CHAPTER - II

REVIEW OF LITERATURE
Hypertensive disorders in pregnancy complicate 1 in 10 pregnancies, often associated with maternal and neonatal mortality and morbidity (Jain, 1997).

2.1. Classification of hypertensive disorders in pregnancy

There were various classifications for hypertensive disorders in pregnancy based on diagnostic criteria (WHO, 1987; Davey and MacGillivray, 1988; Helewa et al., 1997; Brown et al., 2000; NHBPEP, 2000). The widely accepted classification presently is International Society for the Study of Hypertension in Pregnancy (ISSHP) (Brown et al., 2001). According to this classification there are four categories (1) pre-eclampsia (2) chronic hypertension – essential or secondary (3) pre-eclampsia superimposed on chronic hypertension and (4) gestational/pregnancy induced hypertension. The term gestational hypertension was adopted by working group of NHBPEP (2000) to replace pregnancy induced hypertension (Brown and de Swiet, 1999; Leeman and Fontaine, 2008).

Pre-eclampsia as per ISSHP classification is defined as new onset hypertension of more than 140/90 mm of Hg after 20 weeks gestation, proteinuria more than 300mg/day or a spot urine protein/creatinine ratio $\geq 30$ mg protein/mmol creatinine (Brichant et al., 2010). This definition is for the purpose of research. But when there is evidence of foetal growth restriction or end organ damage without proteinuria, the said clinical condition is branded clinically as pre-eclampsia as per ISSHP. This syndrome occurs in 5 to 8% of all pregnancy.

Chronic hypertension is defined as BP $> 140/90$ mm of Hg before pregnancy or before 20 weeks gestation, complicates 3% of pregnancies. When there is proteinuria of more than 300 mg/day or evidence of foetal growth restriction in cases of chronic hypertension this condition is termed as pre-eclampsia superimposed on chronic hypertension. Gestational hypertension is also called as pregnancy induced hypertension. In gestational hypertension there is appearance of hypertension after 20 weeks gestation without proteinuria (Higgins and de Sweit, 2001; Medina Lomeli and Median Castro, 2005). The hypertension subsides after delivery within 12 weeks.

The term gestational hypertension or pregnancy induced hypertension (PIH) and pre-eclampsia are clinically more often considered as same with reference to
management. The transition from pregnancy induced hypertension to pre-eclampsia is ill defined so both are considered as one for management. But prognosis for pregnancy induced hypertension is better than pre-eclampsia (Brown and de Swiet, 1999; Homer et al., 2008). The incidence of pregnancy induced hypertension in India is about 7-10% of all antenatal admission (Shruti et al., 2008).

The blood pressure considered in pregnancy induced hypertension should be more than 140/90 mm of Hg (Wuerzner et al., 2010). Two blood pressure readings 6 hours apart are considered. If previous blood pressure is known, than an increment of 30 mm of Hg systolic and 15 mm of Hg diastolic is also considered. Diastolic blood pressure is more important and Korotkoff V is used to determine diastolic blood pressure.

2.2. Aetiology

There are various etiological factors for pregnancy induced hypertension. This is a disorder of hypothesis and affliction to involve all organs in the body. The potential causes of pregnancy induced hypertension are,

1. Abnormal placentation (Steegers et al., 2010)
2. Vasculopathy and inflammatory changes
3. Immunological factors
4. Genetic factors
5. Nutritional factors (Amir et al., 1998)

1. Abnormal placentation

In normal pregnancy, the spiral arterioles of the placental bed undergo a series of physiological changes. They are invaded by endovascular trophoblast, which breaks down the endothelium, internal elastic lamina and muscular coat of the vessel, replaced by fibrinoid material. These changes occurs in two waves, the invasion of decidual segments of spiral arterioles in the first trimester and myometrial segments, by a subsequent wave in the second trimester. These physiological changes convert the vessels supplying the placenta from muscular end arteries to wide mouth sinusoids, which are unresponsive to vasoactive substances. The vascular supply is
thus transformed into low pressure high flow system to meet the needs of the foetus and placenta (Furuya et al., 2008).

In pregnancy induced hypertension there is inadequate maternal vascular response to placentation, the above changes are restricted to the decidual segments of the uteroplacental arteries, the primary invasion of trophoblast is partially impaired, and second wave of trophoblastic invasion fails to occur. Hence the myometrial segments of spiral arterioles are left with their musculoelastic architecture, there by responsive to hormonal substances. This restriction of normal physiological changes, result in restricted placental flow, which becomes more critical with advancing gestation. Intra myometrial segments of spiral arterioles show changes like endothelial damage, insudation of plasma constituents into vessel wall, proliferation of lipid laden myointimal cells and medial necrosis termed acute atherosis. The vessels affected by atherosis develop aneurysmal dilatation. Obstruction of lumen by atherosis may impair placental blood flow. These changes pathologically diminish the placental blood flow and lead to infarcts, patchy necrosis and intracellular damage to the syncytiotrophoblast and obliterative endarteritis of foetal stem arteries. It has been suggested that there is incomplete development of foetal macrovascular in pregnancy induced hypertension associated with foetal growth restriction (Granger et al., 2001a; Furuya et al., 2008).

2. Vasculopathy and inflammatory changes

In response to ischemic changes, various noxious substances are released from the placenta and decidua, these serve as mediators to provoke endothelial injury. Cytokines such as tumour necrosis factor-alpha (TNF-alpha) and interleukins contribute to the oxidative stress characterized by reactive oxygen species (ROS) and free radicals that lead to formation of lipid peroxides. These in turn generate highly toxic radicals that injure the endothelial cells, modify their nitric oxide production and interfere with prostaglandin balance. Oxidative stress also causes production of lipid laden macrophages foam cells seen in atherosis, activation of micro vascular coagulation seen in thrombocytopenia and increased capillary permeability seen in oedema and proteinuria (Granger et al., 2001b).
3. Immunological factors

Immunological factors may play an important role in the development of pregnancy induced hypertension. This phenomenon in pregnancy induced hypertension include absence of blocking antibodies, decreased cell mediated immune responses, activation of neutrophils and involvement of cytokines. An aberrant immune reaction between foetal trophoblast with maternal tissue in the placental bed is a fundamental factor in the aetiology of pregnancy induced hypertension, supported by the findings that this syndrome most often complicates first pregnancy. Incidence is also increased by change of partner and in a subsequent pregnancy after birth control methods that prevent sperm exposure. Women who develop pregnancy induced hypertension have decreased proportion of helper T cells (Th 1) in early second trimester, compared with those who remain normotensive. The Th 1/Th 2 imbalance may be mediated by adenosine, found in higher concentration in pregnancy induced hypertension women. The helper lymphocytes secrete cytokines that promote implantation and their dysfunction leads to pregnancy induced hypertension (Chen et al., 1993, 1994).

4. Genetic factors

Familial predisposition for pregnancy induced hypertension has been recognized, single gene model and polygenic inheritance has been suggested. 60% concordance in monozygotic female twin pairs has been reported by a Swedish study. Some have reported a HLA-DR4 association with proteinuria in pregnancy induced hypertension. A number of single gene mutation and inherited thrombophilia’s may predispose to pregnancy induced hypertension. Polymorphisms of the genes for TNF, lymphotoxin-alpha and interleukin-1 have been studied with varying results (Haram et al., 2000; Nilsson et al., 2004).

5. Nutritional factors

Many studies have shown a relationship between dietary deficiencies and incidence of pregnancy induced hypertension. A diet high in fruits and vegetables that have antioxidant activity is associated with decrease in the incidence of pregnancy induced hypertension. Antioxidants enzymes and antioxidant nutrients, including
carotenoids, alpha-tocopherol and thiols are the primary defence against oxidative stress and free radical induced damage. Antioxidants protect the endothelial cell membrane against free radical damage by their quenching abilities. When protective mechanisms are compromised, the products of lipid peroxidation increase with decrease in antioxidant carotenoids. This imbalance leads to oxidative stress and tissue injury (Palan et al., 2001). Protective antioxidant systems are deficient in pregnancy induced hypertension as low placental tissue and maternal serum carotenoid level such as β carotenes; lycopene and canthaxanthin have been observed in pregnancy induced hypertension (Sagol et al., 1999). Vitamin C and Vitamin E supplementation between 16 to 22 weeks gestation decreases the incidence of pregnancy induced hypertension by more than 50% (Chappell et al., 1999). In contrast vitamin C and E supplementation at the doses used in high risk pregnant women between 14 to 22 week’s gestations with low nutritional status did not prevent preeclampsia (Villar et al., 2009).

Lycopene is a carotenoid present in high concentrations in tomatoes and tomato products and gives them the characteristic red colour (Hadley et al., 2002). It has no pro-vitamin A activity (Sharma et al., 2003). Lycopene is not converted to Vitamin A; hence it may be entirely available for antioxidation. Lycopene supplementation have been shown to reduce incidence of pregnancy induced hypertension and foetal growth restriction by 51.4% and 49.3% respectively (Sharma et al., 2003; Nilsson et al., 2004; Rumboid et al., 2008).

2.3. PATHOPHYSIOLOGY

2.3.1. Pathogenesis

Pregnancy induced hypertension is characterized by vasospasm, endothelial cell damage resulting in activation of coagulation system (Haram et al., 2000; Granger et al., 2001a; Chandiramani et al., 2010).
1. Vasospasm

A reduction in the synthesis of vasodilator nitric oxide (NO) and an increased production of endothelin by the vascular endothelium in pregnancy induced hypertension could account not only for characteristic vasospasm but also for activation of circulating platelets. Vasoconstriction causes resistance and subsequent hypertension. Associated endothelial damage causes interstitial leakage through which blood constituents, including platelets and fibrinogen are deposited sub endothelially with diminished blood flow because of mal distribution; ischemia of surrounding tissues would lead to necrosis, haemorrhage and other end organ disturbances characteristic of the syndrome.

2. Endothelial cell activation

Various noxious placental factors released by ischemic changes and toxic radicals generated by oxidative stress cause activation and dysfunction of vascular endothelium. Intact endothelium decreases responsiveness of vascular smooth muscles to agonists by release of nitric oxide and it also has anticoagulant properties. Damage or activated endothelium secretes substances that promote coagulation and increased sensitivity to vasopressors. Increased circulating fibronectin, factor VIII

Figure 1: Pathogenesis of pregnancy induced hypertension
antigen and thrombomodulin, all markers of endothelial dysfunction are reported in pregnancy induced hypertension/preeclampsia (Granger et al., 2001b).

A) Enhanced pressor responses

Normal pregnant women are refractory to infused vasopressors like angiotensin II. However women who are destined to develop pregnancy induced hypertension/pre eclampsia have increased vascular reactivity to angiotensin II. This increased sensitivity precedes the onset of hypertension. Autoantibodies are thought to activate AT1 receptors and increased angiotensin II sensitivity. Up regulation of bradykinin receptors (B2) leads to heterodimerisation with angiotensin II type I receptors (ATI). ATI/B2 receptors have been shown to increase responsiveness to angiotensin II in-vitro.

