CHAPTER - VI

DISCUSSION
Pregnancy induced hypertension is one of the common medical disorders of pregnancy. It complicates 6 to 8% of pregnancies (Podm and August, 2010) and is the third common cause for maternal mortality and morbidity next to haemorrhage and infections (Duley, 2009). 18% of maternal deaths are due to pregnancy related hypertension complications. It affects both mother and foetus (Huang, 2001; Soares et al., 2009; Bell, 2010).

Hypertension during pregnancy predisposes to complications like eclampsia, *abruptio placentae*, disseminated intravascular coagulation, pulmonary oedema, blindness, cerebrovascular haemorrhages, HELLP syndrome, foetus growth restriction and foetal demise. Controlling hypertension in pregnancy prevents complications both in mother and foetus.

There are various theories for the aetiology of pregnancy induced hypertension. The common pathophysiological changes seen are imbalance between vasoconstrictor thromboxane and vasodilator prostacyclin resulting in generalised vasospasm. This leads to endothelial damage resulting in release of vasoactive substances. This causes decreased intravascular volume and increased extravascular volume. The effects of this are placental insufficiency resulting in complications (Haram et al., 2000; Granger et al., 2001; Chandiramani et al., 2010).

Controlling hypertension in pregnancy using antihypertensive drugs brings down these complications. The most extensively used antihypertensive drugs in pregnancy are β adrenoceptor antagonists, nifedipine, methyldopa and labetalol (Ghanem and Movahed, 2008). These drugs are used alone or in combinations in routine obstetric practice in our country. Each of these drugs have different mode of action. Nifedipine is vasodilator and calcium channel blocker. Methyl dopa is centrally acting antihypertensive. Labetolol is both α and β blocker.

There were no clinical studies in which these drugs were compared in the same setting, when used orally with respect to their antihypertensive efficacy, side effects, maternal and neonatal outcome both in mild and severe PIH. Therefore the
present study was undertaken to evaluate and compare methyldopa, nifedipine and labetalol in mild and severe PIH.

For this study pregnant women fulfilling the definition of pregnancy induced hypertension, inclusion and exclusion criteria were enrolled. They were divided into three groups based on antihypertensive drugs used. Each treatment group was further divided into two subgroups based on severity of hypertension as mild and severe PIH. Baseline characters of PIH patients were analysed together in mild and severe PIH patients in three treatment groups. Whereas efficacy, maternal and neonatal outcomes were analysed separately in three treatment groups of mild and severe PIH.

**Baseline characters and pre-treatment risk factors**

When baseline characters of PIH patients were analysed between the groups it was found that 44 to 57% of patients were in the age group of 21 to 25 years. There was no significant difference in age distribution between the groups. Primigravida were more often affected than multigravida as there were 39 to 59% primigravida in the study group. This is similar to the hospital based studies of Prakash et al., 2006, in which majority of patients were primigravida (57%).

Incidence of PIH in the present study was high in nulliparous women (46 to 62%). A study conducted to throw light on incidence of preeclampsia in women attending for care and delivery at a hospital, revealed that high proportion of preeclamptic cases were occurring among nulliparous women and those at extreme ends of reproductive age (Al-Mulhim et al., 2003). A study conducted to determine whether maternal and foetal complications in preeclampsia and gestational hypertension differ with both gravidity and parity, concluded that gestational hypertensive groups did not differ in their clinical expression of hypertensive complications. Whereas the preeclamptic, primigravid primiparous and multigravid primiparous groups behaved similarly in their clinical expression of hypertensive complications but differed from the multiparous group by having a higher incidence of HELLP syndrome. The incidence of complications in hypertensive pregnant women varied by parity but not by gravidity (Williams and Wilson, 2002).
In the present study there was 18 to 25% history of PIH in previous pregnancy and a family history of 15 to 27%. These observations are substantiated by an Indian study, which concluded history of preeclampsia in a previous pregnancy, and family history of hypertension in one or more first degree relative is the risk factors of early onset severe preeclampsia in north Indian women (Nanjundan et al., 2011). Also a study to analyse effect of previous preeclampsia and risks of adverse outcomes in subsequent pregnancies, concluded that women with previous preterm preeclampsia have increased risks of adverse pregnancy outcomes in a second pregnancy despite the absence of preeclampsia (Wikstrom et al., 2011). In another study to identify the risk factors for preeclampsia in Asian population stated that women who had a history of preeclampsia were at increased risk of preeclampsia in subsequent pregnancies (Lee et al., 2000). In support of our study, a controlled cohort study showed that the risk of preeclampsia increased in women with a previous history, family history, nulliparity, multiple pregnancies etc (Duckitt and Harrington, 2005).

