Hospital, SOA University, Bhubaneswar 751003, (Odisha),
[6]MD (Professor) Department of Pharmacology, KIMS & Hospital, Bhubaneswar, Odisha, India, Phone no: 8280056315
[7]MD (Assistant Professor) VSS Medical College & Hospital, Burla, Odisha,
[8]MD (Professor) Department of Pharmacology, IMS & SUM Hospital, Bhubaneswar, Odisha, India,
Corresponding E-mail:- drmonalisajena@gmail.com

ABSTRACT

In recent years, incidence of hypertension in pregnancy is increasing manifold. Termed as pregnancy induced hypertension (PIH), it is associated with generalized edema and proteinuria which is known as preeclampsia .Early diagnosis, proper management plays a vital role as this disease causes considerable morbidity and mortality in both the mother and fetus. The objective of our review article is to elaborate on pathophysiology of preeclampsia & give recent insights on the criteria's used for taking clinical decisions at different levels of pregnancy care for patients with PIH & preeclampsia. Our article also highlights the newer diagnostic procedures and treatment modalities for the management of the above conditions.

Key words: PIH, Hypertension, Preeclampsia, Pathophysiology

INTRODUCTION

Pregnancy-induced hypertension (PIH), which occurs in <10% of pregnancies, is a major risk factor for maternal, perinatal morbidity and mortality. [1] PIH includes gestational hypertension as well as preeclampsia and eclampsia. Gestational hypertension is characterized by an abnormal rise in blood pressure that usually develops after 20th week of pregnancy. In addition to hypertension, symptoms of preeclampsia include proteinuria and edema. If the

condition progresses to eclampsia, life threatening convulsions and coma can occur. PIH can also result in preterm labor and low-birth-weight infants.

Preeclampsia is a complex disease otherwise known as hypertensive disorder of pregnancy; result in a wide variety of unpredictable clinical manifestations, as well as adverse health outcomes for both mother and the fetus. Different strategies have been proposed for preventing preeclampsia. These include low-dose aspirin, as well as antioxidants, zinc, magnesium & calcium supplementation.[2] As there is no proper diagnostic methods available for preeclampsia, identification and diagnosis of disease are done by assessment of risk factors and biomarkers.[3, 4, 5]

The National High Blood Pressure Education Programme (NHBPEP) working group classifies hypertensive disease in pregnancy into 4 groups: [6]

1. Gestational Hypertension
2. Chronic Hypertension
3. Pre eclampsia/Eclampsia
4. Superimposed pre eclampsia (on chronic hypertension)

Incidence of pregnancy induced hypertension is higher in developing countries in comparison to developed ones which complicates about 10% of pregnancy.[7]The 8th Confidential Enquiry into maternal & child health revealed pre eclampsia & eclampsia as the second leading cause of direct maternal death [8] accounting for 10 – 15% of maternal mortality.[9] Pre eclampsia is also responsible for various morbidity associated with pregnancy such as seizure (leading to eclampsia), intracranial hemorrhage, pulmonary edema, hematological abnormalities(coagulation defect) & heart, renal, liver failure. Fetus is also not spared from the hypertensive disorder of pregnancy, facing complications including still birth [10], abruptio placentae, intrauterine growth retardation and premature delivery.

ETIOPATHOGENESIS:

Pregnancy-induced hypertension (PIH) is estimated to affect 7% to 10% of all pregnancies in the United States. Despite being the leading cause of maternal death and a major contributor of maternal and perinatal morbidity, the mechanisms responsible for the pathogenesis of PIH have not yet been fully explained. More than 30 years ago Dr. Leon Chesley, a pioneer in the field of hypertension in pregnancy divided the most likely causative factor into four major categories: dietary, renal, immunologic and placental.[11]Subsequently, the theory that poor diet or pre existing renal abnormalities underlie majority of episodes of preeclampsia was abandoned. The role of immunologically mediated vascular injury, as the initiating cause still remained a plausible cause that needs to be explored.

