REVIEW LITERATURE
REVIEW OF LITERATURE

Hypertensive disorders complicating pregnancy were known by 17th century. While the terminology pregnancy induced hypertension (PIH) is used in obstetrics in recent years. Although the disease is known from decades still the etiology of the disease is not known. Extensive research has been done on almost all aspects of the disease and various aetiologies have been put forward from time to time. But not a single of these have been able to draw any conclusion even today.

Most literature have stressed the need for thorough and judicious antenatal care by which PIH can be detected at the earliest and with appropriate care maternal and perinatal mortality and morbidity can be reduced considerably. In developing countries like India, the magnitude of the problem is quite serious. 80% of the population lives in rural area. High incidence of illiteracy and lack of awareness about the value of antenatal care increases the magnitude of problem. Thus incidence of severe preclampsia and eclampsia is much high in comparison to developed countries.

CLASSIFICATION

Hypertension during pregnancy has been variously classified since long time. Unfortunately no classification is adequate if aetiology is unknown. Widely accepted classification is the modified classification of the American College of Obstetricians and Gynaceologists (1996).

According to ACOG (1996) and the Working group on high blood pressure in pregnancy (1990) two etiologic disorders are involved, one disorder develops during pregnancy, labor or the early postpartum period in a previously normotensive non proteinuric woman. The other disorder is related to a preexisting condition.

This has been done to separate hypertension that is some way induced
by pregnancy, from hypertension that merely co exists. Unfortunately chronic hypertension may be aggravated by super imposed preeclampsia or eclampsia.

According to ACOG the diagnosis of hypertension in pregnancy is made by any one of the following criteria:

1. A rise of 30 mmHg or more in systolic blood pressure
2. A rise of 15 mmHg or more in diastolic blood pressure
3. A systolic blood pressure of 140 mmHg or more
4. A diastolic blood pressure of 90 mmHg or more

These alterations in blood pressure should be observed on at least two different occasions at least 6 hours apart.

CLASSIFICATION OF HYPERTENSIVE DISORDERS COMPLICATING PREGNANCY

A. Gestational hypertensive disorders: Pregnancy Induced

Hypertension (PIH)

Hypertension or proteinuria that develops during pregnancy generally after 20 weeks of gestation in the absence of a malai pregnancy or within 7 days postpartum and subsides after delivery.

1. Transient hypertension
2. Gestational proteinuria
3. Preeclampsia
4. Eclampsia

B. Chronic hypertensive disorders

Chronic hypertension and chronic renal disease that pre existed before the pregnancy.

1. Chronic hypertension
2. Preeclampsia or eclampsia super imposed


**DEFINITION**

Each of these forms of hypertension are defined by ACOG 1996 as follows:

**Preeclampsia** - Hypertension associated with proteinuria, greater than 3g/l in a 24 hour urine collection or greater than 1g/l in a random sample, generalised edema, greater than 1" pitting edema after 12 hours of rest in bed or a weight gain of 5lb or more in 1 week or both after 20 weeks of gestation

**Eclampsia** - Convulsions occurring in a patient with preeclampsia

**Chronic hypertension** - The presence of sustained blood pressure of 140/90 mmHg or higher before pregnancy or before 20 weeks

**Preeclampsia or eclampsia superimposed on chronic hypertension** -

The occurrence of preeclampsia or eclampsia in women with chronic hypertension. To make this diagnosis it is necessary to document a rise of 30 mmHg or more in diastolic blood pressure, associated with proteinuria, generalised edema or both

**Transient hypertension**

The development of hypertension during pregnancy or the early puerperium in a previously normotensive women whose pressure normalises within 10 days postpartum. There must be no evidence of preeclampsia.

**Gestational proteinuria**

Development of proteinuria after 20 weeks of gestation in previously non-proteinuric patient without hypertension

**Unclassified hypertensive disorders** -

Those in whom there is not enough information for classification
The most important criterion for differentiation is the magnitude of the blood pressure elevation.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>MILD</th>
<th>SEVERE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>systolic</td>
<td>140-160 mmHg</td>
<td>&gt;160mm Hg</td>
</tr>
<tr>
<td>diastolic</td>
<td>90-110 mmHg</td>
<td>≥110 mm Hg</td>
</tr>
<tr>
<td>2. Proteinuria (24 hr)</td>
<td>3-4g</td>
<td>5g</td>
</tr>
<tr>
<td>Dipstick</td>
<td>+2/+3</td>
<td>+4</td>
</tr>
<tr>
<td>3. Urinary Output</td>
<td>&gt;30ml/hr</td>
<td>&lt;20ml/hr</td>
</tr>
<tr>
<td></td>
<td>&gt;650ml/hr</td>
<td>&lt;500ml/24hr</td>
</tr>
<tr>
<td>4. Convulsions</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>5. Cerebral disturbances</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>Severe headache, hyper reflexia agitation, apprehension, coma, cortical blindness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Red blood cell volume</td>
<td>normal</td>
<td>&lt;32%</td>
</tr>
<tr>
<td>Haematocrit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Visual disturbances</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>scotoma, photophobia blurring or double vision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Pulmonary oedema</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>9. Epigastric or upper abdominal pain</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>10. Fetal distress</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>11. Fetal growth retardation</td>
<td>absent</td>
<td>present</td>
</tr>
</tbody>
</table>
12 HELLP Syndrome
   A Intravascular hemolysis
       Peripheral smear  Normal  Abnormal
       Schistocytes
       S bilirubin   Normal  >1 2 mg %
   B Liver enzymes
       SGOT       Normal  >72 u/l
       SGPT       Normal  >50u/l
       LDH        Normal  >600 u/l
   C Thrombocytopenia  absent  <100,000 /mm³

13 Renal function
   BUN        Normal  >10 mg/dl
   S creatinine Normal  >2 mg/dl
   S uric acid Normal  >10 mg/dl
   creatinine clearance Normal  < 130 ml/min

INCIDENCE

Approximately 6% to 8% of all pregnant women will develop preeclampsia (ACOG; 1996)

The incidence of hypertension, proteinuria and eclampsia vary from different institutions in different countries with widely varying maternal and perinatal mortality. These differences in incidence may result from differences in definition and varying condition of B P measurement as well as differences in age, parity and geographical differences.