B) Prostaglandins

Endothelial prostacyclin (PGI₂), a vasodilator; its production is decreased in pregnancy induced hypertension/pre eclampsia mediated by phospholipase A₂. Thromboxane A₂ (vasoconstrictor and platelet aggregator) levels are increased. The prostacyclin: Thromboxane A₂ ratio decreases, these changes result in vasoconstriction and hypertension. In normal pregnancy, PGI₂ is more than TXA₂=Vasodilation=No hypertension. In Pregnancy induced hypertension, PGI₂ is less than TXA₂=Vasoconstriction=hypertension (Chen et al., 1993).

C) Nitric oxide

Nitric oxide is a potent vasodilator, synthesized from L-arginine by endothelial cells. Nitric oxide maintains the normal low pressure vasodilated state of foeto placental circulation in humans. Pregnancy induced hypertension/preeclampsia is associated with decreased endothelial nitric oxide synthesis which increases the cell permeability.

D) Endothelin

Endothelin-1 is the primary isoform produced by human endothelium. These alpha 1- amino acid peptides are potent vasoconstrictors; levels in pregnancy induced
hypertension/pre eclampsia are higher when compared to normotensive pregnancies in response to endothelial activation.

E) Circulating angiogenic factors

Vascular endothelial growth factors (VEGF) are endothelial specific growth factors plays a key role in promoting angiogenesis; placental growth factor (PLGF) is another member of VEGF family that is made predominantly in placenta. Activity of VEGF is mediated by interaction with two high affinity receptor tyrosine kinases: Kinase insert domain region (KDR) and fms like tyrosine kinase-1 (flt-1). These are expressed an endothelial surface. Alternative splicing of flt-1 results in production of sflt-1; this cannot attach to cell membranes and is secreted in to the maternal blood. It can antagonize VEGF and PLGF by binding to it and preventing its interaction with endogenous receptors. Excess sflt-1 production is seen in pregnancy induced hypertension/pre eclampsia placentas, which creates an antiangiogenic state and plays a causal role in the pathogenesis of maternal syndrome in pregnancy induced hypertension/pre eclampsia. VEGF is known to stimulate angiogenesis as well as to promote vasodilation by increasing production of nitric oxide and prostacyclin, signalling molecules that are decreased in pregnancy induced hypertension/pre eclampsia. PLGF is important in vasculogenesis and control of microvascular permeability (Wang et al., 2009).

2.3.2. Pathological changes in various organs

Vasospasm and endothelial cell damage with subsequent platelet activation and aggregate formation account for many of the pathological changes seen in pregnancy induced hypertension.

1. Brain

Vasospasm and cerebral oedema have been implicated in the cerebral manifestations of pregnancy induced hypertension/preeclampsia. There are small haemorrhages scattered throughout its substance. Massive haemorrhage in the brain may cause death. There may be cerebral oedema, increased intracranial tension, cerebral haemorrhage and hyperaemia.
2. Eye

Retinal haemorrhage, exudates and papilledema are characteristics of hypertensive encephalopathy and are rare in pregnancy induced hypertension. Vasospasm in occipital lobe is the usual cause of temporary blindness sometimes found in severe preeclampsia.

3. Kidneys

Characteristic lesion is glomeruloendotheliosis, it consists of endothelial and mesangial cell swelling, basement membrane inclusions but little disruption of renal endothelial podocytes (Pourrat and Pierre, 2010). There are proteinuria, decreased glomerular filtration rate and decreased urate excretion.

4. Liver

Sub endothelial fibrin deposition is associated with elevated liver enzymes. This can be associated with elevated liver enzymes. This association with haemolysis and a low platelet count due to platelet consumption constitute the HELLP syndrome (haemolysis, elevated liver enzymes, low platelets) (Rath and Bartz, 2004; Anon, 2010; Boudhraa et al., 2010; DI et al., 2010). There may be periportal haemorrhagic necrosis and sub capsular hematoma. The epigastric pain and liver tenderness probably arise from distension of the capsule (Thangaratinam et al., 2011a).

5. Cardiovascular

In early phase cardiac output is high with low peripheral resistance, but as the disease progresses this changes to low cardiac output with high peripheral resistance. There is reduced central venous pressure and pulmonary wedge pressure. Generalized vasospasm is the basic factor. Cardiac arrhythmia, failure and pulmonary oedema can occur due to effect of the disease or drugs used. Rarely peripartum cardiomyopathy is reported in preeclampsia women after delivery (Hsu et al., 2010).
6. Lungs

Pathological changes in lungs results in adult respiratory distress syndrome, bronchopneumonia and airway obstruction.

7. Haematological

Platelet activation and consumptive coagulopathy, decreased plasma volume, increased blood viscosity (ArulKumaran et al., 2005).

2.4. Risk factors (Martin et al., 2000; Al-Mulhim et al., 2003; Roberts et al., 2005; Wu et al., 2010)

1. Pre conceptional and or chronic risk factors
   a) Partner related risk factors
      Nullipara/primi/teenage pregnancy (Amir et al., 1998; Shruti et al., 2008)
      Assisted reproductive techniques
      Partner who fathered a preeclampsia in another women
   b) Non-partner related risk factors
      History of previous PIH (Wikstrom et al., 2011)
      Polycystic ovary disease (Kashyap and Claman, 2000)
      Age interval between pregnancies
      Family history
      Low socio economic class (Amir et al., 1998)

2. Underlying disorders

Chronic hypertension, renal disease, obesity, insulin resistance, low birth weight, gestational diabetes mellitus, protein C resistance, protein S deficiency, antiphospholipid antibody syndrome, hyperhomocystenemia and sickle cell disease.

3. Exogenous factors

Smoking
Steroids

In utero DES exposure
4. Pregnancy associated risk factors
   
   Multiple pregnancies
   Structural anomalies
   Gestational trophoblastic diseases
   Urinary tract infection
   Chromosomal anomalies (trisomy 13, triploidy)

2.5. Prediction and preventions (Meads et al., 2008)

2.5.1. Predictors of PIH (Brown et al., 2007; Anumba et al., 2010; Peacock and Bogossian, 2010)

1. Elevated mean arterial pressure at least 85-90 mm of Hg in second trimester has been reported to have widely varying predictive ability (Ebeigbe and Gharoro, 2004; Onwudiwe et al., 2008).

2. Roll over test (Gant’s roll over test): At first blood pressure is measured in left lateral position and next patient is turned to supine position and blood pressure is measured again. If the rise of diastolic blood pressure is 20 mm of Hg or more, test is considered positive (Schoenfeld et al., 1985).

3. Angiotensin infusion test (invasive test): Pregnant women destined to develop pregnancy induced hypertension/preeclampsia lose their refractoriness to an infusion of angiotensin between 28 and 32 weeks of gestation. Women who exhibit a pressor response with less than 8ng/kg/min, of them 90% were seen to develop the disease.

4. Doppler velocimetry: Uterine artery Doppler measurement of impedance at 18 to 22 weeks using continuous wave Doppler has been used as predictive test for pregnancy induced hypertension/preeclampsia. Those with increased uterine artery resistance underwent repeat test at 24 weeks. The sensitivity of this test was 78% (Pilalis et al., 2007; Onwudiwe et al., 2008; Al-Azad et al., 2010; Espinoza et al., 2010).

5. Urinary Calcium
6. UK to Creatinine ratio (Nasrin et al., 2010)
7. Serum AFP/Hcg ratio
8. Plasma fibronectin
9. Serum inhibin-A (Zeeman et al., 2002)
10. Serum Urate (Anumba et al., 2010)
11. Haematocrit
12. Antithrombin III
13. Plasmin activator inhibitor (1 and 2)
14. Maternal Serum pregnancy associated plasma protein-A (PAPP-A) (Pilalis et al., 2007)

2.5.2. Prevention

1. Calcium supplementation
2. Low dose aspirin (Toppozada et al., 1991; Duhig and Shennan, 2011)
3. Vitamin E supplementation (Chappell et al., 1999)
4. Lycopene supplementation (Rumboid et al., 2008)
5. Rest (Meher and Duley, 2006)

2.6. Complications (Diseasedex, 2006)

Complications can be categorised as maternal and foetal complications.

Maternal complications

HELLP syndrome, temporary blindness, abruptio placentae, disseminated intravascular coagulation (DIC), acute renal failure (ARF), pulmonary oedema, arrhythmias, liver lesions, intracranial or hepatic haemorrhage, adult respiratory distress syndrome (ARDS), hypervolemia and risk of recurrent preeclampsia (Grujic and Milasinovic, 2006).

Foetal complications

Intrauterine growth retardation and foetal death.
1. HELLP syndrome

HELLP syndrome i.e., haemolysis, elevated liver enzymes and low platelet count is form of severe preeclampsia with high rates of neonatal and maternal morbidity (Leeman and Fontaine, 2008). It occurs in 5 to 10% of patients with hypertension in pregnancy. HELLP syndrome was defined by the presence of all of the three following criteria: haemolysis (characteristic peripheral blood smear), serum lactate dehydrogenase $\geq 600 \text{U/l}$, total serum bilirubin $\geq 1.2 \text{ mg/ml}$, elevated liver enzymes (serum aspartate aminotransferase $\geq 70 \text{U/l}$) and low platelet count ($<100,000/\mu\text{l}$). Partial HELLP syndrome (PHS) is defined by the presence of one or two features of HELLP syndrome but not the complete syndrome (Anon, 2010; Erdemoglu et al., 2010).

a) A clinical study conducted in China to describe the outcomes and characteristics of the obstetric patients with concurrent eclampsia and HELLP syndrome revealed that maternal death rate was 35% and significantly higher than the rate in eclampsia without HELLP syndrome (3%). There were more patients complicated with cerebral venous thrombosis and cerebral haemorrhage in eclampsia with HELLP syndrome group (DI et al., 2010).

b) A study conducted on hypertensive disorders in pregnancy, confirmed HELLP syndrome as a severe form of pre eclampsia, associated with high rates of neonatal and maternal morbidity (Leeman and Fontaine, 2008).

2. Blindness

Rarely, temporary blindness may accompany severe preeclampsia and eclampsia which may last a few hours to a week (ACOG, 2002). There are few cases reported of blindness lasting longer than 2 months.

3. Abruptio placentae

It is a maternal complication in 10% of eclamptic patients particularly with antepartum eclampsia. A study conducted to evaluate the maternal and perinatal outcome following expectant management of early onset severe preeclampsia at a tertiary hospital in Mansoura, Egypt, concluded that HELLP syndrome, renal...
impairment, and placental abruption as the main complications (Dafallah and Babikir, 2004; Abdel-Hady et al., 2010).

4. Disseminated intravascular coagulation (DIC)

It occurs in about 5% of patients. DIC may indicate a worsening of HELLP syndrome, a developing *abruptio placentae* or the first sign of sepsis. A study conducted in Turkey to determine the risk factors, prevalence, epidemiological parameters and maternal-perinatal outcome in pregnant women with hypertensive disorder stated that, maternal mortality occurred in 3 cases (1.2%) which were complicated with HELLP syndrome. Intracranial bleeding was the cause of maternal death in one case while the other two cases were lost due to acute renal failure and disseminated intravascular coagulation, respectively (Yucesoy et al., 2005).