Studies during the past decade, however, have provided a better understanding of the potential mechanisms responsible for the pathogenesis of PIH. Delivery of placenta usually leads to resolution of acute clinical symptoms of pre eclampsia, highlighting the fact that placenta plays a central role in preeclampsia pathogenesis. During normal pregnancy, the placenta undergoes dramatic vascularization to enable circulation between fetus and mother. Placental vascularization involves vasculogenesis, angiogenesis and maternal spiral artery remodeling. These processes require a delicate balance of pro angiogenic and antiangiogenic factors. The imbalance of proangiogenic and antiangiogenic factors in preeclampsia is thought to trigger abnormal placental vascularization and disease onset. Numerous conditions predispose to preeclampsia like previous history and family history of preeclampsia, in primipara, twin pregnancy and are also associated with obesity, diabetes and essential hypertension.

a. Uteroplacental Ischemia

The initiating event in PIH starts during early placentation and appears to be caused by reduced uteroplacental perfusion as a result of abnormal cytotrophoblast invasion of spiral arterioles. By the end of the second trimester of normal pregnancy, the uterine spiral arteries are lined exclusively by cytotrophoblast, and endothelial cells are no longer present in the endometrial or superficial myometrial regions. This remodeling of the uterine spiral arteries results in the formation of a low resistance arteriolar system with a dramatic increase in blood supply to the growing fetus. In preeclampsia, invasion of the uterine spiral arteries is limited to the proximal decidua, with 30% to 50% of the spiral arteries of the placental bed escaping endovascular trophoblast remodeling. [12, 13] Myometrial segments of these arteries remain anatomically intact, undilated, and adrenergic nerve supply to the spiral arteries is not affected. This failure of vascular remodeling prevents an adequate response to increased fetal demands for blood flow that occur as gestation progresses. This defect is attributed to inappropriate integrin expression by extravillous

cytotrophoblast. [14] Impaired trophoblast invasion in preeclampsia results in a reduction in uteroplacental perfusion, with the placenta becoming increasingly ischemic as gestation progresses.

b. Endothelial Dysfunction

Endothelial dysfunction is manifested by the altered synthesis and release of endothelial cell products. Nitric oxide synthesis should increase in pregnancy, whereas analysis of tissue and urine samples strongly suggest that nitric oxide production is impaired in preeclamptic women.[15]Imbalance between vasodilating and vasoconstricting prostaglandins lead to decrease in vasorelaxant prostacyclin and increase in vasoconstrictor thromboxane in preeclamsia.

c. Antiangiogenic factor:

Studies by Karumanchi et al have highlighted the role of anti angoiogenetic factors like increased expression of soluble fms-like tyrosine kinase (sFlt1), along with decreased placental growth factor (PGF) and vascular endothelial growth factor (VEGF) signaling. [16] sFlt1 consists of the extracellular ligand-binding domain of Flt1, but lacks the transmembrane and intracellular signaling domain. Hence, it is secreted into the circulation where it binds, antagonizes both vascular endothelial growth factor (VEGF) and placenta growth factor (PGF). Both are potent stimuli for the vascular expansion essential to development of the uteroplacental unit and act via their effects on endothelial cells. Recent clinical data's also support the theory that both circulating and placental levels of this soluble receptor blocker is higher in women with preeclampsia than in women with uncomplicated pregnancy. Circulating levels of sFlt1 and PGF are altered several weeks before the onset of clinical disease and are correlated with severity of the disease. sFlt1 levels normalize several days after delivery, coinciding with improvement in proteinuria and hypertension.[17]Another factor, soluble endoglin (sEng), has now been also found to be up regulated in preeclampsia in a pattern similar to sFlt1 Eng acts as a co-receptor for TGF-, a potent pro angiogenic molecule. Eng mRNA is up regulated in the preeclamptic placenta and extracellular region of Eng is proteolytically cleaved, to release excess of soluble Eng (sEng) into the circulation of preeclamptic patients. This compound not only potentiates the anti-angiogenic actions of s-Flt-1 kinase, but also decreases production of nitric oxide.

d. Renin-Angiotensin System

Renin, angiotensin II & aldosterone decrease in preclamsia unlike normal pregnancy. Numerous studies report the presence of angiotensin II type 1 receptor agonistic antibody (AT1 Ab) found circulating in pre eclamptic women. These auto antibodies could lead to increase in certain factors (Flt1, sEng, Plasminogen activator inhibitor-1, reactive oxygen species, tissue factor, and NADPH oxidase) that lead to endothelial cell dysfunction and vascular damage.

e. Genetics in preeclampsia

Presence of preeclampsia in first degree relatives increases a woman's risk of preeclampsia by 2 to 4 fold. Genetics come to play by altering the angiogenic imbalance found in patients with preeclampsia.[18]Recently, several polymorphisms in sFlt1 and VEGF have been associated with severity of preeclampsia, thus establishing a role of genes. Likewise women with trisomy 13 fetuses have been found to have higher incidence of preeclampsia.[19]

RISK FACTORS:

The risk factors related to pre eclampsia are classified based on various factors such as maternal, paternal &/or specific to pregnancy state. [20,21]

Risk factors that are related to mother:

- Inherent risk factors:
  - Age < 20 or 35 – 40 years, Nulliparity, previous family history of pre eclampsia (four times the risk of maternal death than mothers who did not have preeclampsia/ eclampsia)[22],previous H/O cardiovascular disease, woman born small for gestational age
- Medical conditions:
  - Obesity, Chronic hypertension, Chronic renal disease, Diabetes mellitus, antiphospholipid antibody syndrome, connective tissue disorders, thrombophilia
  - Specific to pregnancy state like Multiple gestation, oocyte donation, new partner, UTI, hydatidiform mole, hydrops foetalis

Risk factors related to father:
Limited sperm exposure, barrier contraception, first time father, donor insemination, partner who fathered a pre eclamptic pregnancy in another woman.