It has been reported that the incidence of preeclampsia is about 70% of all hypertensive disorders of pregnancy (Mclatney 1964, Brown, 1949) Lewis reported (1965) the incidence of preeclampsia is about 3 - 10%. According to Mudahar and Menon (1972) the incidence of preeclampsia is 7 - 9 %
Lewis (1965) mentioned the incidence of eclampsia as about 1 in 1000 in England. The incidence of eclampsia reported from the leading centres of India varies from 0.83 to 16% (Mitra and Dasgupta, 1967).

According to the American College of Obstetricians and Gynaecologists (1996) the factors associated with higher than normal incidence of preeclampsia are:

1. Familial history
2. Preexisting vascular disease such as diabetes or chronic hypertension
3. Exposure to a super abundance of chorionic villi (multiple gestation and hydatidiform mole)
4. Rh incompatibility
5. Anti phospholipid syndrome

The incidence of preeclampsia in developing and developed countries is nearly similar but the incidence of severe variety and of eclampsia is much higher in developing countries and this is mainly due to lack of antenatal care.

AGE

The strongest risk factors for preeclampsia are a primigravida younger than 19 years or older than 40 years (Roberts, 1994a). Age has an important influence on the incidence of hypertensive and proteinuric disorders and on perinatal mortality. Young primigravida under 20 and all patients over the age of 30 years have increased perinatal mortality. Nelson reported that hypertensive disorders in pregnancy increased with increasing incidence of latent or overt essential hypertension.

PARITY

Parity has similarly an important influence on the incidence of hypertension and proteinuria and on associated perinatal mortality. Dewhurst found that primigravides have approximately double the incidence of hypertension with proteinuria.
The incidence of hypertension only or superimposed preeclampsia however apparently increases with rising parity and it is due to increase in age, particularly over the age of 30 yrs. PIH is occasionally seen in multipara with multiple pregnancy or fetal hydrops. Mudaliar and Menon (1972) and Dawn (1974) reported that the incidence of preeclampsia in primigravida is about 70%.

SOCIAL STATUS

Lower socioeconomic groups are reported to have a high incidence of pre eclampsia and eclampsia. PIH is more common in the poor and underprivileged communities and it is due to poor dietary habits with ignorance and apathy leading to poor antenatal care. However, Duffus and Mc Gilivary (1968) found that difference between social classes are small if allowance is made for age and parity for the level of antenatal care and intrapartum care and smoking habits.

Obesity predisposes the women more susceptible to hypertensive disorder during pregnancy. Hobson (1948) presented evidence that dietary deficiency predispose to toxaemia. It has been suggested that hypoproteinaemia or vitamin deficiency might play causative role. Ian Donald also had opinion that diet low in calories, protein, vitamins and minerals may play a causative role. The WHO expert committee on pregnancy and lactation (1965) concluded that there is no scientific basis.

FAMILIAL AND GENETIC FACTORS

The tendency of preeclampsia and eclampsia is inherited. It is shown that close relatives of sufferers from this condition also have a high incidence of this disease. (Chesley Cooper, 1968) Some studies support the
immunologic factors in preeclampsia

Kilpatrick and associates (1989) reported on association between the histocompatibility antigen HLA-DRH and proteinuria and hypertension but Hayward et al. (1992) found no such association Therefore an appropriate genetic marker has not been identified.

Chesley and Cooper (1986) reported that hypertension and proteinuria in pregnancy are most likely due to a Mendelian recessive trait. A molecular variant of angiotensinogen gene has also been reported by Ward and associates (1993). Dizon - Townsend and coworkers (1996) described an association of factor I Leiden mutation with severe preeclampsia.

ETIOLOGY

Theories about the cause of PIH must account for that the PIH is more likely to develop in

1. Exposed to chorionic villi for the first time
2. Super abundance of chorionic villi e.g., twins or hydatidiform mole
3. Genetic predisposition

(a) Immunological mechanisms

The risk of PIH is enhanced in circumstances where formation of blocking antibodies to antigenic sites on the placenta might be impaired. This may arise during immunosuppressive therapy to protect a renal transplant, where effective immunisation by previous pregnancy is lacking or where the number of antigenic sites provided by the placenta is unusually great compared with the amount of antibody as in multiple fetus (Beer 1978)
Hotmeyri and colleagues (1991) reported C4 concentrations to be reduced in hypertensive pregnant women with proteinuria. Hoff and associates (1992) found a maternal-fetal HLADR relationship with PIH. Haeger and associates (1992) reported that complement, neutrophils, and macrophages are activated in women with severe preeclampsia.

(b) **Genetic Predisposition**

Chesley and Cooper (1986) studied the possibility of preeclampsia being related to a single recessive gene. Ward and associates (1993) reported that women carrying the angiotensinogen gene variant T235 had a higher incidence of PIH. Rizos Townsend and colleagues (1996) found a higher incidence of factor V Leiden mutations in preeclampsia.

(c) **Dietary deficiencies**

A correlation may exist between adequate magnesium and a decreased risk of preeclampsia (Repke 1991). Incidence of hypertension is higher in obese women and the incidence increases with prepregnancy weight (Sibai and coworkers 1995a).

Calcium supplementation appears to reduce the risk of preeclampsia (Catioli and colleagues 1994) as calcium can decrease the vascular sensitivity to angiotensin by stimulating prostacyclin or nitric oxide synthesis.