5. Acute renal failure (ARF)

Usually due to acute tubular necrosis or bilateral cortical necrosis, rare complications, associated with DIC and *abruptio placentae* (Yucesoy et al., 2005). It occurs in about 5% of eclamptic patients.

6. Cardiogenic pulmonary oedema

It is uncommon, occurring in about 3 to 4% of patients. It indicates severe hypertension in pregnancy (ACGO, 2002). A study conducted to identify the risk factors of adverse pregnancy outcomes in expectant management of pregnant women with early onset severe pre-eclampsia (EOSP) stated that and HELLP syndrome, placental abruption, heart failure and pulmonary oedema as main complications in adverse outcome group (Wu et al., 2010).

7. Haemorrhage

Any patient with clinical evidence of preeclampsia and right upper quadrant abdominal pain, particularly in presence of thrombocytopenia and elevated liver enzymes should be considered risk for hepatic haemorrhage from sub capsular or intrahepatic hematoma (with or without rupture) associated with high maternal and fetal mortality. A study conducted in South Africa to learn the maternal deaths
associated with hypertension, stated that cerebral complications as final cause of death in 45.5% (Moodley, 2011). A study conducted in the incidence of concurrent eclampsia and HELLP syndrome, mortalities were more due to cerebral haemorrhage (DI et al., 2010).

8. Arrhythmias

Malignant ventricular arrhythmias not related to electrolyte imbalance, deranged acid base status or hypoxia has been described in patients with severe hypertension in pregnancy.

9. Intra uterine growth retardation

IUGR is defined as pathological decrease in the rate of foetal growth (Rajan, 2005). Increased risk of IUGR in hypertensive pregnancies, particularly those associated with severe and early-onset pre-eclampsia. Multiparous with preeclampsia are at higher risk of IUGR than are nulliparous (chauhan et al., 1999).

a) A study conducted to assess the global impact of pre-eclampsia and eclampsia stated preeclampsia can result in the risk for the baby as poor growth and prematurity (Duley, 2009).

b) A study conducted to examine the association between PIH and perinatal mortality, concluded that intra uterine growth restriction secondary to PIH is associated with significantly increased perinatal mortality (Xiong et al., 2007).

c) In an editorial on monitoring and outcome of PIH, pre-eclampsia and eclampsia, found that new born infants of mother with PIH, had intra uterine growth retardation, prematurity, dysmaturity and necrotizing enterocolitis. Also concluded that PIH is one of the major cause of maternal and foetal/neonatal morbidity and mortality (Grujic and Milasinovic, 2006).

d) A study conducted for clinical significance liver dysfunction in PIH stated hepatic dysfunction as one of the frequent manifestations of multisystem involvement in pre-eclampsia. Liver dysfunction was associated with intra uterine growth
retardation and prematurity, and is an independent risk factor for maternal and perinatal complications (Romero et al., 1988).

e) In a study to analyse if preeclampsia, gestational hypertension and IUGR are related or independent conditions concluded that preeclampsia and gestational hypertension shared many risk factors. Conversely, preeclampsia and unexplained IUGR often assumed to be related to placental insufficiency seem to be independent biological entities (Villar et al., 2006).

10. Foetal death

PIH is one of the major causes of maternal and foetal/neonatal morbidity and mortality (Grujic and Milasinovic, 2006).

a) In a study to determine the risk factors, prevalence, epidemiological parameters and maternal-perinatal outcome in pregnant women with hypertensive disorder, found that 24 cases of intrauterine foetal demise out of 255 cases, and 10 foetuses died during the intrapartum period. Perinatal mortality rate was found to be 144/1,000 births (Yucesoy et al., 2005).

b) In a population based, retrospective, cohort study based on 16,936, intrauterine growth retardation secondary to pregnancy induced hypertension was associated with significantly increased perinatal mortality (Xiong et al., 2007).

11. Recurrent hypertension in pregnancy

Risk of recurrent preeclampsia in a second pregnancy varies according to gestational age at delivery in the first pregnancy, with greatest risk to women who delivered earliest in previous pregnancy. Further risk increases with increasing birth interval, along with increasing maternal age, weight gain, change in paternity, or the development of chronic diseases (Wikstrom et al., 2011).

2.7. Diagnosis of pregnancy induced hypertension (Magee et al., 2008)

Diagnosis is based on measurement of BP and proteinuria.
2.7.1. Measurement of BP

1. BP should be measured with women in the sitting position with the arm at the level of the heart.

2. An appropriately sized cuff (i.e., length of 1.5 times the circumference of the arm) should be used.

3. Korotkoff phase V should be used to designate diastolic BP.

4. If BP is consistently higher in one arm, the arm with the higher values should be used for all BP measurements.

5. BP can be measured using a mercury sphygmomanometer.

2.7.2. Measurement of proteinuria

1. All pregnant women should be assessed for proteinuria.

2. Urinary dipstick testing may be used for screening for proteinuria, when suspicion on preeclampsia is low.

3. More definitive testing for proteinuria (by urinary protein: creatinine ratio or 24 hour urine collection) is encouraged when there is a suspicion of preeclampsia.

2.7.3. Diagnosis of hypertension

1. The diagnosis of hypertension should be based on office or in-hospital BP measurements.

2. Hypertension in pregnancy should be defined as a diastolic BP of $\geq 90$ mm Hg, based on the average of at least two measurements, taken using the same arm.

3. Women with a systolic BP of $\geq 140$ mm Hg should be followed closely for development of diastolic hypertension.

4. Severe hypertension should be defined as a systolic BP of $\geq 160$ mm Hg or diastolic BP of $\geq 110$ mm Hg.
5. For non-severe hypertension, serial BP measurements should be recorded before a diagnosis of hypertension is made.

6. For severe hypertension, repeat measurements should be taken for confirmation in 15 minutes.

2.7.4. Diagnosis of clinically significant proteinuria

1. Proteinuria should be strongly suspected when urinary dipstick protein is $\geq 2$.

2. Proteinuria should be defined as $\geq 0.3$g/d in a 24-hour urine collection or $\geq 30$ mg/mmol urinary creatinine in a spot (random) urine sample.

3. There is insufficient information to make a recommendation about accuracy of the urinary albumin: creatinine ratio.

2.7.5. Proteinuria

Proteinuria is defined as the abnormal presence of protein in the urine. Normally a small amount of protein is present in the ultra-filtrate produced by the glomerulus, but much of this protein is absorbed by the tubules (and some additional proteins are secreted into the urine). Ultimately, very little protein is present in the urine that leaves the kidney.

Proteinuria is often measured using a dipstick assay. In this assay the test area is impregnated with tetrabromophenol blue buffered to an acid pH, which reacts with albumin producing a colour change. The dipstick is reported on a semi-quantitative scale: negative, trace (10-20 mg/dl), 1+ (30 mg/dl), 2+ (100mg/dl), 3+ (300 mg/dl), 4+ (1000-2000 mg/dl). Of note, the dipstick test for proteinuria suffers from both false positive errors. False negative tests are often seen in dilute urine (specific gravity < 1.005), and when a protein other than albumin is present in the urine. False positives can be seen in a concentrated urine, a basic urine (pH > 8), and a urine contaminated by gross haematuria or by antiseptic agents (chlorhexidine or benzalkoniumchloride).

In adults, the normal value for proteinuria is $< 150$ mg protein per day. Using the dipstick assay, 1+ protein may be significant in a dilute sample (Specific gravity 1.005 - 1.015), and 2+ protein may be significant in a concentrated sample Specific
gravity (>1.015). In addition to the dipstick method, the gold standard for measuring proteinuria is 24 hr urine however; this test is often a logistical nightmare for both parents and hospital personnel (Gribble et al., 1995). Instead of a 24 hr collection, studies have shown that the ratio of protein to creatinine in a random sample correlates with the value obtained with a 24 hr collection. In fact, the ratio often reflects the grams of protein obtained in a 24 hr collection (i.e. Protein: Creatinine, 2:0 on a random sample equals 2g/24hr). Protein: Creatinine ratio can be falsely positive if there is only a small amount of creatinine in the sample.

Figure-2: Grades of urine protein estimated using sulfosalicylic acid (SSA) precipitation

Figure-3A: Standard colour range for estimating grades of urine proteins
Protein in urine can also be estimated using sulfosalicylic acid (SSA) precipitation. The SSA reagent is added to a small volume of urine. Acidification causes precipitation of protein in the sample (seen as increasing turbidity), which is subjectively graded as trace, 1+, 2+, 3+ or 4+ (see image above).

Unlike the protein test on the dipstick, the SSA reaction will detect albumin and globulins (although it is more sensitive to albumin). In addition, the SSA detects Bence-Jones proteins (which are usually not picked up by the dipstick), although it often underestimates them (Gribble et al., 1995). In the past, the SSA reaction was used to confirm positive reactions for protein on the dipstick in alkaline urine. However, studies have shown that the SSA reaction (which is also a highly subjective assessment) is no more accurate (and in fact can be less accurate) than the dipstick for measurement of urine protein. For this reason, the SSA reaction is no longer routinely performed on urine samples at Cornell University. If there is concern that the urine protein on the dipstick is falsely increased in an alkaline urine sample, measurement of urine protein (or protein to urine creatinine ratio) on a chemistry analyser is advised. The most accurate measurement of urine protein output is measurement of urine protein excretion over 24 hours. A good alternative to this test is the urine protein to creatinine ratio. Women with pregnancy induced hypertension with massive
proteinuria (preeclampsia) are a marker of severity of disease and progression to severe pre eclampsia. Neonatal morbidity appears to be not related to proteinuria (Newman et al., 2003).

**False positives**

- Contrast media

- Antibiotics in high concentration, e.g. penicillin and cephalosporin derivatives

- Uncentrifuged turbid urines can look positive. Therefore, SSA should always be performed on urine supernatant.

**False negatives**

- Highly buffered alkaline urine. The urine may require acidification to a pH of 7.0 before performing the SSA test.

- Dilute urine

- Turbid urine - may mask a positive reaction

The sulfosalicylic acid test requires centrifugation of the urine followed by addition of 2.5 ml of the supernatant to 7.5 ml of 3% sulfosalicylic acid. The degree of turbidity is quantified.

**2.8. Investigations** (Magee et al., 2008)

Women with suspected preeclampsia should undergo testing (outlined in Table1) for end organ dysfunction or to rule out important differential diagnoses (acute fatty liver of pregnancy). The validity of various tests in Table1, alone or in combination has not been established. If initial testing is reassuring, maternal and foetal testing should be repeated if there is on-going concern about preeclampsia (e.g. change in maternal and /or foetal conditions).

Uterine artery Doppler velocimetry may be useful in hypertensive pregnant women to support a placental origin for the hypertension, proteinuria, and /or adverse conditions; obstetric consultation would then be warranted. Umbilical artery Doppler
velocimetry may be useful. Absent or reversed end diastolic flow in the umbilical artery would be more consistent with placental dysfunction than with decreased biological growth potential, uncertain dates or aneuploidy as a cause of IUGR.