At presentation about 48 to 54% of PIH patients were in 37 to 40 weeks of gestational age followed by 33 to 36 weeks (19 to 23%). Early onset PIH was 3 to 4% i.e. between 20 to 24 weeks of gestation.

Socioeconomic status is an important risk factor, indirectly reflecting the micro and macro nutrient status of the pregnant women. Socioeconomic status was determined by Kuppuswamy classification based on three variables in urban community namely education, occupation and income (Kuppuswamy, 2005). In the present study PIH was commonly encountered in middle socioeconomic class (56 to 59%) followed by lower class (34 to 38%). PIH patients with high socioeconomic status were least in number (7%). There was no significant difference found in socioeconomic status with respect to severity of PIH. A population based cohort study to examine whether maternal socioeconomic status is associated with preeclampsia concluded that low socioeconomic status is a strong risk factor for preeclampsia (Silva et al., 2008). Since this study was conducted in Netherlands which is a developed country, their low socioeconomic status may be equivalent to middle socioeconomic status in our country.
In the present study 10 to 17% of consanguineous marriages had PIH compared to 83 to 90% of non-consanguineous marriages. There is no relationship between consanguinity and pregnancy induced hypertension. This observation is supported by a study conducted at Vellore, South India where consanguineous marriages are common (George et al., 1992).

In a study to determine the risk factors in pregnant women with hypertensive disorders, gestational diabetes was noted in 3.9% of the patients (Yucesoy et al., 2005). In our study risk factors such as gestational diabetes was absent, one case placenta previa was found in methyldopa and labetalol group of mild PIH, whereas only one case of chronic renal failure was present in labetalol group of severe PIH.

Anaemia in pregnancy was one of the common predisposing risk factor for development of pregnancy induced hypertension, since anaemia with evidence of haemolysis (bur cells and schistocytes on peripheral smear) is indicative of HELLP syndrome. In the present study incidence of anaemia was less than 31% and there was no significant difference in mild and severe PIH.

Fundoscopic changes in PIH patients are mainly due to arteriolar narrowing which results in ischemic changes, haemorrhages, oedema, papilledema or optic disc oedema (malignant hypertension and visual acuity loss, typically due to macular involvement). There is an association between the grade of retinopathy and mortality (Saito et al., 1990). Fundoscopy was done to assess hypertensive retinopathy. Fundoscopy was found to be normal in most of the cases in mild PIH while in severe PIH, 43 to 55% of them had grade-1 retinopathy, higher grades was not found.

Non stress test (NST) is done using Cardiotocography (CTG) machine. This test is done for foetal well-being in women not in labour. A continuous record of foetal heart pattern along with foetal movement marking is traced. A reassuring or reactive NST has 2 or more foetal movements associated with foetal heart acceleration of 15 beats per minute from base line for 15 seconds or more in 20 minutes recording with no decelerations. NST has high sensitivity and low specificity. CTG is done for monitoring foetal condition in women with labour. In CTG foetal heart rate, movements and uterine pressure are recorded. Early deceleration is seen in
late labour due to head compression. Late deceleration is seen in placental insufficiency due to PIH. Variable deceleration is seen in cord compression (Arulkumaran, Penna and Bhasker Rao, 2005). Foetal well-being test, i.e. NST was found to be assuring in almost all cases in mild PIH, and majority of cases in severe PIH.

In the present study incidence of PIH was found to be high in the age group of 21 to 25 years, primigravida, nulliparous women with middle/low socioeconomic status. Patients with past and family history were significant. Consanguineous marriage was not a risk factor for development of PIH. Significant proteinuria (≥ 2+ dipsticks), DBP more than 110 mm of Hg, early gestational age and partial HELLP syndrome were major risk factors.