Sanchez-Ramos (1994b) reported that after mid-pregnancy daily dietary supplementation with 2g of elemental calcium reduced the incidence of hypertension. Proteins promote cellular growth and are important in maintaining a normal serum osmotic pressure, therefore protein could be signifi-
cant in preventing edema and elevated blood pressure (Wotherspoon Roberts Williams 1997)

(d) Vasoactive compounds

High levels of endothelin -1 have been reported in preeclamptic women (Clark 1992) Wang and colleagues (1991 a, b) concluded that vasodilating actions of prostacyclin and antioxidant activity of vit E is used with advancing gestation. But in preeclampsia the ratio of prostacyclin to TXA2 and vitamin E to lipid peroxides was reversed. Thus increased TXA2 resulted in increased vasospasm and platelet destruction and increased lipid peroxides increased endothelial damage.

Cigarette smoking has been reported to reduce the incidence of PIH by stimulating the decrease in the activity of platelet-activating factor acetohydrolase

(e) Endothelial dysfunction

Immunologically mediated deficiency in trophoblast invasion of the spiral arteries leads to poorly profused fetoplacental unit resulting in vascular endothelium dysfunction (de Groot and colleag 1995)

Bakei et al (1995) have shown that vascular endothelial growth factor VEGF levels are elevated in serum of preeclamptic women which may activated endothelial cells. Similarly platelet derived growth factor may be operative (Guiski et al 1996)
PATHOPHYSIOLOGY

Abnormal placentation is one of the initial events of the disease. In the first 12 weeks of normal pregnancy cytotrophoblastic cells proliferate and invade intra decidual portion of spiral arteries. They spread up the lumen, invade the vessel walls, replacing the maternal endothelium and destroying the elastic and muscular tissue which is replaced by fibrinoid material, thus opening up the spiral arteries, increasing blood flow and making them unresponsive to normal vasoconstrictor stimuli.

Between 12 and 16 weeks there is a further secondary wave of invasion by the cytotrophoblast into myometrial stroma and lumen of intra myometrial segments of the spiral arteries extending as far as distal portion of radial arteries thus producing further increase in chorio-decidual blood flow. This change has been designated as physiological change of pregnancy (Brosens et al 1972).

Preeclampsia is characterised by a failure in the second wave of trophoblastic invasion, so that the musculo elastic media of the spiral arteries in the myometrium is retained, the vessels fail to dilate and remain responsive to vasoconstrictor stimuli resulting in decreased chorio-decidual flow (Dixon and Robertson 1961) The resulting placental ischemia stimulates the release of a factor that is toxic to endothelial cells (De Groot et al 1995).

With endothelial damage there is less production of vasodilators such as prostacyclin and nitric oxide and increased production of such vaso pressors as thromboxane, endothelin - 1, oxygen free radical and lipid peroxides causing an increased vascular sensivity to angiotensin II (de Jong et al 1991 Wallen buig et al 1991) Decreased production of nitric oxide by terminal placental vessels, along with increased TXA2 causes platelet adhesion to the surface of the trophoblast resulting in intervillous thrombi (Ghabour et al 1995) thus further altering blood flow to the fetus.

Endothelin - 1, free radicals and lipid peroxides inactivate the vasodilator
effect of nitric oxide (Zeeman, Dekker 1992) Multiple organ endothelial cell injury ensues, (Nova et al 1991), generalised vasospasm results, leading to poor tissue perfusion, increased total peripheral resistance with subsequent elevation of blood pressure and increased endothelial cell permeability which allows intra vascular protein and fluid loss (Friedman 1991)

Some times atheroma like lesions are present in the spiral arteries hence the name acute atherosis (Zeek and Assoli 1950)

Vasospasm is basic to the pathophysiology of preeclampsia and eclampsia (Volhard 1981) This concept is based upon direct observations of small blood vessels in nail beds, ocular fundi and bulbar conjunctivae and it has been suised from histological changes in various affected organs (Hinselmann 924 Landesman et al 1954)

**Resulting Pathophysiologic changes**

- **Hyperdynamic circulation**
  Increase in maternal cardiac output, rather than increased peripheral vascular resistance is the most common haemodynamic feature (Easterling et al 1990) This elevation in cardiac output is already apparent at 11 weeks The systemic vascular resistance of preeclampsia eclampsia patients was always less than that of normotensive patients

- **Change in intravascular volume**
  The increase in intravascular volume that normally occurs during pregnancy is absent in preeclampsia patients The reduced volume is predominantly of plasma and as a result hemoconcentration results as the disease progresses

- **Increased pressor response**
  Gent and workers (1973) demonstrated that increased vascular sensitivity to angiotensinogen II clearly preceded the onset of pregnancy induced hypertension
• Utero placental Insufficiency

Utero placental perfusion is compromised 50% even before preeclamptic symptoms, related to pathologic spiral arteriole lesions and a deficiency of prostacyclin (Usta, Sibai 1996)

• Renal damage

In 70% of preeclamptic cases, glomerular endothelial damage, fibrin deposition and resulting ischemia reduces renal plasma flow and glomerular filtration rate (Friedman 1991) Protein mainly albumin is lost. Urine acid and creatinine clearance is decreased

• Fluid and electrolyte balance

Decreased serum albumin causes a decrease in the plasma colloid osmotic pressure, an increase in intracellular edema and haemoconcentration (ACOG 1996)

Worsening Pathophysiologic changes.

As preeclampsia progresses, the following systemic changes occur, which are signs that the condition is worsening and result in maternal complications.

