4. PREECLAMPSIA

4.1 PREECLAMPSIA

Preeclampsia is a hypertensive disorder of pregnancy. It is a pregnancy specific syndrome that can virtually affect every organ system. It is described as a condition with occurrence of hypertension, proteinuria and edema after 20 weeks of gestation in previously normotensive woman. It can be mild or severe.\textsuperscript{19}

4.1.1 CLASSIFICATION OF HYPERTENSION IN PREGNANCY : \textsuperscript{19}

\textbf{Gestational hypertension} : It is also called transitional hypertension of pregnancy. This is characterized by elevation of blood pressure alone without proteinuria for the first time during pregnancy. High blood pressure reverts back to normal within twelve weeks of pregnancy.

\textbf{Preeclampsia} : It is a multisystem disorder specific to pregnancy defined as gestational hypertension after 20 weeks of gestation associated with proteinuria. It can be mild or severe.

\textbf{Eclampsia} : It is defined as onset of convulsions in pregnant woman who is having preeclampsia. Onset of convulsions is after 20 weeks of gestation or 7 days postpartum.

\textbf{Preeclampsia or Eclampsia superimposed on chronic hypertension} : Preeclampsia or eclampsia may develop on preexisting chronic hypertension. The criteria include onset of proteinuria, hyperuricemia, thrombocytopenia and convulsions in case of eclampsia.

\textbf{Chronic hypertension} : This persists beyond 84 days of pregnancy. It is hypertension detected before 20 weeks of gestation.

4.1.2 DIAGNOSTIC CRITERIA FOR PREECLAMPSIA : \textsuperscript{9,19}

\textbf{Hypertension} : That occurs after 20 weeks of gestation in a woman with previously normal blood pressure.

- Systolic BP : $\geq$ 140 mmHg.
- Diastolic BP : $\geq$ 90 mmHg.
Proteinuria: Urinary excretion of > 300 mg protein in a 24 hours specimen.

Oedema: Generalized oedema or weight gain of atleast 5 pounds in one week.

Any two of the above confirms preeclampsia.

4.1.3 PREECLAMPSIA CAN BE CLASSIFIED INTO MILD OR SEVERE:

Mild-moderate

BP is 140 to 159 mmHg systolic and/or 90 to 109 mmHg diastolic that occurs after 20 weeks of gestation (on 2 occasions at least 6 hours apart) and proteinuria is 300 mg/24 hours.

Severe

BP is ≥160 mmHg systolic and/or ≥110 mmHg diastolic (on 2 occasions at least 6 hours apart, while the patient is on bed rest) and proteinuria is 300 mg/24 hours.

4.1.4 RISK FACTORS:

- Nulliparous women
- Multiple pregnancy
- History of hypertension during previous pregnancy
- Hydatiform mole
- Maternal age more than 35 years
- Diabetes mellitus
- Obesity
- Low socioeconomic status
- Genetic predisposition
- Family history of preeclampsia

4.1.5 ETIOLOGY:

Important factors considered to cause preeclampsia are:

- **Immunological Factors**: A theory cited to account preeclampsia syndrome is dysregulation of maternal immune tolerance to paternally derived placental and
fetal antigens. There is also data that suggests that the risk of preeclampsia is enhanced in circumstances in which formation of blocking antibodies to placental antigenic sites might be impaired. Immune maladaptation has a major role in pathophysiology of preeclampsia.

- Maternal maladaptation to inflammatory and cardiovascular changes of normal pregnancy.

- **Genetic factors**: The hereditary predisposition in preeclampsia is likely to be the result of hundreds of genes, both maternal and paternal that control enzymatic and metabolic functions throughout every organ system.

### 4.1.6 PATHOGENESIS:

- **Abnormal trophoblastic invasion**: In normal pregnancy many cytotrophoblasts remain as single cells that detach from the basement membrane and form cell columns. Cytotrophoblasts from the distal ends of these columns invade the uterus and its arterioles. Thus endovascular invasion is a process in which these cells replace the endothelial and muscular linings of uterine arterioles and initiates maternal blood flow to the placenta and greatly enlarges the vessel diameter. Cells participating in endovascular invasion have two types of interaction with maternal arterioles.

1) Large aggregates of cells are found in vessel lumen adjacent to the apical surface of endothelium or replace it in such a way that they appear directly attached to the vessel wall. Cytotrophoblasts colonize the smooth muscle layer of the vessel and lie within the vessel wall subjacent to the endothelium.