Since the etiology of pre-eclampsia is not well classified and well understood [23], investigation & identification of the most important risk factors is vital for diagnosis, prevention & proper management of pre eclampsia.

TYPES OF PRE ECLAMPSIA:
Classification of pre eclampsia is mainly based on severity (mild, moderate, severe) and time of onset according to gestational age (pre term or term).It is again sub typed pathophysiologically according to the presence of maternal and/or placental factors.[24]In placental pre-eclampsia, failure in trophoblast differentiation plays the central role whereas in maternal pre-eclampsia, pathogenesis lies in interaction between a normal placenta and maternal factors increasing susceptibility to microvascular damage. Redman describes a continuum in the severity of both of these etiologies, with the extremes being isolated SGA (placental) and term pre-eclampsia (maternal), and the most common presentation involving dysfunction of both the placenta and the maternal system to varying degrees.

1. Mild: diastolic blood pressure (DBP) 90–99 mmHg, systolic blood pressure (SBP) 140–149 mmHg.
2. Moderate: DBP 100–109 mmHg, SBP 150–159 mmHg.
3. Severe: DBP ≥110 mmHg, SBP ≥160 mmHg.

a. HELLP syndrome

One of the following features is necessary for a diagnosis of severe preeclampsia:
- CNS symptoms (severe headache, blurry vision, altered mental status, Stroke)
- Signs and symptoms of liver disease (nausea and/or vomiting with abdominal pain)
- Twofold rise in liver enzymes
- Very high blood pressure (> 160 systolic or 110 diastolic)
- Thrombocytopenia (low platelet count)
- > 5g of protein in a 24-hour sample
- Very low urine output (< 500mL in 24 hours)
- Signs /symptoms of respiratory involvement (pulmonary edema, bluish tint to the skin)
- Severe fetal growth restriction

The distinction between mild and severe preeclampsia carries importance as the management strategies differs.

HELLP syndrome: It is a life-threatening liver disorder (a type of severe preeclampsia) characterized by **H**emolysis (destruction of red blood cells), **E**levated **L**iver enzymes (which indicate liver damage), and **L**ow Platelet count. About 10% to 20% of women who have severe preeclampsia develop HELLP. [25, 26]

DIAGNOSIS & TREATMENT MODALITIES IN PRE-ECLAMPSIA:
Diagnosis:
Screening for preeclampsia during first prenatal visit after 20 weeks of gestation is always an important measure. Women who are at risk of developing pre eclampsia must undergo uterine artery Doppler velocimetry at 20 – 24weeks. [27] After diagnosis, the patient must be hospitalized for proper care & follow up. Assessment of proteinuria, full blood count, liver function tests (bilirubin, transaminase), electrolyte & kidney function tests must be done to evaluate the stage & severity of pre eclampsia. The aim of antihypertensive medications must be considered to maintain the SBP below 150mm Hg and DBP between 80 – 100mm Hg.

PREVENTION OF PRE ECLAMPSIA & PREGNANCY INDUCED HYPERTENSION:
Not well established and no full proof methods have been developed till date for the prevention of pre eclampsia; only an assumption has been made that calcium clearly benefit high risk women in the communities where low dietary intake of calcium is always a problem. A Cochrane systemic review in 2010 concludes that with adequate calcium supplementation there was around half reduction rate of risk of pre eclampsia, reduce the rate of preterm birth and risk of death & serious morbidities. [28]

Antiplatelet therapy with low dose aspirin (75 – 150mg) in early gestational period (<16 weeks) not only reduces the development of pre eclampsia with abnormal uterine artery but also reduces the incidence of gestational hypertension & intrauterine growth retardation. [29]

MANAGEMENT PROTOCOL:
The treatment of gestational hypertension follows different guidelines in comparison to the treatment of general high blood pressure. The main goal of treatment in pregnant women is to prevent the development of more serious conditions like fetal growth restriction or placental abruption. The most commonly used treatment options for pregnant women with high blood pressure are:

- Bed rest
- Short-term (acute) drug therapy
- Long-term (chronic) drug therapy

In choosing a specific treatment plan, details such as whether the high blood existed before the pregnancy, how far along the pregnancy is, and how well the baby is doing must all be considered.