• Pulmonary edema

It is due to volume overload as a result of left ventricular failure, excessive fluid infusion or postpartum diuresis

• Central nervous system

Endothelial damage to cortical region leads to fibrin deposition, edema, haemorrhage thus causing hyperreflexia, severe headache & seizures (Cilastrap, Gant 1990)

• Ophthalmic involvement

Usual change, such as scotoma, photophobia blurring of double vision, can occur due to retinal artery spasm (Wallenburg, 1989)
• **Haemodynamic change**
  Normal to increased cardiac output is due to decreased ventricular preload occurs (Sibai Mabie 1991)

• **Coagulation involvement**
  Inappropriate activation of coagulation system leading to disseminated intravascular coagulopathy (DIC)

• **Hepatic involvement**
  Hepatic ischemia leading to Beiportal haemorrhagic necrosis and subcapsular haemtoma occurs in 10% of all preeclamptic patients (Sibai 1996a) Warning signs of hepatic involvement such as right upper quadrant pain or epigastric pain nausea and vomiting (Phelans Easter 1990) can indicate impending eclampsia

• **HELLP Syndrome Development**
  In 2% to 12% of pre eclamptic cases, the HELLP syndrome characterised by hemolysis of red blood cells, elevated liver enzymes and low platelets may develop (Martin et al 1995, Sibai et al 1993a, Weinstein, 1985).

  This cascade of event is the result of endothelial cell damage leading to platelet activation and aggregation and fibrin deposition which results in decreased platelets and red blood cells are torn while passing through narrowed vessels (Walsh 1990)

  Hyperbilirubinemia (jaundice) may develop as a result of hemolysis
  Liver enzymes are elevated when liver tissue is necrotic
  Normal blood pressure is found in approximately 10% to 20% of the patients with HELLP syndrome (Sibai et al 1993a)
Pathophysiologic changes of preeclampsia

Decreased placental perfusion. Placental production of a substance toxic to endothelial cells.

- Vasospasm
  - Decreased nitric oxide
  - Increased endothelin-I
  - Fluid shifts from intra vascular to intracellular space (Decreased plasma volume, Increase haematocrit)
  - Intravascular coagulation

Endothelial cell damage

- Generalised vasoconstriction
- Uteroplacental arteole lesions
- Increased uterine contractility

HYPERTENSION
- Intrauterine growth restriction
- Abruptio placentae

PROTIENURIA
- Increased plasma uric acid and creatinine
- Oliguria
- Increased sodium retention

Glomerular damage
- Visible edema of face, hands, and abdomen
- Pitting edema after 12hr of bed rest

Generalised edema
- Headaches
- Hyperreflexia
- Seizure activity

Cortical brain Spasms

Pulmonary edema
- Dyspnoea

Retinal arteriolar spasms
- Blurred vision
- Scotoma

Hemolysis of red blood cells (Torn red blood cells)
- Decreased hemoglobin
- Maternal hyperbilirubinemia

- Elevated Liver enzymes (AST and LDH)
- Nausea/vomiting
- Epigastric pain
- Right upper quadrant pain

Hepatic microemboli liver damage
- Decreased blood glucose
- Liver rupture

Platelet aggregation and fibrin deposition Low Platelet count (thrombocytopenia), DIC
Usual change, such as scotoma, photophobia blurring or double vision, can occur due to retinal arteriolar spasm (Wallenburg, 1989)

**Maternal effects**

Preeclampsia is a very serious disease and is the second leading cause of maternal mortality (ACOG 1996) If preeclampsia is treated early and effectively maternal mortality is very low Eclampsia is a major complication of hypertensive disease of pregnancy with a perinatal mortality of up to 30-40% and maternal mortality of 3-4% (Dewhurst 1995) In most cases, the eclamptic convulsion is preceded by certain premonitory symptoms and signs These include aura with increasing headache, visual disturbances, epigastric pain, vomiting, raised B.P, marked increase in proteinuria, rapidly increasing generalized edema oliguria and hyperreflexia (Dewhurst 1995)

Pulmonary edema may develop due to cardiac failure secondary to hypertension, prolonged hypoxia causing adult respiratory distress syndrome Preeclamptic patient develops pulmonary edema more easily due to her reduced plasma proteins and plasma oncotic pressure.

As per Chesley (1998) cerebrovascular accident causes 15-20% death in eclampsia and 80% of fatal cases have petechial and punctate haemorrhages to massive bleeding According to (Evan et al 1983,) occurrence of haemorrhage is the major cause of maternal death However Ballentine (1985) reported that it is usual except as a terminal event of fatal eclampsia

Sometimes periportal and subcapsular haemorrhage may occur in preeclampsia and eclampsia Weinstein (1982) stated that when hepatic pain epigastric pain and right hypochondrial tenderness is associated with abnormal liver function tests and low platelet count the condition is called HELLP syndrome
Mackena et al (1983) stated that the importance of this syndrome is not so much except that it may be an indication for immediate delivery. Acute renal failure complicating PIH may be due to a range of lesions from simple hypovolemia with reduced renal blood flow to patchy or complete tubular or cortical necrosis.

Chesley (1978) reported that tubular necrosis was the commonest finding on renal biopsy and patchy cortical necrosis was present in 257 of cases. Walls et al (1978) had described a case where after oliguria for 60 days continuing improvement up to 3 years had occurred.

DIC is a common feature of hypertensive disorder in pregnancy. Redman et al (1978) and Williams (1983) stated that decreased platelet count is an essential feature of preeclampsia due to DIC and it often precedes the onset of hypertension. Pritchard et al (1976) reported platelets count of less than 150,000/mm³ in 26% and less than 1,00,000/mm³ in 10% of eclamptic women.

Pritchard et al (1954) found presence of fragmented RBC and reticulocytes in peripheral blood smear in pre-eclamptic and eclamptic women. Braill et al (1962) reported that haemoglobinuria and hemoglobinuria in association with PIH is due to microangiopathic hemolytic anaemia.