Table 1: Investigations to diagnose or monitor maternal well-being in preeclampsia*

<table>
<thead>
<tr>
<th>Investigations for diagnosis</th>
<th>Investigations for prognosis</th>
<th>Description in women with preeclampsia.</th>
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<tbody>
<tr>
<td>Haemoglobin</td>
<td>Haemoglobin</td>
<td>Higher (due to haemoconcentration)</td>
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<tr>
<td>WBC and differential</td>
<td>WBC and differential</td>
<td>Higher (largely due to exaggerated neutrophilia)</td>
</tr>
<tr>
<td>Platelet count</td>
<td>Platelet count</td>
<td>Lower</td>
</tr>
<tr>
<td>Blood film</td>
<td>-</td>
<td>Microangiopathy with RBC fragments.</td>
</tr>
<tr>
<td>INR and aPTT</td>
<td>INR and aPTT</td>
<td>Higher with DIC</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Fibrinogen</td>
<td>Lower</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>Serum creatinine</td>
<td>Higher (due to haemoconcentration and/or renal failure)</td>
</tr>
<tr>
<td>Serum uric acid</td>
<td>Serum uric acid</td>
<td>Higher</td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td>Low in acute fatty liver of pregnancy</td>
</tr>
<tr>
<td>AST</td>
<td>AST</td>
<td>Higher</td>
</tr>
<tr>
<td>ALT</td>
<td>ALT</td>
<td>Higher</td>
</tr>
<tr>
<td>LDH</td>
<td>LDH</td>
<td>Higher</td>
</tr>
<tr>
<td>Albumin</td>
<td>Albumin</td>
<td>Lower</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Bilirubin</td>
<td>Higher (unconjugated from haemolysis or conjugated from liver dysfunction)</td>
</tr>
<tr>
<td>Urinalysis (routine and microscopy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria (assessed by urinary protein dipstick, spot or 24 hr.)</td>
<td>Proteinuria</td>
<td>Higher</td>
</tr>
<tr>
<td>Fundoscopy</td>
<td>Fundoscopy</td>
<td>Grade1 to grade 4(severity of vasospasm)</td>
</tr>
</tbody>
</table>

*(Noted as in Magee et al., 2008)
Fundoscopy (Saito et al., 2010)

Grade-1: Mild generalized attenuation, particularly of small branches, with broadening of arteriolar light reflex, increased tortuosity of arterioles and vein concealment.

![Figure 4: Grade-1 hypertensive retinopathy](image)

Grade-2: More severe generalized as well as focal arteriolar constriction associated with deflection of veins at AV crossing (Salu’sign). Increased light reflection of the artery, lumen irregularity (irregularity of caliber).

![Figure 5: Grade-2 hypertensive retinopathy](image)

Grade-3: Copper wiring of arterioles, banding of veins distal to AV crossing (Bonnet’s sign), tapering of veins on either side of the crossings (Gunn’s sign). Flame
shaped haemorrhages, cotton wool spots and hard exudates are also present. Marked attenuation of retinal arteries and dilatation of retinal veins and ‘star figure’.

![Figure 6: Grade-3 hypertensive retinopathy](image)

Grade-4: Silver wiring of arterioles and disc swelling, preg nous pad, termination of pregnancy warranted. Swelling of the optic disc and retinal nerve fibres, narrow arterioles, dilated veins, flame shaped haemorrhages, cotton wool spots and ‘star figure’.

![Figure 7: Grade-4 hypertensive retinopathy](image)
Table 2: Investigations to diagnose or monitor foetal well-being in preeclampsia*

<table>
<thead>
<tr>
<th>Investigations for diagnosis</th>
<th>Investigations for prognosis</th>
<th>Description in women with preeclampsia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foetal movement count</td>
<td>Foetal movement count</td>
<td>Decreased</td>
</tr>
<tr>
<td>Non stress test</td>
<td>Non stress test</td>
<td>Non-reassuring FHR</td>
</tr>
<tr>
<td>Biophysical profile</td>
<td>Biophysical profile</td>
<td>Lower scores</td>
</tr>
<tr>
<td>Deepest amniotic fluid pocket</td>
<td>Deepest amniotic fluid pocket</td>
<td>Lower</td>
</tr>
<tr>
<td>Ultrasonographic assessment of foetal growth</td>
<td>Ultrasonographic assessment of foetal growth</td>
<td>Usually asymmetrical intrauterine foetal growth.</td>
</tr>
<tr>
<td>Umbilical artery Doppler</td>
<td>Umbilical artery Doppler</td>
<td>Increased resistance, absent or reversed end-diastolic flow.</td>
</tr>
</tbody>
</table>

*(Noted as in Magee et al., 2008)

2.8.1. Minimal standards for maternal monitoring in patients with PIH

1. 4th Hourly blood pressure recording
2. Daily urine for protein (Onwudiwe et al., 2008)
3. Alternate day weight recording
4. Twice weekly platelet count and serum uric acid
5. Weekly liver function tests
6. Maternal symptoms (Thangaratinam et al., 2011a)

2.8.2. Foetal assessment

1. Cardiotocogram (Non stress test) (Bailey and Walton, 2005; Roger, 2008)
2. Biophysical profile (Roger, 2008)
3. Obstetric scanning for assessment of foetal growth
4. Doppler ultrasound scans (Yang, 1989; Per Olofsson et al., 1993)

2.8.3. Review on investigations in pregnancy induced hypertension

1. In a retrospective analysis of a database of clinical laboratory records of 560 women referred with suspected gestational hypertension for preeclampsia and other adverse outcomes, the predictive value of blood pressure and serum uric acid are improved when they are standardized as z-scores but there appears to be no value to assessing other laboratory indices when women first present with gestational hypertension without proteinuria (Anumba et al., 2010).
2. In a study to determine the value of combined screening for preeclampsia by maternal history, and mid trimester uterine artery Doppler imaging and maternal blood pressure, it was found that these above parameters are effective screening tool for the prediction of preeclampsia (Onwudiwe et al., 2008).

3. In a study to find the value of routine urine dipstick screening for protein at each prenatal visit, it was found that in low risk women with no objective signs of a possible hypertensive disorders, routine dipstick proteinuria screening at each prenatal visits did not provide any clinical important information regarding pregnancy outcome (Gribble et al., 1995).

4. In a study of platelet count in 100 cases of pregnancy induced hypertension, it was found that low platelet count is a risk for development of postpartum haemorrhage, disseminated intravascular coagulation, eclampsia and low birth weight. Platelet count is a very important investigation for antenatal mothers having pregnancy induced hypertension, as it is directly related to maternal and perinatal outcome (Rahim et al., 2010).

5. In a study to identify the risk factors for adverse pregnancy outcomes during expectant management of early onset severe preeclampsia, it was found that elevated RBC count, reduced platelet count and earlier delivery weeks are risk factors of adverse pregnancy outcomes during the expectant management of early onset preeclampsia (Wu et al., 2010).

6. In a study to evaluate the usefulness of serum albumin level as a marker of severity in pregnancy-related hypertension, it was found that serum albumin level is a significant determinant of disease severity and may be considered as a useful marker for predicting time to delivery, severe proteinuria, and pregnancy outcomes (Seong et al., 2010).

7. In a retrospective study to find whether routine investigations are helpful in preeclampsia and gestational hypertension, it was found that test abnormalities were only increased in preeclampsia and in gestational hypertension before term. CTG might only be of use in selected cases (Bailey and Walton, 2005).
8. In a prospective study to find the role of uterine artery Doppler and PAPP-A at 11-14 weeks gestation as a screening test, it was found that combination of maternal history with abnormal uterine artery Doppler and low PAPP-A level at 11-14 weeks were more useful as a screening test for PIH than does either test alone (Pilalis et al., 2007).

2.9. Management

2.9.1. Obstetric management

The only definitive treatment for the pregnancy induced hypertension is delivery. For this reason, delivery is indicated in women with pregnancy induced hypertension at term (37 weeks or more completed weeks) of any severity and in preterm with severe disease (Sarsam et al., 2008). There are however several exceptions to these general rules (Chung et al., 2001; Weeks et al., 2005; Koopmans et al., 2007; Abdel-Hady et al., 2010).

a) Less than 24 weeks

Incidence of pregnancy induced hypertension within 24 weeks is very less. In this situation with early onset pregnancy induced hypertension, continuation of pregnancy will be risky. Generally termination of pregnancy will be offered to this group (Barton et al., 2001; Brichant et al., 2010).

b) 25 to 34 weeks (Witlin et al., 2000; Briones-Garduno et al., 2003; Haddad et al., 2004)

This gestational age group is intermediate; it requires close surveillance of maternal and foetal condition. The main aim is to prolong pregnancy at least till 32-34 weeks. Foetal lung maturation occurs during this 32-34 weeks gestation. If there is deterioration in the maternal and fetal condition, termination of pregnancy is indicated. If the situation warrants delivery within 32-34 weeks gestation, maternal betamethasone administration is done to enhance fetal lung maturation.
c) More than 34 weeks (Suzuki, 2010; Barton et al., 2011)

Pregnancies which has crossed 34 weeks the complication of Hyaline Membrane Disease of new born is less. Pregnancy can safely be prolonged if blood pressure is well controlled and foetal parameters are within normal limits. Pregnancy prolongation till 37 completed weeks is desirable. After 37 completed weeks, irrespective of severity of pregnancy induced hypertension, termination of pregnancy is to be done (Koopmans et al., 2009; Abdel-Hadey et al., 2010; Brichant et al., 2010).

2.9.2. Anaesthesia

An assessment of the patient must take place as early as possible in view of anaesthesia. It is recommended to perform a clotting screen as close as possible to the performing of an epidural anaesthesia. The use of aspirin, if indicated for prevention of pregnancy induced hypertension, does not as such, constitute a contraindication to performing an epidural anaesthesia if, with regards to the minimum platelet count, the recommended cut-off value for the epidural and spinal anaesthesia are 75,000/l and 50,000/l respectively. Only if all of the following conditions are met; it is recommended to quickly set up an epidural anaesthesia because this will improve the blood pressure as well as the uteroplacental haemodynamic and also anaesthesia because this will facilitate the management in case of a caesarean section. Whereas methergin is contraindicated in pregnancy induced hypertension, it is possible to use oxytocin during and after labour. Before performing a spinal anaesthesia, it is recommended to restrain the administration of crystalloids to a maximum of 1000 ml. Also the intravenous antihypertensive treatment should be reduced or interrupted until complete establishment of the anaesthetic. In case a general anaesthesia is to be performed, an assessment of the criteria for difficult intubation should be performed immediately prior to the induction. The technique employed should be a rapid sequence induction with intubation, while preventing a surge in blood pressure induced by tracheal intubation. Difficulties to extubate should systematically be anticipated. It is possible to perform a loco-regional anaesthesia following an eclamptic crisis if the following conditions are met: In case of overlapping seizures
and/or impaired consciousness, a general anaesthesia is recommended (Aya et al., 2010).