2) Uterine spiral arterioles are invaded by endovascular trophoblasts and undergo extensive remodelling. Muscular linings and vascular endothelium is replaced by trophoblastic cells to enlarge the diameter of the vessel. The veins are superficially invaded. By late second trimester endothelial cells are no longer visible on spiral arterioles and they are lined exclusively by cytotrophoblasts.

However in preeclampsia there is incomplete trophoblastic invasion thus myometrial vessels are not lined with endovascular trophoblasts. Thus the deeper myometrial arterioles do not lose their endothelial lining and musculoelastic tissue and their mean external diameter is only half that of vessels in normal placentae. There is shallow
cytotrophoblastic invasion of the uterus and endovascular invasion does not proceed beyond terminal portions of spiral arterioles. Even if cytotrophoblasts gain access to the vessel wall they spread out in the vessel and fail to aggregate. They tend to remain as single cells and poorly anchor to vessel wall. This trophoblastic invasion correlates with severity of hypertensive disorder. Early preeclamptic arterial changes include endothelial damage, insudation of plasma constituents into the vessel wall, myointimal cell proliferation and necrosis. Accumulation of lipid in myointimal cells and macrophages cause atherosis. Vessels affected by atherosis develop aneurysmal dilatation. Abnormally narrow lumen of spiral arterioles impairs placental blood flow. Diminished perfusion and hypoxia eventually leads to release of placental debris and incites inflammatory response.\(^9,12\)

**Figure 2**

Fig 2: Normal placental implantation shows proliferation of extravillous trophoblasts from an anchoring villus. These trophoblasts invade the decidua and extend into the walls of spiral arterioles to replace the endothelium and muscular wall to create low-resistance vessel. In preeclampsia there is incomplete invasion of spiral arteriolar wall by extravillous trophoblasts. This results in small caliber vessel and high resistance to flow.

- **Endothelial cell activation:** Endothelial cell activation is defined as altered state of endothelial cell differentiation. Various factors such as hypoxia, anti-endothelial cell antibodies and cytokines, reactive oxygen products, physical shear forces may be responsible for endothelial cell dysfunction in preeclampsia.
Endothelial activation or damage leads to secretion of variety of endothelial cell products which can provoke a vicious cycle of vasospasm, disruption of vascular integrity and micro thrombosis that persist until inciting factor is eliminated. Activation and dysfunction of vascular endothelium is provoked by secretion of unknown factors of placental origin in maternal circulation. Widespread endothelial cell changes are seen in preeclampsia. Significantly elevated levels of circulating endothelial cells are found in peripheral blood of preeclamptic women. Damaged endothelial cells produce less nitric oxide and secrete substances that promote coagulation.9

- **Atherosis:** Lesions in the spiral arteries at placental sites called acute atherosis and endothelial cell injury might be a mechanism responsible for diffuse vascular disease in patients with preeclampsia. Histologic changes in placental beds in preeclamptic women showed resemblance to vascular pathology associated with allograft rejection. The extent and severity of vascular lesions seem to be parallel to clinical severity of this syndrome.12

- **Vasospasm:** Increased resistance due to vascular constriction subsequently causes hypertension. Endothelial cell damage causes interstitial leakage through which blood constituents are deposited subendothelially. Mal distribution causes diminished blood flow, ischemia and leads to necrosis and other end organ disturbances.9

- **Nitric oxide:** Nitric oxide is a potent vasodilator which is synthesized form L arginine by endothelial cells. Inhibition of nitric oxide synthesis increases mean arterial pressure, decreases heart rate and reverses pregnancy induced refractoriness to vasopressors. Nitric oxide is likely the compound that maintains normal low pressure vasodilated state which is characteristic of fetoplacental perfusion. It is also produced by fetal endothelium. It appears that preeclampsia is associated with decreased endothelial nitric oxide synthase expression, thus increased nitric oxide inactivation.9

- **Prostaglandins:** Prostaglandins are among the primary vasoactive products of endothelial cells. These bioactive lipids play an important role in physiologic and pathophysiologic modulation of vascular tone as they have profound regulatory effects on vascular smooth muscle cells. The major product produced by endothelial cells is prostacyclin. Prostacyclin is a potent vasodilator and inhibitor
of platelet aggregation. As compared to normal pregnancy endothelial prostacyclin production is decreased in preeclampsia which ultimately leads to vasoconstriction.\textsuperscript{12}