Preeclamptic patients often complain of visual disturbances which include blurring of vision, diplopia and amaurosis. Schiotz (1921) noted retinitis in 13% of pre-eclamptic women and 42% in eclamptic women and retinal detachment in 7 out of 122 eclamptic mothers.
Fetal and Neonatal effects

Perinatal mortality related to mild eclampsia ranges from 1% to 8% increasing to an overall average of 15% in severe preeclampsia, with a higher incidence found with an early onset and lower incidence if the onset develops after 37 weeks of gestation (Sibai et al 1990)

Placental abruption is regarded as a complication of hypertension in pregnancy. Hypertension and proteinuria are very commonly found after placental abruption.

Mac Gillivray (1961) found that 38% of primigravida and 49% of multigravida remain normotensive after placental abruption. Chesley (1978) stated that placental abruption is more common in essential hypertension than to preeclampsia and eclampsia.

The majority of perinatal losses are related to placental insufficiency, which causes intrauterine growth restriction (IUGR), prematurity associated with preterm delivery or abruptio placentae.

The occurrence of IUGR in hypertensive disorders in pregnancy is influenced by many factors such as level of B.P., the presence of proteinuria, nutrition, and smoking.

Leather et al. (1968) reported intrauterine fetal demise and IUGR were related to duration of hypertension and presence of proteinuria. Mclellan et al. (1972) showed that placental hypoxia is an important part of pathophysiology of hypertension and the ultrastructural changes in the placenta of preeclamptic women paralleled the severity of the disease.

Chamberlain et al. (1970) mentioned increased incidence of perinatal loss and IUGR in severe preeclampsia.
Mac Gillivray (1977) noticed that in hypertension alone, the mean birth weight for gestational age was the same as in normotensive women, but in presence of proteinuria the birth weight was reduced at all gestational ages.

Long et al (1980) found that the prevalence of IUGR in early onset preeclampsia was 18.2%, compared with 5.6% in late onset disease. Redman (1983) and Wei (1978) also reported that IUGR is a common complication of preeclampsia. McDonald and Gant (1985) found IUGR is less common with PIH than with pregnancy aggravated hypertension. If the disease progresses into the HELLP syndrome or eclampsia or exists in the presence of preexisting hypertension, perinatal mortality can be as high as 35% to 60% (Sibai 1988).

**Signs and Symptoms**

The cardinal signs of preeclampsia are hypertension and proteinuria or overt generalised edema or both. Except in the presence of a hydatidiform mole, these signs develop after 20 weeks of gestation. An elevated blood pressure is usually the first sign to develop in the early stages, however the disease may be diagnosed without the presence of proteinuria.

**Hypertension**

Hypertension is diagnosed if one of the following is present: the systolic blood pressure is 140 mmHg or greater, the diastolic blood pressure is 90 mm Hg or greater. The mean arterial pressure (MAP) is 105 or greater or an increase in MAP is 20 or more. In 1955, Nelson stated that a diastolic blood pressure (Point IV of Korotkoff sound) of 90 mmHg or more should be considered as hypertension. The blood pressure mostly the diastolic pressure,
normally drops, slightly during the second trimester of pregnancy due to marked peripheral vasodilation and return to its original baseline level during the third trimester. This fall in B P occurs in both normotensive and hypertensive women & women with chronic hypertension may be normotensive in early pregnancy Macgillivary (1901) has shown that absolute level of B P gives as much information in terms of prognosis and management as the rise during pregnancy It also overcomes the difficulties with regard to B P measurement made in early pregnancy which may be falsely low and lead to an apparent false rise in B P

Page (1992) used the MAP in the definition of hypertension and regarded the B P as abnormal when MAP is 105 mm Hg or greater. However Friendman and Neff 1977 stated that MAP requires calculation and is therefore unlikely to be used in clinical practice and no better than the diastolic blood pressure as an indicator of fetal outcome.

To avoid false diagnosis of hypertension on the basis of transient rise in B P due to excitement and stress, it is necessary to record B P at least two occasions 6 hours or more apart. The B P should be measured in the same arm and with the patient in the same position each time. If the patient is sitting, her arm should rest on a 30-degree tilt on her left side and the blood pressure cuff should be on her right arm so the cuff is at the same level as the heart (Working group on high blood pressure in pregnancy 1990)

During pregnancy Korotkoff phase V most accurately reflected intra arterial pressure (Brown and other 1994) but because of high cardiac output stalive of pregnancy the DBP falls to zero before the Korotkoff phase V is heard in 15% woman (WHO 1987) therefore according to the Working Group on High blood pressure in pregnancy 1990, the systolic and diastolic phase IV and V
blood pressure readings should be recorded during pregnancy.

**Proteinuria**

A small amount of protein is normally present in urine. In pregnancy due to increased glomerular filtration rate more amount of protein may be normally present, it is up to 300mg/24 hours of urine. The Committee on Terminology of American College of Obstetricians and Gynaecologists (Hughes 1972) recommended that a total protein concentration of 300 mg/L should be regarded as abnormal. McCartney and co-workers (1971) in their extensive experience, studying renal biopsy specimens of hypertensive pregnant women, invariably found that proteinuria was present when the glomerular lesion characteristic of preeclampsia was evident.

Sheehan and Lynch 1973 said that proteinuria is the main clinical distinguishing feature of preeclampsia to the extent of being pathognomonic in the absence of renal disease. Chesley found only 2 5% cases of eclampsia without proteinuria in urine, examined immediately before convulsion and in 50% of cases of eclampsia there was a + proteinuria. Moore and Redman (1987) stated that the kidney is the principal, target organ for preeclamptic process and proteinuria one of the cardinal signs of preeclampsia, is a sign of advanced preeclampsia with a limited prognosis and a less favourable fetal outcome.