2.9.3. Mode of delivery

Since the treatment of pregnancy induced hypertension is delivery. Deliveries before term poses risks to the new born like hyaline membrane lung disease, hypoglycaemia, hypomagnesaemia, hyperviscosity, low birth weight etc., (Ye et al., 2010). These problems can be averted if pregnancy is prolonged till term provided blood pressure is under control and satisfactory maternal and foetal conditions. Induction of labour is done on reaching 37 completed weeks, uncontrolled maternal blood pressure and deterioration in maternal and foetal condition (Brichant et al., 2010; Haddad et al., 2010). Close monitoring of blood pressure and maternal and foetal parameters are integral part of management of pregnancy induced hypertension. Use of diuretics for preventing preeclampsia and its complications cannot be recommended (Churchill et al., 2007).

Induction of labour is done if Bishop Score of Cervix are favourable. Bishop score takes considers the following (Suzuki, 2010).

a) Cervical length
b) Cervical position
c) Cervical consistency
d) Cervical dilatation
e) Position of foetal head

Each parameter is given score 0, 1 and 2. Total score more than 6-7 is considered favourable. In unfavourable cervix, pre-induction cervical ripening (to improve Bishop Score of cervix) is done using dinoprostone gel (Prostaglandin E2) intracervical application. In some cases distended Foley's catheter bulb is also used for pre cervical ripening.

Induction of labour is done using intravenous escalating dose of injection oxytocin in the dose 5 to 25 mU/minute with increments every 20 to 30 minutes. The effective uterine contractions to be achieved are 3-5 contractions per 10 minute each lasting 30 to 40 seconds. Active labour (cervical dilation more than 4 centimetres) is
monitored for progressive descent of foetal head and cervical dilation using WHO pictogram. If there is abnormality in the progression of labour, foetal or maternal condition deterioration, then caesarean section is indicated (Bao and Liu, 1990; Ye et al., 2010, 2009). Operative vaginal delivery like outlet forceps or vacuum suction is done in second stage of labour, when there are foetal condition deterioration (foetal distress), poor maternal bearing down efforts and to cut short second stage of labour in severe pregnancy induced hypertension.

Caesarean section involves three fold increased risk to the mother and foetus compared to vaginal delivery (Ye et al., 2010).

2.9.4. Postnatal assessment

High blood pressure at 6 weeks postnatal period is significant. Postnatal visit to a physician has to be performed to rule out underlying disorders such as chronic arterial hypertension, nephropathy, autoimmune disease or thrombophilia. This visit is also needed to provide information to the women about what occurred during pregnancy as well as to consider which would have to be done in case of a subsequent pregnancy. Long term outcome had also to be taken into account considering risks for cardiac, arterial, renal and metabolic diseases. This visit is of outmost importance after very early-onset preeclampsia, and especially if it has already occurred. The postnatal visit after pregnancy induced hypertension/preeclampsia represents a very demonstrative example of the role that the physician can afford to the obstetrician in the management of medical disorders occurring during pregnancy and needing a specific expertise as well as a long term follow-up (Pourrat and Pierre, 2010). Recurrence of pregnancy induced hypertension is around 1.9-24.9%. Mothers who had pregnancy induced hypertension have their daughters 3% of them developing pregnancy induced hypertension. Mothers who had eclampsia and pre eclampsia have their daughters 25% of them developing eclampsia and pre eclampsia (Palmsten et al., 2010).
2.9.5. Antihypertensive therapy

Antihypertensive therapy does not prevent preeclampsia or the associated adverse perinatal outcomes, but it decreases by half the incidence of development of severe hypertension among women with mild hypertension (Lowe and Rubin, 1992; Magee et al., 2008). Antihypertensive agents are mainly used to prevent and treat severe hypertension; to prolong pregnancy for as long as safely possible, thereby maximizing the gestational age of the infants; and to minimize foetal exposure to medications that may have adverse effects. During pregnancy the challenge is in deciding when to use antihypertensive medications and what level of BP to target. The choice of antihypertensive agents is less complex, since only a small proportion of currently available drugs have been adequately evaluated in pregnant women and many others are contraindicated (Podymow and August, 2008). As there are no guidelines available in India regarding antihypertensive treatment in pregnancy, it is left to the decision of obstetrician to choose appropriate antihypertensive agent based on clinical experience. Methyldopa remains the most widely used drugs in pregnancy. Other drugs used in India are labetalol, nifedipine, hydralazine and β-blockers such as acebutolol, metoprolol, pindolol and propranolol.

2.9.6. Principles of management of severe pre eclampsia (Lowe et al., 2008; Chandiramani et al., 2010; Diemunsch et al., 2010)

a) Fluid management and cardiovascular system monitoring
b) Blood pressure monitoring (Beucher et al., 2010)
c) Seizure prophylaxis (Alexander et al., 2006)

2.9.7. Review on management options

1. In a study to assess the effects of rest or advice to reduce physical activity during pregnancy for preventing preeclampsia and its complications in women with normal blood pressure, it was found that daily rest with or without nutrient supplementation, may reduce the risk of preeclampsia for normal blood pressure, although the reported effect may reflect bias and/or random error rather than a true effect. Current evidence is insufficient to support recommending rest or reduced activity to women for preventing pre-eclampsia and its complications (Meher and Duley, 2006).
2. In an editorial article regarding the use of antihypertensive drugs in pregnancy, it was stressed that there is an urgent need to treat hypertension in pregnancy when blood pressure is more than 170/110 mm of Hg to prevent cerebral vascular damage. Labetolol intravenous appears to be safe and effective in acute severe cases. Delivery of the fetus is usually the definitive option. After initial treatment the maintenance oral therapy is considered. The drugs advised for oral therapy include methyl dopa and Labetolol. The indications for antihypertensive drugs for mild to moderate cases are less clear. The main role of antihypertensive drugs is to control hypertension not the evolution of disease in pregnancy induced hypertension (Naden and Redman, 1985).

3. In an editorial on management of preeclampsia, it is stated that the antihypertensive treatment improves maternal outcome but has the potential to be delirious for the fetus. Magnesium sulphate is the anticonvulsant of choice to treat or prevent eclampsia. Antenatal corticosteroids are recommended in severe preeclampsia with 26-34 weeks. Timing of delivery is based upon gestational age, severity of preeclampsia, maternal and fetal risk (Brichant et al., 2010).

4. In a randomized trial comparing one or more antioxidants with either placebo or no antioxidants during pregnancy for prevention of preeclampsia, it was found that this review does not support routine antioxidants supplementation during pregnancy to reduce the risk of preeclampsia and other serious complication in pregnancy (Rumboid et al., 2008).

5. In a study to identify parameters that may assist clinicians in predicting which women will develop preeclampsia after initially presenting with gestational hypertension, it was found that 24 hours ambulatory may provide a non-invasive method of identifying at risk gestational hypertension particularly in early presentation (Homer et al., 2008).

6. In a review article on the use of anaesthesia for caesarean section in pregnancy induced hypertension, it is recommended to use epidural anaesthesia or general anaesthesia. Blood clotting factors tests are to be done before epidural anaesthesia (Aya et al., 2010).
7. In a multicentre randomised controlled trial, induction of labour vs. expectant monitoring in PIH, it is recommended induction of labour at term to reduce maternal complications. But there is increased incidence of instrumental vaginal delivery and caesarean section (Koopmans et al., 2009).

2.10. Current treatment options

The benefits of antihypertensive therapy for mild to moderately elevated BP in pregnancy (≤ 160/110 mm Hg) either chronic or pregnancy induced, have not been demonstrated in clinical trials. Recent reviews including a cochrane meta-analysis concluded that there are insufficient data to determine the benefits and risk of antihypertensive therapy for mild to moderate hypertension. With antihypertensive therapy there seems to be less risk of developing severe hypertension, but no difference in outcomes of preeclampsia, neonatal death, preterm birth, and small for gestational age babies with treatment (Podymow and August, 2008).

International guidelines for the treatment of hypertension in pregnancy vary with respect to thresholds for starting treatment and targeted BP goals, but all are higher than the Joint National Committee guidelines for treatment of (no obstetric) hypertension. In United States therapy is recommended for BP of ≥ 160/105 mm Hg (NHBPEP, 2000) with no set treatment target; in Canada, therapy is considered at ≥ 140/90 mm Hg targeting diastolic pressure to 80 to 90 mm Hg (Helewa et al., 1997) and in Australia, elevations ≥ 160/90 mm Hg be treated to a target of ≥ 110 systolic. In India as there are no guidelines available the decision is left to individual practicing obstetrician with respect to thresholds for starting treatment and targeted BP goals as well as choosing antihypertensive agents. In a recent retrospective review of 28 patients who suffered stroke in the setting of preeclampsia, 18 of them did not reach a diastolic BP of 110mm Hg. This case series underscores the need for clinical trials and evidence-based guidelines for antihypertensive treatment in pregnant women. In the present study antihypertensive treatment was initiated when BP was ≥ 140 / 90 mm Hg. The following recommendations are made by the society of obstetricians and gynaecology of Canada for treatment of pregnancy induced hypertension (Table 3 and 4).
1.10. **Antenatal treatment**

With reference to dietary and lifestyle changes there is insufficient evidence to make recommendations about the usefulness of the following.

On-going salt restriction among women with pre-existing hypertension, heart healthy diet, calorie restriction for obese women, exercise, workload reduction or stress reduction and bed rest. In-patient hospital care is recommended for women with severe hypertension or severe preeclampsia. A component of care through hospital day units or home care can be considered for women with non-severe preeclampsia or hypertension (Magee *et al.*, 2008).