**Efficacy of antihypertensive agents**

Efficacies of antihypertensive agents were assessed based on their effectiveness in control of hypertension and proteinuria. Assessment of BP values for 72 hours of treatment period was to analyse the effectiveness of drug therapy with respect to onset of action, and also to make decision to either change the drug or terminate pregnancy if hypertension was not controlled. Sudden reduction is not desirable, since it affects foetal haemodynamic leading to foetal distress (Magee et al., 2008).

In the present study, nifedipine was able to reduce SBP to normotensive by 24 hrs of treatment period, while reductions in DBP and MAP to normotensive were observed at 48 hrs of treatment period in mild PIH. Nifedipine was effective in controlling hypertension in 77% of patients of mild PIH by 72 hrs of treatment.

In severe PIH, nifedipine significantly reduced SBP by 24 hrs, but was not able to achieve control at the end of 72 hrs of treatment. The severity reduced to mild PIH range. DBP started reducing significantly after 24 hrs of treatment and was almost controlled to normotensive values by 72 hrs of treatment period. MAP started reducing very significantly after 6 hrs of treatment; even though reduction progressed MAP was not normotensive at 72 hrs of treatment. Although BP values are not
normotensive, nifedipine achieves the goal of treatment to reduce DBP to 90-100 mm of Hg in pregnancy.

BP was controlled to normotensive values in only in 6.82% patients by 72 hrs of treatment. Hypertension was not controlled in majority of the patients. However as the duration of treatment progressed, hypertension was controlled in 62.07% of patients almost similar to labetalol, and was significant compared to methyl dopa group at the time of discharge. Therefore it is evident that nifedipine was effective in mild PIH, where as in severe PIH even though hypertension was not normotensive in majority of patients at 72 hrs, over the period of time control was achieved similar to labetalol.

The pathophysiology of pregnancy induced hypertension (PIH) is centred on vasospasm due to various factors like increased pressor response, vasoactive agents, and endothelial damage, inflammatory response, genetic pre-disposition and immunological factors (Chen et al., 1993; Granger et al., 2001b). As nifedipine is a calcium channel blocker; it does not act directly on the basic pathophysiology of PIH, which may be the reason for not controlling hypertension in majority of the patients in severe PIH at 72 hrs. However due to vasodilation over the time period, it reduces peripheral resistance and reverses vasospasm induced by vasoactive substances in PIH.

From the results it was evident that methyldopa gradually decreased maternal BP in mild and severe PIH as evidenced by significant reduction in SBP and DBP at 24 hrs of treatment. A significant reduction in MAP was observed at 6 hrs in mild PIH and 24 hrs in severe PIH. Methyldopa was able to control hypertension to normotensive within 48 to 72 hrs of treatment in mild PIH, where as in severe PIH even at 72 hrs of treatment period DBP was more than 90 mm of Hg (90-100 mm of Hg). By 72 hrs of treatment period, hypertension was controlled in 59.32% and 6.82% of patients in mild and severe PIH respectively. Like nifedipine even methyldopa was not able to control hypertension in majority of patients at 72 hrs.

As the time of treatment progressed, maternal BP was normotensive in 82.76% and 34.93% of patients in mild and severe PIH respectively. From these
results we can conclude that methyldopa was very effective in controlling hypertension of mild PIH, but not in severe PIH. However it was effective in reducing the severity of disease in severe PIH. Since methyldopa is a centrally acting antihypertensive, it crosses the blood brain barrier and is decarboxylated to active α-methyl norepinephrine. This mechanism may be responsible for delayed action. When methyldopa is given orally its effect reach 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 (Campbell et al., 1988). This was supported by results of present study, where methyldopa produced maximum hypotensive effect between second and third day (48 to 72 hours) of continuous treatment in mild PIH.

From the study results, labetalol was found to be most effective in controlling hypertension both in mild and severe PIH. Labetalol has rapid onset of action as evidenced by reduction in SBP of severe PIH and MAP both in mild and severe PIH at 6 hours of treatment. Control over hypertension was achieved by 24 to 48 hours and 72 hours of treatment in mild and severe PIH respectively. Labetalol was able to reduce BP to normal, whereas nifedipine and methyldopa reduced the DBP between 90-100 mm Hg.