- **Increased pressor response:** Pregnant women normally develop refractoriness to infused vasopressors. Studies showed that normotensive nulliparas remained refractory to infused angiotensin II while those who subsequently became hypertensive lost their refractoriness several weeks before the onset of hypertension.\textsuperscript{9}

- **Endothelins:** The endothelins are a family of 21 amino acid peptides. They are the most potent vasoconstrictors. Endothelin -1 is a vasoactive peptide. It exerts its biological actions on vascular smooth muscle cells. Vascular endothelin is secreted in insufficient amounts under normal conditions. Elevated Endothelin -1 concentration is found in preeclampsia which is a potent vasoconstrictor of human uterine and renal vascular beds, both of which are affected in this syndrome.\textsuperscript{12}
COMPLICATIONS

MATERNAL COMPLICATIONS:

- **Eclampsia**: The major complication of preeclampsia is eclampsia. Onset of convulsions in a woman with preeclampsia is termed as eclampsia. The seizures are generalized and may appear before, during or after labor. The incidence of eclampsia is reported to be 1 in 2000 deliveries in developed countries.\(^9\)

- **HELLP syndrome**: Hemolysis, Elevated liver enzymes and Low platelet count comprise of HELLP syndrome which is one of the serious complications of preeclampsia. Among women with severe preeclampsia 10% manifest with all three abnormalities which eventually leads to adverse outcomes like maternal deaths. HELLP syndrome accounts for most maternal deaths associated with hypertension.\(^20\)

- **Oliguria and Renal failure**: Increased glomerular permeability and damage which eventually causes proteinuria is an integral part of diagnosis of preeclampsia. Oliguria may occur secondary to hemoconcentration and decreased renal perfusion. Persistent oliguria may indicate acute tubular necrosis and acute renal failure in preeclampsia.\(^21\)

- **Cerebrovascular accident**: Acute and severe hypertension leads to cerebrovascular overregulation and vasospasm.\(^9\) Neurological complications like cerebral oedema, cerebral haemorrhage and seizures are associated with preeclampsia. Other central nervous system manifestations include headache, blurred vision, hyperreflexia.\(^21\)

- **Preterm labour and Postpartum hemorrhage.\(^9\)**

- **Shock**: Intravascular volume is already reduced in preeclampsia. Thus even slight loss of blood can lead to shock.\(^9,19\)

- **Sepsis**: Sepsis is due to increased incidence of induction, low resistance and operative interference.\(^19\)

- **Death**: Increased risk for maternal and fetal morbidity and mortality is associated with preeclampsia.\(^22\)
FETAL COMPLICATIONS

- **Growth restriction**: One of the major fetal complications in preeclampsia is growth retardation due to uteroplacental vascular insufficiency. Different degrees of fetal injury is associated with severe preeclampsia. The main impact on the fetus is undernourishment due to utero-placental vascular insufficiency which leads to growth retardation. Studies have shown that babies who suffered intrauterine growth retardation are more likely to develop hypertension, coronary artery disease and diabetes in adult life. Weight of the fetus is highly compromised. Fetal growth restriction is due to impaired gaseous exchange and unavailability of nutrients.\textsuperscript{23,24}

- **Intrauterine asphyxia**: Utero-placental hypoxia is related to abnormal placentation which is seen in preeclampsia. Depending on the severity of the preeclampsia it may lead to intrauterine hypoxia in the fetus.\textsuperscript{25}

- **Intrauterine death**: In severe preeclampsia fetal health and fetal weight is highly compromised leading to various degrees of fetal damage such as to cause fetal death. Intrauterine fetal death may also be due to accidental haemorrhage which is another complication of preeclampsia.\textsuperscript{19} Major complications seen in preeclampsia are intrauterine death, low birth weight and intrauterine growth restriction, thus preeclampsia has great implication on adverse neonatal outcome.\textsuperscript{26}

- **Prematurity**: Spontaneous onset of labour due to accidental haemorrhage or induction of labour are the causes for prematurity.\textsuperscript{19}

- **Oligohydramnios**: Renal agenesis, uteroplacental insufficiency and rupture of amnion results to chronic leakage of the amniotic fluid and may cause oligohydramnios. This may further lead to deformities like flattened facies, dislocated hips and positional abnormalities of hands and feet.\textsuperscript{24}

- **Placental infarction**: A localized area of ischemic tissue necrosis that is due to obstruction of the villous blood supply is termed as placental infarction. A large proportion of the placentae had histological signs of ischemia in pregnancies with mild or severe preeclampsia.\textsuperscript{27}