2.10.1. **Recommendations for severe PIH**

Antihypertensive therapy for severe hypertension (BP of $>160$ mm Hg systolic or $\geq 110$ mm Hg diastolic)

1. BP should be lowered to $<160$ mm Hg systolic and $<110$ mm Hg diastolic.

2. Initial antihypertensive therapy should be with labetalol, nifedipine capsules or hydralazine.

3. MgSO$_4$ is not recommended as an antihypertensive agent.

4. Nifedipine and MgSO$_4$ can be used contemporaneously.
Table 3: Drugs for urgent control of severe hypertension in pregnancy (BP of \( \geq 160/110 \text{ mm Hg} \))

<table>
<thead>
<tr>
<th>Drug (FDA risk)*</th>
<th>Dose and route</th>
<th>Concerns or comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labetalol (C)</td>
<td>Start with 10 to 20 mg IV, then 20 to 80 mg every 30 min, for infusion; 1 to 2 mg/min, maximum of 300 mg (then switch to oral)</td>
<td>Best avoided in women with asthma or congestive heart failure. Because of a lower incidence of maternal hypotension and other adverse effects, its use now supplants that of hydralazine. Parenteral labetalol may cause neonatal bradycardia.</td>
</tr>
<tr>
<td>Hydralazine (C)</td>
<td>Start with 5 mg IV or IM, repeat 5 to 10 mg IV every 30 min, or 0.5-10 mg/hr IV to a maximum of 20 mg IV or 30 mg IM</td>
<td>A drug of choice according to NHBPEP; long experience of safety and efficacy. May increase risk of maternal hypotension.</td>
</tr>
<tr>
<td>Nifedipine (C)</td>
<td>5 to 10 mg capsule p.o., every 30 min or 10-30 mg tablet p.o., repeat in 45 min, if needed</td>
<td>Long acting preparations are preferred, although obstetric experience with short acting has been favourable, it is not approved by FDA for management of hypertension.</td>
</tr>
<tr>
<td>Diazoxide (C)</td>
<td>30 to 50 mg IV every 5 to 15 min</td>
<td>Use is warning; may arrest labour; causes hyperglycaemia</td>
</tr>
<tr>
<td>Nitroprusside (C)* Relatively contraindicated</td>
<td>Constant infusion of 0.25 to 5.00 ( \mu )g/kg per min</td>
<td>Possible cyanide toxicity if used for &gt;4 hrs., agent of last resort</td>
</tr>
</tbody>
</table>

(Noted as in Magee et al., 2008; Podymow and August, 2008)

Drugs indicated for acute elevation of diastolic BP \( \geq 105 \text{ mm Hg} \); the goal is gradual reduction to 90 to 100 mm Hg. NHBPEP indicates National High Blood Pressure Education Program Working Group Report on High Blood pressure in Pregnancy; FDA, Food and Drug Administration.

*We would classify in category D: there is positive evidence of human foetal risk, but the benefits of the use in pregnant women may be acceptable despite the risk.

*FDA classification, category C indicates that studies in animal have revealed adverse effects on the foetus (teratogenic, embryocidal or other) and/or there are no controlled studies in women or studies in women and animals are not available. Drug should be only be given if the potential benefits justify the potential risk to the foetus.
2.10.2. Recommendations for mild PIH

Antihypertensive therapy for non-severe hypertension (BP of 140-159/90-99 mm Hg)

1. Women without comorbid conditions, antihypertensive drug therapy should be used to keep systolic BP at 130-155 mm Hg and diastolic BP at 80-105 mm Hg.

2. For women with comorbid conditions, antihypertensive drug therapy should be used to keep systolic BP at 130-139 mm Hg and diastolic BP at 80-89 mm Hg.

3. Initial therapy can be with one of a variety of antihypertensive agents: methyldopa, labetalol, other β-blockers (acebutolol, pindolol and propranolol) and calcium channel blocker nifedipine.

4. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers should not be used.

5. Atenolol and prazosin are not recommended.
### Table 4: Drugs for control of mild hypertension in pregnancy (BP of 140-159/90-105 mm Hg)

<table>
<thead>
<tr>
<th>Drug (FDA risk)*</th>
<th>Dose and route</th>
<th>Concerns or comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methyldopa (B)</td>
<td>250 to 500 mg <em>p.o.</em> bid to qid (maximum 2g/d)</td>
<td>Drug of choice according to NHBPEP; safety after first trimester well documented. There is no evidence to support loading dose of methyldopa.</td>
</tr>
<tr>
<td>Second-line agents†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labetalol (C)</td>
<td>100 to 400 mg <em>p.o.</em>, bid to qid (maximum 1200mg/d)</td>
<td>Some expert recommend a starting dose of 200 mg <em>p.o.</em>, bid. May be associated with foetal growth restriction.</td>
</tr>
<tr>
<td>Nifedipine (C)</td>
<td>Intermediate release tablets (10 to 20 mg <em>p.o.</em>, bid to tid, maximum 180 mg/d) or slow release preparation 20 to 60 mg <em>p.o.</em>, OD, maximum 120 mg/d)</td>
<td>Caution should be exercised in ensuring that the correct form of nifedipine has been prescribed. May inhibit labour and have synergistic action with magnesium sulphate in lowering BP.</td>
</tr>
<tr>
<td>Hydralazine (C)</td>
<td>50 to 300 mg/d in 2 to 4 divided doses.</td>
<td>Few controlled trials, long experience with few adverse events documented; useful in combination with sympatholytic agent; may cause neonatal thrombocytopenia.</td>
</tr>
<tr>
<td>β-Receptor blockers (C)</td>
<td>Depends on specific agent</td>
<td>May decrease uteroplacental blood flow; may impair foetal response to hypoxic stress; risk of growth restriction when started in first or second trimester (atenolol); may be associated with neonatal hypoglycaemia at higher doses.</td>
</tr>
<tr>
<td>Hydrochlorothiazide (C)†</td>
<td>12.5 to 25.0 mg/day</td>
<td>Majority of controlled studies in normotensive women rather than hypertensive women; can cause volume contraction and electrolyte disorders; may be useful in combination with methyldopa and vasodilator to mitigate compensatory fluid retention.</td>
</tr>
<tr>
<td>Contraindicated ACE-inhibitors and angiotensin type 1 receptor antagonists (D)†</td>
<td></td>
<td>Leads to foetal loss in animals; human use associated with cardiac defects, footopathy, oligohydramnios, growth restriction, renalagenesis and neonatal anuric renal failure, which may be fatal.</td>
</tr>
</tbody>
</table>

(Noted as in Magee et al., 2008; Podymow and August, 2008)

No antihypertensive has been proven safe for use during first trimester.

2.10.3. Review on current management options

1. In a comparative study of maternal-foetal clinical intercurrences and effectiveness of treatment in the different clinical forms of hypertensive syndromes during pregnancy, it was found that antihypertensive therapy during gestation was of fundamental importance for health improvement and pressure control of the pregnant women with hypertensive syndrome of pregnancy. It has been of little help for prevention of perinatal intercurrences. This was substantiated by the absence of improvement in the gestational conditions between the treated groups when compared to the non-treated group. Medication did not significantly improve the maternal-foetal blood flow and consequently in the birth condition of the child (Ferrao et al., 2006).

2. In an update on the use of antihypertensive drugs in pregnancy by American Heart Association is stressed that antihypertensive agents are mainly used to prevent and treat severe hypertension, to prolong pregnancy for as long as possible, thereby maximizing the gestational age of the infant and to minimize foetal exposure to medications that may have adverse effects. The choice of antihypertensive agents is less complex, because only a small proportion of currently available drugs have been evaluated in pregnant women, and many others are contraindicated. The benefits of antihypertensive therapy for mild-to-moderate PIH have not been demonstrated in clinical trials. International guidelines for the treatment of hypertension in pregnancy vary with respect to thresholds for starting treatment and targeted blood pressure goals. In general clinical practice is to initiate treatment when blood pressure is more than 150 mm of Hg systole and 90 to 100 mm of Hg diastolic. When the diagnosis is preeclampsia, the gestational age, as well as the level of blood pressure, influences the use of antihypertensive therapy. At term, women with preeclampsia are likely to be delivered, treatment of hypertension (unless severe) can be delayed, and blood pressure can be reevaluated.
postpartum. If preeclampsia develops remote from term, and expectant management is undertaken, treatment of severe hypertension is initiated, and blood pressure can usually be safely lowered to 140/90 mm of Hg. Most antihypertensive agents used in pregnancy are designated as “category C”, which states that human studies are lacking, animal studies are either positive for foetal risk or are lacking, and the drugs should be given only if potential benefits justify potential risks to the foetus. Acceptable agents include methyldopa, labetalol, and Nifedipine in standard doses (Podymow and August, 2008).

3. In a study to determine the criteria of pregnancy termination in women with preeclampsia, maternal criteria were a severe uncontrolled hypertension, eclampsia, acute pulmonary oedema, retro placental hematoma, oliguria resistant to fluid therapy, persistent signs of imminent eclampsia, persistent epigastric pain, HELLP syndrome, new-onset renal failure and a gestational time within first 24 weeks. The foetal criteria were prolonged and variable foetal heart rate decelerations, a short term variability in foetal heart rate less than 3 beats per minute, a Manning score less than 4 on two occasions, severe oligohydramnios, an estimated foetal weight below the 5th percentile beyond 32 weeks and an inverted diastolic flow in the umbilical artery beyond the 32 weeks. In case of non-severe preeclampsia beyond 36th week of amenorrhea, interruption of the pregnancy must be considered (Haddad et al., 2010).

4. In a review article on diagnosis and treatment of hypertensive disorders during pregnancy, to reduce the risk of maternal and foetal complications due to hemodynamic maladaptation, the current management includes rest at home or in the hospital, close monitoring of maternal and foetal survival chances. Threshold to initiate blood pressure lowering treatment during pregnancy are 160 mm of Hg or 110 mm of Hg diastole. Below these thresholds, treatment must be individualized because current evidence does not support aggressive medical interventions. Alpha-methyldopa and nifedipine were among the recommended antihypertensive (Fabry et al., 2010).

5. In an editorial article on the use of magnesium sulphate prophylaxis for prevention of eclampsia in women with gestational hypertension, it is recommended to use
magnesium sulphate prophylaxis for prevention of eclampsia in PIH even in non-severe hypertension (Alexander et al., 2006)

6. In an editorial on intra hospital management of women with preeclampsia, it is recommended that in severe preeclampsia, the pregnancy is continued with close monitoring of maternal and foetal wellbeing. Corticosteroids are advised before 34 weeks in addition. The benefit of antihypertensive drugs in mild PIH was very limited (Diemunsch et al., 2010).

2.11. Need for the study

The hypertensive disorders of pregnancy are a leading cause of maternal and perinatal mortality and morbidity in India and internationally. The management of pregnancy induced hypertension is aimed at termination of pregnancy, but this cannot be done in all cases, as most cases are preterm or very preterm. The pregnancy can be prolonged by using antihypertensive agents by till a period where in foetal survival is good ,there by maximizing the gestational age of infant and minimizing the foetal exposure to medication that may have adverse effects. The antihypertensive agents have a role in controlling hypertension and there by maternal and foetal complications can be avoided (Naden and Redman, 1985; Brown et al., 2000; Fabry et al., 2010).

A review article in Portuguese stated that, data from literature research have been controversial about benefits of antihypertensive treatment, but not on treatment of hypertensive emergency instituted. The ideal medication used in those cases is not defined, therefore the real benefits of maintenance of antihypertensive treatment in preeclampsia remains unclear (Souza et al., 2010).

The decision to treat elevated arterial pressure in pregnancy depends on the risk and benefits imposed on the mother and the foetus. Treatment for mild to moderate hypertension may not reduce maternal or foetal risk, but progression to severe hypertension can be prevented. Severe hypertension, on the other hand, should be treated to decrease maternal risk. Methyldopa and beta adrenoceptor antagonists have been used most extensively. In acute severe hypertension, intravenous labetalol or oral nifedipine may be the reasonable choices (Ghanem and Movahed 2008).
Uncertainty remains about the potential harmful effects of antihypertensive therapy on developing foetus (Ray et al., 2001). Many of the clinical studies on antihypertensive agents are either with one drug or two drugs with respect to efficacy, or maternal outcome or perinatal outcome either in mild or severe pregnancy induced hypertension. There are insufficient data available to favour one antihypertensive agent over other. In a review of randomized controlled trials, observational studies and animal studies to evaluate if there are alteration in foetal or neonatal heart rate characteristics due to use of antihypertensive drugs, available data are inadequate to conclude whether oral methyldopa, labetalol, nifedipine or hydralazine adversely affect foetal or neonatal heart rate and pattern. Until definitively available, FHR changes cannot be reliably attributed to drug effect, because of progression of the underlying maternal and placental disease (Waterman et al., 2004).