In mild PIH, by 72 hours of treatment, BP was controlled in almost all the patients (97%) in labetalol group which is significant compared to 59 and 76% of patients in methyldopa and nifedipine groups respectively. Hypotensive effect was sustained as treatment progressed, i.e. hypertension was controlled in 97% of patients at the time of discharge and effect was significant compared to methyldopa group.

Where as in severe PIH, BP was normotensive in 57% of patients at 72 hours of treatment and was significant compared to nifedipine and methyldopa groups. Hypotensive effect further progressed as control over hypertension was achieved in 67% of patients at the time of discharge and was significant compared to methyldopa group.

Therefore, we can conclude that effectiveness of labetalol was greater than nifedipine and methyldopa both in mild and severe PIH and this may be because of its rapid onset of action. This effect of labetalol can be attributed to its mechanism of
action, since it is a selective $\alpha$-blocking and non-selective $\beta$-adrenergic blocking agent with weak intrinsic sympathomimetic activity.

Rapid onset of action may be due to its pharmacokinetics. Labetalol is readily absorbed from gastrointestinal tract. Peak plasma concentration achieves about 1 to 2 hrs after oral dose. Labetalol is metabolised mainly in the liver. The elimination half-life at steady state is reported to be about 6 to 8 hrs. The physiological changes of pregnancy include an altered hepatic metabolism which might affect the clearance of various drugs. Studies have reported higher metabolic clearance rates of labetalol in pregnant women (Nylund et al., 1984).

From the present study we can conclude that labetalol has rapid onset of action, faster control over hypertension, and DBP values were less than 80 mm of Hg in mild PIH at 72 hrs of treatment. This effect also reflects the concern that a DBP < 80 mm of Hg may limit uteroplacental perfusion. Therefore it may be prudent to continuously monitor foetal heart rate (FHR) until BP has stabilised.

Literature suggests that decrease in BP to normotensive values by labetalol may compromise uteroplacental blood flow evidenced by changes in FHR. Until definitely available FHR changes cannot be reliably attributed to drug effect, due to progression of the underlying maternal or placental disease (Waterman et al., 2004). In the present study labetalol has not affected FHR, even though BP decreased to normotensive values, as there were no differences in perinatal outcome between the groups.

This is further supported by a study in which effect of labetalol on uteroplacental blood flow was examined in PIH. It was found that uteroplacental blood flow did not decrease following the injection of labetalol, despite the fact that a significant reduction in systemic blood pressure was achieved. This indicates that the uteroplacental vascular resistance was reduced (Jouppila et al., 1986; Nylund et al., 1984). These finding are consistent with a decrease in resistance in the placental vascular bed.

Finally it is concluded that all the three drugs were effective in the treatment of mild PIH. Labetalol was most effective antihypertensive agent in both mild and
sever PIH. Efficacy of nifedipine was equivalent to methyldopa in mild PIH. While in severe PIH, nifedipine was more effective than methyldopa. Methyldopa was found to be least effective in severe PIH.

In a randomized controlled trial conducted to assess the efficacy and safety of labetalol comparing with methyldopa in the management of mild and moderate pregnancy induced hypertension, it was concluded that labetalol is better tolerated than methyldopa and with more efficient control of blood pressure and may have a ripening effect on the uterine cervix (El-Qarmalawi et al., 1995). Our study results substantiate these results.

In another randomized controlled trial in pregnant women with mild to moderate hypertension, labetalol was compared with methyldopa, DBP below 86mm of Hg was obtained in a similar proportion and perinatal outcome did not differ between two treatment groups. The trial concluded that maternal beta-blocked with labetalol is as safe as methyldopa for the fetus and the newborn (plouin et al., 1988). In our study DBP was 86 mm of Hg in methyldopa group, similar to the above study, while in labetalol group DBP was below 80 mm of Hg in mild PIH. Even in our study perinatal outcome did not differ between the groups.

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 were effective in the management of acute hypertensive emergencies of pregnancy, however, nifedipine controls hypertension more rapidly and was associated with a significant increase in urine output (Vermillion et al., 1999). In our study contradictory results were observed in which labetalol was found to be more effective in controlling severe hypertension than nifedipine. The difference may be due to the fact that their study was conducted in acute hypertensive emergency cases with a small sample size and intravenous labetalol (20 mg) unlike our study setting.