Mild preeclampsia: For mild preeclampsia that is not rapidly getting worse, reducing level of activity, monitoring, frequent office visits and testing.

Moderate to severe preeclampsia with HELLP SYNDROME: For moderate or severe preeclampsia, or for preeclampsia that is rapidly getting worse, patient may need to go to the hospital for expectant management. This typically includes bed rest, medicine, and close monitoring of mother and foetus.

Severe preeclampsia/life threatening preeclampsia or an eclamptic seizure is treated with magnesium sulphate. Intravenous magnesium sulphate is the drug of choice both for prevention and treatment of seizures. [30]

If pregnancy is near term, delivery may be planned. If gestational age is less than 34 weeks, and 24- to 48-hour delay is possible, antenatal corticosteroids to speed up the baby's lung development before delivery can be given. Delivery before 34 weeks is only indicated in maternal/fetal compromise or if blood pressure doesn't come down irrespective of proper management. [31, 32, 33]

PHARMACOTHERAPY:
The antihypertensive agents used should be efficacious and safe to the mother and foetus. Methyldopa is recommended for women whose hypertension is first diagnosed during pregnancy. Calcium channel blocker, labetalol can be used.[34]Regular blood pressure measurement, proteinuria assessment & inpatient maintenance of patient is always mandatory till the stabilization of blood pressure. ACEI (Angiotensin converting enzyme inhibitors), ARBs (Anngiotensin receptor blockers), sodium nitroprusside are contraindicated in pregnancy. Use of low dose diuretics is discouraged, since, pre-eclampsia is a volume –depleted state. [35]

In the past, Hydralazine (arteriolar dilator) has been used for the management of acute rise of BP. To prevent the maternal hypotension & subsequent fetal distress, 500 ml of crystalloid fluid before or with the first dose of IV hydralazine is recommended. [36]

Labetalol is the first line treatment given intravenously either as bolus doses or as an infusion to manage severe hypertension. [37] In conditions such as bronchial asthma where beta blockers are contraindicated other groups of drugs are indicated such as calcium channel blockers such as oral; not sublingual nifedipine (contraindicated before 20 weeks of gestation), methyldopa, a central sympatholytics, atenolol & metoprolol (cardioselective beta blockers). Recent studies have proved that instead of hydralazine, nifedipine and labetalol have better outcome in the management of pre eclampsia. [36]

Antiplatelet drugs, primarily low dose aspirin, reduce the relative risk of pre-eclampsia by 19% (95% confidence interval 12% to 25%) and of stillbirth or neonatal death by 16% (4% to 26%; 38 trials, 34 010 women). Women at high risk should be offered low dose aspirin. [38]

Magnesium sulphate is an agent that is mainly used in the management of eclampsia (treatment of choice) but it is also used in severe pre eclampsia for prevention of eclampsia and is usually considered once decision for delivery is made or in immediate postpartum period. Use the Collaborative Eclampsia Trial [39] regimen for administration of magnesium sulphate, loading dose of 4 g should be given intravenously over 5 minutes, followed by an infusion of 1 g/hour maintained for 24 hours recurrent seizures should be treated with a further dose of 2–4 g given over 5 minutes. Do not use diazepam, phenytoin or lytic cocktail as an alternative to magnesium sulphate in women with eclampsia. It can interact with nifedipine to produce profound muscle weakness, maternal hypotension & fetal distress.[40,41,42]

If preeclampsia is rapidly getting worse or fetal monitoring suggests that the foetus cannot safely handle labor contractions, a cesarean section delivery is needed. If moderate to severe preeclampsia case, risk of seizures (eclampsia) continues for the first 24 to 48 hours after delivery .So magnesium sulfate can be continued for 24 hours after delivery.

ACUPUNCTUR THERAPY IN PRE ECLAMPSIA:

Acupuncture is used to balance and relax the body, and is most successful in combination with lifestyle adjustments especially regular exercise, stress relief, and a healthy diet. Acupuncture and Pregnancy in Labour, Debra Betts writes, “positive changes are clearly achievable with acupuncture, indicating that it can help the body to normalize and allow women to progress naturally through their pregnancy. These changes include reduction in uric acid to normal levels and stabilization of liver enzymes, as well as the more obvious signs of blood pressure readings remaining within acceptable medical limits”

As per NICE guideline, fluid restriction (total fluid limited to 80ml/hr in women with severe pre eclampsia) to reduce the chance of fluid overload and ultimately leading to pulmonary edema is always a measure if there is no association of maternal hemorrhage.