In a prospective study of antihypertensive medications in pregnancy and the risk of adverse perinatal outcome, it was found that the maternal use of antihypertensive medications other than β blockers was associated with both major perinatal morbidity and mortality, while β blocker monotherapy was not. The combined use of β blockers and non-β blockers medications demonstrated the strongest association with a higher risk for IUGR, SGA, preterm births, and admission to the NICU. Before definitive conclusions can be drawn, a large multicentre randomized controlled trial is needed to address the issues of both maternal efficacy and foetal safety with the use of one or more antihypertensive agents in pregnancy (Ray et al., 2001). There are no consensuses among obstetricians of India in choosing the antihypertensive agents in pregnancy, as evidence based guidelines are lacking. Some obstetricians start with monotherapy and then shift to multiple drug therapy if BP is not controlled.

In the present study the drugs chosen were methyldopa, nifedipine and labetalol as they belong to different class based on their mode of action and are most recommended agents (Magee et al., 2008; Podymow and August, 2008). Outcome of monotherapy with these drugs were studied, since multiple therapy had the strongest association for adverse perinatal outcomes. Methyldopa is widely used in pregnancy induced hypertension. It is not thought to be teratogenic based on limited data and a 40 year history of use in pregnancy (Podymow and August 2008). Labetalol was
selected for the study based on a comparative study of labetalol vs. methyldopa in the treatment of PIH, which concluded that labetalol is better tolerated than methyldopa as it gives more efficient control of blood pressure. Study included small group of patients and only maternal outcome was assessed with respect to control of blood pressure and frequency of side effects (El-qarmalawi et al., 1995). Nifedipine is found to be safe and more effective than hydralazine in controlling severe preeclampsia; however lack of adequate data has created uncertainty about the safety of calcium channel blockers. Nifedipine has been reported to be teratogenic in animals, but no cases of possible human malformation or deformity have been reported (Tranquill and Giannubilo, 2009).

Hence the present study was undertaken to evaluate and compare the use of methyldopa, nifedipine and labetalol in mild and severe pregnancy induced hypertension with respect to efficacy, side effects, and adverse effects, maternal, perinatal and neonatal outcome.

2.12. Clinical trials on methyldopa, nifedipine and labetalol

1. In comparison of labetalol plus hospitalization versus hospitalization alone in the management of preeclampsia remote from term, treatment of maternal BP with labetalol did not improve perinatal outcome and was associated with a higher frequency of fetal growth retardation (Sibi et al., 1987).

2. In a randomized double-blind controlled trial of labetalol versus placebo in PIH, labetalol was found to be effective in the management of mild to moderate PIH. The study suggested possible advantages and no apparent disadvantages for the fetus during its use (Pickles et al., 1989).

3 Anti-hypertensive intervention therapy in mild to moderate PIH has been examined using a placebo controlled double blind trial of labetalol. The maximum BP prior to labour and the incidence of proteinuria was reduced in women on active therapy. However the length of gestation was not significantly prolonged and indices of clinical outcome were not significantly altered (Pickles et al., 1992).
4. In a comparative study to find the effectiveness of nifedipine or hydralazine as a first line agent to control hypertension in severe preeclampsia, it was found that nifedipine is safe and more effective than hydralazine in controlling blood pressure in severe preeclampsia. It has the advantage of being cheaper and more widely available than the latter and is easily administered (Aali and Nejad, 2002).

5. In a study to find the efficacy and safety of nifedipine tablets for acute treatment of severe hypertension in pregnancy, it was found that slower and longer acting nifedipine were as effective and safe as the rapid onset and short-acting nifedipine capsules for the treatment of acute severe hypertension in pregnancy (Brown et al., 2002).

6. In a randomized controlled trial to assess the efficacy and safety of labetalol compared with methyl dopa in the management of mild and moderate PIH it was concluded that labetalol is better tolerated than methyldopa, with more efficient control of blood pressure and may have a ripening effect on the uterine cervix (El-Qarmalawi et al., 1995).

7. In a randomized double-blind trial of oral nifedipine (10 mg) and intravenous labetalol (20 mg) in 50 patients, it was found that both oral nifedipine and intravenous labetalol are effective in the management of acute hypertensive emergencies of pregnancy, however, nifedipine controls hypertension more rapidly and is associated with a significant increase in urine output (Vermillion et al., 1999).

8. In review article on the comparative risk-benefit assessment of drugs used in the management of hypertension in pregnancy, it was found that both intravenous hydralazine and oral nifedipine are effective drugs to treat severe hypertension acutely, the latter having the advantage of ease of administration. For long term therapy, methyldopa is the only drug which has been fully assessed and shown to be safe for the neonate and infant. Beta-adrenoceptor antagonists are safe to use in the third trimester but cause significant intrauterine growth retardation when used for longer periods. ACE inhibitors are contraindicated and diuretics should be avoided. Although calcium antagonists appear to have much potential they require further assessment of their use in pregnancy (Phillipa and Christopher, 1992).
9. In a randomized control trial comparing labetalol with methyldopa for treatment of hypertension in pregnancy, it was found that maternal beta-blockade with labetalol is as safe as methyldopa for the foetus and the new born (Plouin et al., 1988).

10. In a randomized double blind trial to compare the hemodynamic effects of orally administered nifedipine and intravenously administered labetalol in preeclamptic hypertensive emergencies nifedipine increases the cardiac index, whereas labetalol did not (Scardo et al., 1999).

11. In a prospective clinical trial to compare nifedipine with methyldopa in the management of PIH, nifedipine was as effective as methyldopa in the treatment of PIH (Jayavardana and Lekamge, 1994).

2.13. Pharmacology

1. Nifedipine

\[
\text{N} \quad \begin{array}{c}
\text{CH}_3 \\
\text{H}_3\text{C} \\
\text{H}_2\text{CO} \\
\text{OCH}_3 \\
\text{NO}_2
\end{array}
\]

\[\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_6 \quad \text{Molecular weight.346.3}\]

Dimethyl 1,4-dihydro-2, 6-dimethyl-4-(2-nitrophenyl) pyridine-3, 5-dicarboxylate(Indian Pharmacopoeia,2010a).

Nifedipine is dihydropyridine calcium channel blocker. It is a peripheral and coronary vasodilator. Administration of nifedipine results primarily in vasodilatation, with reduced peripheral resistance, blood pressure and afterload, increased coronary blood flow, and a reflex increase in heart rate. This in turn results in an increase in myocardial oxygen supply and cardiac output (Sorkin et al., 1985).
Nifedipine is usually given by mouth. It is available in a number of formulations. Liquid-filled capsules with a relatively rapid onset but short duration of action are administered three times a day. This short acting preparation is not recommended for the management of hypertension. There are also tablets and capsules with a slower onset and longer duration of action, enabling twice daily administration (Fisher and Grotta, 1993).

Nifedipine is one of the commonly used antihypertensive drugs in the management of pregnancy induced hypertension. Nifedipine does not seem to cause a detectable decrease in uterine blood flow (Rizzo et al., 1987; Lindow et al., 1988). It lowers blood pressure without compromising uteroplacental blood flow. Administration of short acting nifedipine capsules has been in case reports associated with maternal hypotension and foetal distress (Puzy et al., 1991; Impey, 1993). One study has shown efficacy and safety of long acting oral nifedipine in pregnant patients with severe hypertension in pregnancy (Fanakel et al., 1991; Brown et al., 2002).

Foetal nifedipine concentrations have been reported to be 75% of maternal values 2 to 3 hours after sublingual administration (Pirhonen et al., 1990). However nifedipine in a single 20 mg oral dose lowered blood pressure without compromising blood flow in the fetus in 9 women in the third trimester with normal haemodynamic (Hanretty et al., 1989). In higher doses it is used to inhibit pre-term labour contractions. It is superior to ritodrine in inhibiting pre term uterine contractions. The dose given is 30 mg stat followed by 20 mg every 8 hours by mouth. Dose in management of pregnancy induced hypertension is 10 to 20 mg orally three times a day.

A concern with calcium channel blockers for BP control in preeclampsia has been the concomitant use of magnesium sulphate to prevent seizures; drug interactions between nifedipine and magnesium sulphate were reported to cause neuromuscular blockade, myocardial depression or circulatory collapse in some cases (Waisman et al., 1988; Ales 1990; Ben-Ami et al., 1994). In practice (Scardo et al., 1996; Magee 2001) and in a recent evaluation (Magee et al., 2005), these medications are commonly used together without increased risk.
Breast feeding: Nifedipine is distributed into breast milk (Penny and Lewis 1989; Ehrenkranz et al., 1998), but the amount present is probably too small to be harmful. There have been no reports of any clinical effects in breast fed infants whose mothers were receiving nifedipine (American Academy of Paediatrics, 2001).

The common adverse effects are associated with its vasodilator action and often diminish on continued therapy. They include dizziness, flushing, headache, hypotension, peripheral oedema, tachycardia and palpitations. Nausea and other gastrointestinal disturbances, increase urination, lethargy, eye pain, visual disturbances and mental depression are other adverse effects.

Headache, visual disturbances and dizziness are often mistaken as symptoms of imminent eclampsia. Sudden fall of blood pressure especially if the drug is given sublingually can cause sudden placental insufficiency, blindness and chest pain due to myocardial ischemia.

There have been reports of rashes (including erythema multiforme), fever and abnormalities in liver function including cholestasis due to hypersensitivity reactions. Gingival hyperplasia, myalgia, tremor have been reported in long term use. Over dosage may be associated with bradycardia and hypotension; hyperglycaemia, metabolic acidosis, and coma may also occur. Management of over dosage include gastric lavage, supine positioning, foot elevation, plasma expanders, calcium gluconate, dopamine and atropine. Dialysis is not useful as nifedipine is highly protein bound. Plasmapheresis may be beneficial (Martindale, 2006). Nifedipine has been reported to be teratogenic in animals (Constantine et al., 1987). Orally administered nifedipine do not seem to pose teratogenic risks to foetuses exposed in the first trimester (Magee et al., 1996).

2. Methyl dopa

\[
\text{C}_{10}\text{H}_{13}\text{NO}_4\cdot\frac{11}{2}\text{H}_2\text{O}
\]

Molecular weight. 238.2
3-(3, 4-dihydroxyphenyl)-2-methyl-L-alanine sesquihydrate (Indian Pharmacopoeia, 2010b).