Proteinuria is diagnosed if one of the following is present:

- More than 300mg of protein per litre of urine is found in a 24-hour urine collection.
- More than 100mg of protein per litre of urine is found in at least two random urine specimens collected on two or more occasions at least 6 hours
apart when the specific gravity is 1.030 or less and the pH is less than 8. (This is indicated as +2 or greater on a dipstick)

**Pathologic edema**

Pathologic edema must be differentiated from normal physiologic edema that occurs in approximately 80% or all pregnancies (Mc Anulhy and others 1995)

Pathologic edema is indicated by non dependent edema of the face, hands and abdomen, non responsive to 12 hours of bed rest or by a rapid weight gain of more than 2 pounds in 1 week

**Degree of edema**

<table>
<thead>
<tr>
<th>Physical finding</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal edema of lower extremities</td>
<td>+1</td>
</tr>
<tr>
<td>Marked edema of lower extremities</td>
<td>+2</td>
</tr>
<tr>
<td>Edema of lower extremities, face, hand</td>
<td>+3</td>
</tr>
<tr>
<td>Generalised massive edema</td>
<td></td>
</tr>
<tr>
<td>Involving abdomen and sacrum</td>
<td>+4</td>
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</table>

**Subjective signs**

Subjective signs of preeclampsia suggesting end organ involvement are:

- Headaches
- Visual changes such as blurred vision
- Rapid onset or edema of the face or abdomen
- Pitting edema of feet after 12 hours of bedrest
- Oliguria
- Hyper reflexia
- Nausea or vomiting
- Epigastric pain

**HELLP Syndrome signs**

These are epigastric pain or right upper quadrant tenderness, nausea or vomiting, headaches, malaise, jaundice and haematuria
Morphologic changes

Kidney has been the most studied organ in women with preeclampsia and the lesion is known as glomerular endotheliosis Winemiller (1959). Deposits of osmophilic material that reacts with antibodies against fibrinogen and fibrin are present between basal membrane and the endothelial cells along with an increase in the cytoplasm.

PREDICTIVE TESTS -

Because the antihypertensive disease process begins long before signs and symptoms appear several tests have been proposed to identify women at risk of developing preeclampsia.

a) Cold pressor test
b) The isometric hand grip exercise
c) Roll over test
d) Second trimester mean arterial pressure
e) Urinary calcium, serum iron and carboxy hemoglobin
t) Plasma fibronectin, antithrombin III
g) Doppler ultrasound

Rollover test remains an effective screening test to identify women at risk of developing PIH.

A positive test when the patient rolls over from the lateral decubitus to the supine position (Gant and workers 1974)

Urinary calcium - Sanchez Romas 1991 have demonstrated that preeclampsia is associated with hypocaliuria

A urinary calcium equal to or less than 12mg/dl in a 24 hr collected urine or determination of the calcium/creatinine ratio in a randomly ob-
tained single voided urine sample

(Lockwood 1990) that increased plasma levels of endothelium ori-
nated fibronectin precede the clinical signs of preeclampsia
Dekker and Sibai 1991 concluded that there is currently no ideal predictive test

Prevention of PIH

Several approaches to the prevention of preeclampsia have been pro-
posed.

Diuretics

Administration of diuretics in 1960's was based on the theory that so-
dium retention was etiologically related to the disorder.

But several cases of diuretic induced maternal volume depletion elec-
trolyte imbalance and pancreatitis, neonatal thrombocytopenia, jaundices and adverse effect on placental perfusion precludes its use.

Adequate nutrition

Administration of 600mg per day of supplemental calcium to normal
gravidae enhanced pressor resistance to infused angiotensin (Kawasaki el al).
Deficiency of magnesium has been been employed in the pathogenesis of
hypertension and vasospasm of preeclampsia. All pregnant patients should
receive a nutritious balanced diet containing at least 60 to 70g of protein,
1200 mg of calcium, and and adequate intake of magnesium and sodium
(salt).
A supplement of 2g of total calcium gluconate per day has been shown to
decrease the risk of preeclampsia (Sanchez Ramos et al 1994)
Adequate rest.

Bed rest in lateral recumbent position takes the pressure of the gravid uterus off the inferior vena cava. This facilitates venous return, increases the circulatory volume which increases renal blood flow and promotes diuresis thus enhancing placental perfusion.

Release of Angiotensin II is also decreased (Sibai 1988). Bed rest also mobilises oedematous fluid back into the intravascular space (Zuspan 1991a).

Water therapy

In the presence of edema, immersion in water can mobilize extravascular fluid, initiate diuresis and decrease the renin, angiotensin, aldosterone and vasopressin levels (Katz and others 1990). It has also been shown to reverse oligohydramnios resulting from uteroplacental insufficiency (Strong 1993).
**Low dose aspirin**

Low dose aspirin therapy 60 to 80 mg/day may reduce the incidence of preeclampsia in some women at risk for the disease (Hauth, Cunningham 1995, Royal college of obstetricians and Gynecologists 1996) Aspirin in small amounts (30-100 mg/day) inhibits 5 platelet thromboxane synthesis to a greater degree thus inhibiting platelet aggregation Dekkei and Sibai stated that low dose aspirin increases pressor refractoriness to ANG-II in both normal and hypertensive gravidas

This low dose appears to have no harmful effect on fetus (CLASP collaborative group 1995) There is an increased incidence of abruptio placentae (Hauth and other 1993)

**Early and appropriate prenatal care**

Early detection of PIH is helpful in lowering the high maternal and fetal mortality associated with the disease

**Antihypertensive therapy of PIH**

Hypertension in pregnancy is a different entity unlike hypertension in non-pregnant individual. Here patients are exposed to hypertension for a short period, so most obstetricians agree that drug therapy has little place in the management of mild hypertension occurring late in the third trimester Perinatal mortality has been shown to be similar in both treated and untreated group (Sibai et al, 1983). But in severe PIH particularly associated with proteinuria perinatal mortality is raised and active management results in lower rate (Redman et al, 1977). Severe hypertension in pregnancy has been shown to damage small arteries and arterioles quickly (Mac Gillivary et al 1962), and is a direct threat to maternal well being.
The aim of treatment of severe hypertension is to prevent maternal convulsion and to deliver a live baby in best condition possible.