Pre anaesthetic assessment is also a important measure to be looked as these patients are at risk of edema pharyngo - larynx and require airway assessment. [43,44] Pulmonary edema is a rare but serious complication increasing maternal & perinatal mortality.[45] After delivery, simple analgesics like paracetamol or NSAIDs are used with caution. Oxytocics of choice is syntocinon,

Evaluation of fetus: Fetus is main target to be evaluated in pre eclamptic mother to exclude the IUGR which is done by ultrasound assessment of fetal growth & amniotic fluid volume along with umbilical artery Doppler velocimetry. An ultrasound should be done at 16-20 weeks to see the growth rate of the baby, a “non stress test” along with an “amniotic fluid index” or a “biophysical profile” on a weekly basis towards the end of the pregnancy, to ensure the progress of normal growth.

How to manage the delivery? In mild to moderate pre eclampsia, women may be delivered between 34 – 37 weeks of gestation depending upon the present condition of both mother & baby, presence of risk factors & availability & facility of neonatal ICU. In cases where the blood pressure is severely elevated, or preeclampsia, early delivery is often considered. In general, most of the women with pregnancy-induced hypertension have successful full-term delivery with healthy infants.

RECENT TRENDS OF MANAGEMENT:

Pharmacotherapy is proved to be an effective measure for moderate blood pressure during pregnancy but that must be totally depending on the selection and administration of a proper drug as drug therapy during pregnancy may be risky for both the mother and baby (Teratogenic effect of many drugs). That is the reason why drugs are reserved for use only in cases where the blood pressure is very high, typically >150/100 mmHg.

Short term pharmacotherapy in pre eclamptic women is:

- Labetalol – a beta blocker, Hydralazine – arterial dilator
- Sustained release nifedipine & immediate release nicardipine – a calcium channel blocker
- If the above three modalities of drug treatments failed to control the blood pressure, a drug called diazoxide is used if immediate blood pressure control needed.

Long term pharmacotherapy: (for weeks or months)

- Drug of choice - Labetalol (safe during pregnancy)
- Methyldopa
- Long-acting calcium channel blockers (Nifedipine)

CALCIUM SUPPLEMENTATION IN PRE ECLAMPSIA:

JAMA published a study that reported that consuming sufficient calcium during pregnancy can reduce the risk of PIH and preeclampsia. The researchers found that 1500 – 2000 mg daily of calcium supplementation can lower the risk of PIH by 70% and the risk of preeclampsia by over 60%. Supplemental calcium may exert an effect only in women whose diets are inadequate in calcium. [46] At present, there is not enough evidence to support routine calcium supplementation of all pregnant women. However, high-risk groups, such as pregnant teens, populations with inadequate calcium intake, and women at risk of developing PIH, may benefit from consuming additional dietary calcium.

A study on exercise and gestational hypertension concluded that the most active women were 43% less likely to develop preeclampsia than sedentary women. [47]

THE DANGERS OF PREECLAMPSIA

Though majority of preeclamptic females experience only mild symptoms, some may lead to severe preeclampsia associated with various complications in terms of mother & fetus.

Maternal complications

- ↑ risk of stroke d/t high BP, kidney and liver dysfunction
- Eclampsia (pre eclamptic features associated with seizures), HELLP syndrome

Fetal complications: IUGR d/t high BP and narrow uterine arteries, placental blood flow→ less o2 and nutrients to the fetus→ born with a low birth weight.

- Acidosis d/t less oxygen supply to fetus → produces a toxic byproduct known as lactic acid; if high level accumulates → baby unconscious.
- Preterm Birth: sometimes necessary to deliver baby before 36 weeks may lead to developmental problems and even fetal death.

FUTURE AREA OF INTEREST:

The best way to lower the risk of preeclampsia is to maintain routine prenatal care and regular screening for the condition. Till date, there are no full proved studies available to support routine calcium supplementation of all pregnant women. But definite benefit was seen from consuming additional dietary calcium with high-risk groups, mentioned above.

Therefore the above statement may be an area of future research to identify

- Effect of increasing calcium intake in women with risk of pre eclampsia
- To determine whether women with PIH have impaired calcium absorption
- Whether the timing of calcium supplementation is important,[eg, early in pregnancy when alterations in calcium homeostasis are already beginning to occur [48]
- Whether consumption of dairy foods has a larger impact than does supplemental calcium alone.

Pre conception counseling is always a better option for these women for their subsequent pregnancies to lower the risk of maternal & fetal risks and they require all the preventive measures starting from their antenatal period.

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