Methyl dopa is the hydrochloride of the ethyl ester of anhydrous methyl dopa. Its antihypertensive action is mainly through central action. It is decarboxylated in the central nervous system to alpha-methyl noradrenaline, which is thought to stimulate alpha-2 adrenoceptors resulting in reduction of sympathetic tone and a fall in blood pressure. It may also act as a false neurotransmitter, and have some inhibitory actions on plasma renin activity (weidmann et al., 1974; Podjarny et al., 2001). Methyl dopa reduces the tissue concentrations of dopamine, noradrenaline, adrenaline, and serotonin.

Following oral use methyldopa is variably and incompletely absorbed, apparently by an amino acid active transport system. The mean bioavailability has been reported to be about 50%. It is extensively metabolized and excreted in urine mainly as unchanged drug and the O-sulphate conjugate. It crosses the blood brain barrier and is decarboxylated in CNS to active alpha-methyl noradrenaline.

The elimination is biphasic with a half-life of about 1.7 hours in the initial phase: the second phase is more prolonged. Plasma protein binding is reported to be minimal. Methyldopa crosses the placenta; small amounts are distributed in to breast milk. In hypertension the usual initial adult dose by mouth is 250 mg of methyldopa two or three times daily for 2 days; this is then adjusted not more frequently than every 2 days according to response, up to a usual maximum dose of 3g daily. Methyldopa when given by mouth its effect reaches a maximum in 4 to 6 hours after a single dose, although the maximum hypotensive effect may not occur until the second or third day of continuous treatment (Kranz et al., 1974; Martindale, 2006).

Methyl dopa is widely used in pregnancy induced hypertension. It has been assessed in a number of prospective trials in pregnant women compared with placebo (Redman, 1976; Sibai et al., 1990) or with alternative antihypertensive agents (Fidler et al., 1983; Gallery et al., 1985; Poulin et al., 1988). Treatment with methyldopa has been reported to prevent subsequent progression to severe hypertension in pregnancy (Redman et al., 1977) and does not seem to have adverse effects on uteroplacental or
foetal hemodynamic (Montan et al., 1993) or on foetal wellbeing. When given orally its effect reach a maximum in 4 to 6 hours after a single dose, although the maximum hypotensive effect may not occur until the second or third day of continuous treatment. When given intra venous the hypotensive effect may be obtained within 4 to 6 hours and last for 10 to 16 hours. Usual adult dose is 250-500mg three to four times a day (Martindale, 2006). The only significant adverse findings reported in one of the studies was a small decrease in head size of male infants who had been exposed to methyl dopa between 16 to 20 weeks gestation (Moar et al., 1978). It is suggested to defer methyl dopa initiation before 20 weeks gestation. A separate clinical study did not uncover any association between head size and methyl dopa exposure (Fidler et al., 1983).

Methyl dopa crosses placenta with foetal serum concentration similar to maternal serum concentration (Jons and Cummings, 1978). There is little evidence of adverse effects on foetal development. However it crosses the placenta and reduced blood pressure has been reported in infants born to mothers receiving the drug (Whitelaw 1981).There has also been a report of tremor in 7 infants associated with maternal methyldopa use in pregnancy (Bodies et al., 1982). Nasal congestion has been reported as a side effect. Transient nasal obstruction has also been observed in prenatally exposed neonates (Le Gras et al., 1990). Methyl dopa may be hepatoxic during pregnancy. It is not thought to be teratogenic based on limited data and a 40 year history of use in pregnancy.

Adverse effects are consequences of central alpha-2 agonism or decreased peripheral sympathetic tone. It acts at sites in the brain stem to decrease mental alertness and impair sleep, leading to a sense of fatigue or depression in some patients. Methyldopa can also cause elevated liver enzymes in 5%; hepatitis and hepatic necrosis have also been reported (Schweitzer and Peters, 1974). Methyl dopa may produce amenorrhoea, hyperprolactinamia, positive Coomb test and galactorrhoea.

Breast feeding: Methyl dopa is distributed in to breast milk in small amounts (Jones and Cummings, 1978). It was estimated that the amount of methyldopa breast fed infant would receive about 0.02% of the maternal dose (White et al., 1985). In
another study (Hauser et al., 1985) over a 3 month period no adverse effects were found in a breast fed infant whose mother was taking methyldopa although the drug was detectable in infant’s urine.

3. Labetolol

\[
\text{C}_{19}\text{H}_{24}\text{N}_{2}\text{O}_{3} \cdot \text{HCl} \quad \text{Molecular weight.364.9}
\]

Labetalol hydrochloride is a racemate, chemically designated as 2-hydroxy-5-[1-hydroxy-2-[(1—methyl-3-phenyl propyl amino) ethyl] benzamide hydrochloride. Labetalol hydrochloride is a white or off-white crystalline powder, soluble in water. Each tablet, for oral administration, contains 100 mg, 200 mg or 300 mg labetalol hydrochloride (Indian Pharmacopoeia, 2010b).

Labetalol is an adrenergic receptor blocking agent that has both selective competitive alpha-1-adrenergic and non-selective competitive beta-adrenergic receptor blocking actions in a single substance. It is reported to possess some intrinsic sympathomimetic and membrane stabilising activity. In man, the ratios of alpha- to beta-blockade have been estimated to be approximately 1:3 and 1:7 following oral and intravenous (IV) administration, respectively. \(\beta_2\)-agonist activity has been demonstrated in animals with minimal \(\beta_1\)-agonist (ISA) activity detected. In animals, at doses greater than those required for alpha or beta-adrenergic blockade, a membrane-stabilizing effect has been demonstrated.

The capacity of labetalol hydrochloride to block alpha receptors in man has been demonstrated by attenuation of the pressor effect of phenylephrine and by a significant reduction of the pressor response caused by immersing the hand in ice-cold water (“cold pressor test”). Labetalol hydrochloride’s \(\beta_1\)-receptor blockade in man was demonstrated by a small decrease in the resting heart rate, attenuation of tachycardia produced by isoproterenol or exercise, and by attenuation of the reflex tachycardia to the hypotension produced by amyl nitrite. \(\beta_2\)-receptor blockade was demonstrated by inhibition of the isoproterenol-induced fall in diastolic blood
pressure. Both the alpha- and beta-blocking actions of orally administered labetalol hydrochloride contribute to a decrease in blood pressure in hypertensive patients. Labetalol hydrochloride consistently, in dose-related fashion, blunted increases in exercise-induced blood pressure and heart rate, and in their double product. The pulmonary circulation during exercise was not affected by labetalol hydrochloride dosing.

Labetalol hydrochloride produces dose-related fall in blood pressure without reflex tachycardia and without significant reduction in heart rate, presumably through a mixture of its alpha-blocking and beta-blocking effects. Hemodynamic effects are variable with small, no significant changes in cardiac output seen in some studies but not others, and small decreases in total peripheral resistance. Elevated plasma renin is reduced (Burnton et al., 2006; Marindale, 2006).

Doses of labetalol hydrochloride that controlled hypertension did not affect renal function in mild to severe hypertensive patients with normal renal function. Due to the $\alpha_1$-receptor blocking activity of labetalol hydrochloride, blood pressure is lowered more in the standing than in the supine position and symptoms of postural hypotension (2%), including rare instances of syncope, can occur. Following oral administration, when postural hypotension has occurred, it has been transient and is uncommon when the recommended starting dose and titration increments are closely followed. Symptomatic postural hypotension is most likely to occur 2 to 4 hours after a dose, especially following the use of large initial doses or upon large changes in dose.

The peak effects of single oral doses of labetalol hydrochloride occur within 2 to 4 hours. The duration of effect depends upon dose, lasting at least 8 hours following single oral doses of 100 mg and more than 12 hours following single oral doses of 300 mg. The maximum, steady-state blood pressure response upon oral, twice-a-day dosing occurs within 24 to 72 hours.

The antihypertensive effect of labetalol has a linear correlation with the logarithm of labetalol plasma concentration and there is also a linear correlation between the reduction in exercise-induced tachycardia occurring at 2 hours after oral
administration of labetalol hydrochloride and the logarithm of the plasma concentration. About 70% of the maximum beta-blocking effect is present for 5 hours after the administration of a single oral dose of 400 mg with suggestion that about 40% remains at 8 hours.

Labetalol hydrochloride is completely absorbed from the gastrointestinal tract with peak plasma levels occurring 1 to 2 hours after oral administration. The relative bioavailability of labetalol hydrochloride tablets compared to an oral solution is 100%. The absolute bioavailability (fraction of drug reaching systemic circulation) of labetalol when compared to an intravenous infusion is 25%; this is due to extensive “first-pass” metabolism. Despite “first-pass” metabolism, there is a linear relationship between oral doses of 100 mg to 3000 mg and peak plasma levels. The absolute bioavailability of labetalol is increased when administered with food.

The plasma half-life of labetalol following oral administration is about 6 to 8 hours. Steady-state plasma levels of labetalol during repetitive dosing are reached by about the third day of dosing. In patients with decreased hepatic or renal function, the elimination half-life of labetalol is not altered; however, the relative bioavailability in hepatically impaired patients is increased due to decreased “first-pass” metabolism.

The metabolism of labetalol is mainly through conjugation to glucuronide metabolites. These metabolites are present in plasma and are excreted in the urine and, via the bile, into the faeces. Approximately 55 to 60% of a dose appears in the urine as conjugates or unchanged labetalol within the first 24 hours of dosing (MaCarthy and Bloomfield, 1983).

Labetalol has been shown to cross the placental barrier and is distributed in to breast milk in humans. Only negligible amounts of the drug crossed the blood-brain barrier in animal studies. Labetalol is approximately 50% protein bound. Neither haemodialysis nor peritoneal dialysis removes a significant amount of labetalol hydrochloride from the general circulation (<1%).

The concentration of labetalol has been found to be lower in amniotic fluid (Lunell et al., 1985) and foetal plasma (Michael, 1979) than in maternal plasma. A ratio of infant to maternal drug concentration of 0.2 to 0.8 has been reported based on
concentration in infant cord blood at delivery (time since last maternal dose not stated). In another study, (Boulton et al., 1999) however higher concentrations were found in cord plasma than in maternal plasma at delivery when infants were delivered 12 to 24 hours after last maternal dose.

Labetalol has gained wide acceptance in pregnancy. When administered orally to women with chronic hypertension, it seems as safe (Sibai et al., 1987; Plouin et al 1988; Pickles et al., 1989; Sibai et al., 1990) and effective as methyldopa, although neonatal hypoglycaemia with higher doses has been reported (Munshi et al., 1992). Of some concern, one placebo controlled study reported an association with foetal growth restriction in the management of preeclampsia remote from term (Sibai et al 1987). Parenterally it is used to treat severe hypertension, and because of a lower incidence of maternal hypotension and other adverse effects, its use now supplants that of hydralazine (Magee et al., 2003).

Adverse effects may be predicted as consequences of β-receptor blockade. Fatigue, lethargy, exercise intolerance (because of β₂ blocking effects in skeletal muscle vasculature), peripheral vasoconstriction, sleep disturbance and bronchoconstriction may be seen; however, discontinuation because of adverse effects is uncommon (Podymow and August, 2008).