Blood pressure of 170 to 180/110 to 120 mm hg represent MAP of 130 to 140 mmhg. This is close to the limit where experimental hypertensive vascular damage begins. Thus on general principle, blood pressure at or above 170/110 mm Kg should be treated promptly.

There is still a controversy about the need to treat mild hypertension in pregnancy. Recently, Sibai and associates (1987) reported their result from a well designed randomised comparative study done to evaluate the effectiveness of labetalol and hospitalisation done alone for 200 nulliparous woman with proteinuic mild PIH diagnosed between 26 and 35 wk of pregnancy. Although women given labetalol had significantly lower MAP there was no differences between the groups for mean pregnancy prolongation, gestational age at delivery or birth weight. The cesarean section rates were similar, as were the number of neonates admitted to NICU.

Rubin and colleagues (1983) randomised 120 women of mixed parity who were mildly to moderately hypertensive during last trimester to be given atenolol or placebo. There was a significant reduction of BP, less frequently developed proteinuria and had few hospital admission. There was no advantage found for infants born to mothers.

**METHYLDOPA**

Methyldopa is primarily a central alpha-receptor stimulant which causes peripheral vasodilatation by reducing sympathetic nervous system outflow, rather than cardiac output. It is the antihypertensive agent most frequently used by British obstetricians (Chamberlain, 1978).
Initial dose is 250 mg BD which can be increased to a maximum of 2g/day in divided doses.

The fall in arterial pressure is maximum 6-8 hours after an oral or intravenous dose. Renal blood flow is maintained and renal function is unchanged during treatment. The drug is generally given single dose at night to decrease the side effect of sedation. It may produce some other side effects including depression, nightmares, galactorrhoea, postural hypotension and less commonly cholestatic jaundice, hemolytic anaemia and a positive coombs test but these are uncommon.

Methyldopa has a long history of effective use in pregnancy and has been prospectively evaluated in randomized clinical trials.

Redman et al studied 242 gravidas with diastolic blood pressures of 90 to 110 mm Hg randomised to receive either methyldopa or no treatment. There were nine pregnancy losses in the control group while there was only one fetal loss in the treated group.

Based on these results which were similar to a study by Leather et al (1968) where 100 woman were randomly allocated to no treatment and methyldopa combined with Bendrofluoride the authors concluded that the benefits could not be attributed to the control of hypertension per se and suggested that some as yet undefined action of methyldopa may have been responsible.

Sibai et al failed to demonstrate any reduction in midtrimester fetal loss consequent to methyldopa treatment. Redman and Colleagues, reported that the frequency of severe hypertension occurring antenatally or in labor was significantly reduced by methyldopa.
The maternal adverse effects are mild & well tolerated Redman et al gave reassuring data regarding the fetal and neonatal safety of methyldopa Birth weights, neonatal complications and progress in the first year of life were similar in methyldopa and control group

Methyldopa remains the drug of first choice because of wide experience of its use in pregnancy and the reassuring follow up of 100 children exposed to the drug in utero and at 7 years of age (Clock burn 1982) The average head circumference of the neonate was slightly but significantly smaller in treated cases 34.2 ± 1.7 cm versus control of 46 ± 1.3 cm of (Moar et al, 1978) This difference was not associated with the total dose of methyldopa prescribed, duration of treatment or average daily dose

No effect of methyldopa on head circumference were seen in a smaller trial (Fidler et al, 1983) There is no contraindication to the administration of methyldopa during lactation (Jones et al, 1978 and White et al 1985)

In the study done by Redman, Belin, Bonnar & Ounsted there were 9 pregnancy losses in the control group compared with 1 in the treated group a significant reduction associated with active treatment The highest perinatal mortality of 60% was in the severely hypertensive group The mean length of gestation at delivery, birth weight and placental weights of viable pregnancies were similar in the early entry group For the late entry group, the treated pregnancies resulted in heavier infants.

Oedema is known to be an unreliable sign of preeclampsia as it is also present in normal pregnancies Since methyldopa may cause fluid retention, it was not demonstrated in this trial

The concentration of proteinuria reported were low in the treated group There was a decrease in the plasma urate values In the trial reported by Leather
1968 antihypertensive treatment prolonged gestation.

Blood pressure were significantly reduced in the treated patients. It has been suggested that chronic lowering of blood pressure in pregnancy may cause placental underperfusion and fetal deprivation. The multivariate analysis of fetal growth showed no effect, favourable or unfavourable which could be ascribed to treatment despite effective reduction of blood pressure.

The use of methyldopa for chronic maternal hypertension is therefore safe for mother and fetus. All though methyldopa is considered to have a wide safe margin of safety in the treatment of chronic hypertension in pregnancy, potentially serious adverse effects can occur. It is important to monitor serum aspartate transferase levels after initiation of methyldopa therapy (Smith 1995).

Short term treatment with methyldopa in last trimester in women with PIH reduced maternal blood pressure and heart rate but had no adverse effects on utero-placental and fetal haemodynamics (Ingemarsson, Ralnam).

Methyldopa decreases placental vascular resistance measured as pulsatility index (Pl) in mild preeclampsic chronic hypertensive woman (Rey 1992).

Infants of mothers on high 1.25 - 2 g/day or low 1 gm/day methyldopa had gestational age, head circumference, acid base balance, Apgar score, blood pressure similar to those born in healthy control mother. The birth weight of infants of the high methyldopa group however were significantly lower than in the low dose or control group (Sulgok, Hartman 1991).

**NIFEDIPINE**

Nifedipine is a calcium channel blocking drug, widely used in non pregnant patients in the treatment of angina and the acute and chronic treat-
ment of hypertension. In the latter roles it has proved very effective (Bertel et al. 1983) but mild side effects such as headaches, flushing, and ankle swelling appear which are rarely trouble some. In obstetrics it has been used as a tocolytic agent (Ulmsten et al. 1980, Read & Well by 1986) and one trial included patients with hypertension (Ulmsten 1984). In acute hypertensive situations in pregnancy and puerperium, oral or sublingual capsules have been shown to be effective, rapid in onset and to cause no deterioration in the fetal heart rate recording (Walters & Redman 1984).

It has been used in severe preeclampsia for periods up to 8 days (Greer et al. 1986) as a second line treatment when labetalol alone had failed to control the blood pressure. In study of G. Constantine, Beevers, Reynolds, Luesly (1987). The addition of nifedipine to the antihypertensive regimen was effective in controlling the blood pressure in 20 patients, the mean pre and post nifedipine blood pressure being 149/98 mmHg (SD 11/6) and 132/81 mm Hg (SD 17 6/14) respectively. This suggests that the slow release preparation of nifedipine to be an effective antihypertensive agent in pregnancy.

This mean gestational age at delivery was 35 weeks. Of the 21 live born infants 15 (71%) were born by cesarean section. There were three perinatal deaths in the study of Constantine measured in term of perinatal mortality and comparing the results with the studies of (Liebesman et al. 1978, Rubin et al. 1982, Sibai et al. 1983, Maibe et al. 1986) the use of nifedipine was found to be useful.

In utero studies have demonstrated that nifedipine causes vasodilation in human pregnant uterine vessel as well as in foetal placental vessels (Maigaard et al. 1984, 1986). Thus it may be anticipated that nifedipine at least maintains and possibly increases uteroplacental perfusion.
Both nifedipine (Walters and Redman 1984) and nitrendipine (Allen et al 1987) have been assessed in the acute treatment of PIH. They were found to be effective in controlling blood pressure without any maternal and foetal adverse effect. It has been used as a second line anti-hypertensive agent in PIH (Constantine et al 1987, Greer et al 1987, Johan R. Bort et al 1990).

A steady decrease in mean arterial pressure, systemic vascular resistance & a mirrored increase in cardiac index with no effect on maternal and fetal heart rate (Scardo et al., Newman et al 1996) was observed.

Nifedipine reduces TXA2 production in platelet rich plasma in hypertensive pregnancy (Manninen A 1996). The reduction of Middle cerebral artery flow velocities following administration of nifedipine and methyldopa may suggest that cerebral vasodilation is occurring which is consistent with the concept that cerebral vasospasm is present in women with pre-eclampsia (Serra V et al 1997).

The antihypertensive effect of nifedipine in PIH was especially pronounced during evening and night while in Chronic hypertension it was more constant during the 24 hour period (Renedello et al 1997). Nifedipine increases urinary excretion of prostacyclin metabolite 6-keto-PGF, alpha excretion in hypertensive pregnancy (Manninen et al 1991).

Nifedipine is present in significant concentrations in maternal and umbilical serum, amniotic fluid, breast milk and urine of mother and offspring (Manninen et al 1991).

Intra-platelet free calcium and calcium regulating hormones in plasma are not related to the antihypertensive effect of nifedipine (Lewin et al 1994).
stated that nifedipine provides maternal benefit by lowering blood pressure and reducing the risk of cerebral haemorrhage and end organ damage.

Jayawardana, Lekamge 1994 in their comparative study of nifedipine and methyldopa allocated 126 patients alternately to either group. The patients received nifedipine 30 to 90 mg/day and in group 2 methyldopa 750 to 2000 mg/day.

Blood pressure, the extra days added to the pregnancy, number of pt treated for acute hypertensive episodes, maturity of fetus at birth, mode of delivery, maternal side effects and complications were measured.

On comparison the two groups on admission to the study had similar periods of gestation, 33 6 ± 5.9 in nifedipine and 34 1 ± 4.2 in methyldopa group.

Blood pressure on admission was 151 ± 22 / 108 ± 12 in nifedipine and 154 ± 24 / 108 ± 12 in Methyldopa group.

The results showed no differences between the two group with respect to maturity of fetus at delivery (35 1 ± 5.5) in nifedipine and (35 7 ± 2.9) in methyldopa group, mode of delivery, Intra uterine deaths, average systolic and diastolic blood pressure 148 ± 14 / 102 ± 8 in nifedipine and 152 ± 16 / 104 ± 9 in methyldopa group, birth wt in kg 2.015 ± 0.957 in nifedipine and 1.922 ± 0.660 in methyldopa group and number of days added to the pregnancy.

The Apgar score for methyldopa group was better and less patients in this group required treatment for acute hypertension. They concluded that nifedipine was as effective as methyldopa in the treatment of PIH.

In 1990 the combined effects of nifedipine and labetalol in severe preeclampsia has been studied in a total of 150 patients in Burdwan.
Medical College and Hospital (Mitra Khatna and Sapui) They have observed that the combined effect of Paobetalal and nifedipine in severe preeclampsia is very encouraging and no fetal bradycardia has been observed. Blood pressure is reduced below the critical level after 24 hour in most patients 55% and with in 48 hours B P come down below critical level in 82% of patients.

In 1996 Anti hypertensive efficacy and perinatal safety of methyldopa, nifedipine and metoprolol in PIH has been studied in a total of 75 patients in Government medical college and SMGS Hospital (Vaneet, Madan, Mallhotra) All the drugs had considerable antihypertensive effect but the mean percentage fall in B P was more in patients taking nifedipine.

The mean gestational age in all the groups was comparable. In perinatal outcome, there was no significant difference in the mean birth weight of the babies in the three groups, the Apgar score at 5 minutes was better and also the duration of stay in NICU was minimum in nifedipine group. No perinatal death was reported in nifedipine group while 2 each were reported in other two groups.

With the above back ground knowledge and to assess the efficacy of nifedipine and methyldopa in the drug treatment of PIH, a study has been conducted at the Department of Obstetrics and Gynaecology, Maharani Laxmi Bai Medical College Jhansi.