In a prospective trial nifedipine was compared with methyldopa in the management of PIH, similar effects were observed between the groups with respect to reduction in BP, maternal and perinatal outcome. Less patients in methyldopa group required treatment for acute hypertension. Results of the study indicated that
nifedipine is as effective as methyldopa in the treatment of PIH (Jayavardana and Lekamge, 1994). In our study nifedipine was as effective as methyldopa in mild PIH in all aspects, while in severe PIH, nifedipine was more effective in reducing BP. But less patients in methyldopa group required magnesium sulphate. Similarity was observed to above study.

As per literature methyldopa remains one of the most widely used drugs for the treatment of hypertension in pregnancy. It has been assessed in a number of prospective trials in pregnant woman comparing with placebo (Leather et al., 1968; Redman, 1976; Sibai et al., 1990) or with alternative anti-hypertensive agents (Fidler et al., 1983; Gallery et al., 1985; Plouin et al., 1988). Treatment with methyldopa in mild to moderate PIH has been reported to prevent subsequent progression to severe hypertension. The results of present study substantiate this effect. Even in our study use of methyl dopa in mild PIH has prevented the progression to severe PIH. When methyldopa is evaluated in severe PIH, even though control was not achieved 72 hrs of treatment period but severity was reduced to mild PIH status. Therefore, from the results it can be concluded that methyldopa is effective in mild PIH but not in controlling hypertension in severe PIH.

Proteinuria and hypertension are major clinical manifestations in PIH and should be considered an important marker on maternal and perinatal outcome (Coelha et al., 2004). Preeclampsia is a pregnancy specific syndrome of reduced organ perfusion secondary to vasospasm and endothelial activation. Proteinuria is an important sign of preeclampsia. But end organ complications can occur even in the absence of proteinuria (Magee et al., 2008).

Some degree of proteinuria is the evidence to establish the diagnosis of preeclampsia- eclampsia. Urinary dipstick of 1+ proteinuria or greater was predictive of at least 300 mg per 24 hrs in 92% cases. Conversely trace or negative proteinuria had a negative predictive value of only 34% in hypertensive women. Urine dipstick values of 3+ to 4+ were positively predictive of severe preeclampsia in only 36% cases (Cunningham et al., 2010).
In our study significant proteinuria ($\geq 2+$ dipstick) was present in less than 25% in mild PIH. In severe PIH, majority of patients were proteinuric and incidence of 3+ and 4+ dipstick was higher predictive of severe preeclampsia.

In a study to assess the clinical significance of proteinuria in PIH found that maternal and foetal complications were common as proteinuria became more severe (Kim et al., 2000; Lao et al., 1988). Contradicting conclusion was found in another study, which stated that women with preeclampsia and massive proteinuria did not have increased maternal morbidity compared with women with severe or mild proteinuria. Neonatal morbidity appears to be a function of prematurity rather than of massive proteinuria itself (Newman et al., 2003).

Delivery is the cure for preeclampsia. The use of antihypertensive drugs in attempts to prolong pregnancy or modify perinatal outcomes in pregnancies complicated by various types and severities of hypertensive disorders has been of considerable interest, since the reduction in morbidity and mortality in the treatment of preeclampsia is significant (Chung et al., 2001). In severe preeclampsia, proteinuria and oedema ordinarily disappears within a week of delivery. In case of antihypertensive intervention to prolong pregnancy or modify perinatal outcome, reversal of vasospasm may gradually reverse proteinuria.

In the present study proteinuria was measured daily, during treatment with antihypertensive agents, by dipstick method. The results were analysed between the groups both in mild and severe PIH, mainly in proteinuric cases, in whom urine proteins were measured continuously for 8 days. In mild PIH, a significant reduction in proteinuria was first observed in methyldopa group on day 2. However on day 4, significant reductions were observed in all three groups and on day 6, proteinuria was almost negligible and completely controlled on day 8. All the three drugs were equally effective in reducing proteinuria of mild PIH.

In severe PIH, proteinuria started reducing significantly from day 4 compared to baseline values in all three groups. On day 8 only in labetalol group proteinuria was controlled, since proteinuria was less than 1+ dipstick. Even though all three drugs were effective in reducing proteinuria, efficacy of labetalol was greater compared to
methyl dopa and nifedipine since urine proteins were reduced to traces may be because of effective control on hypertension.

Vasospasm is basic to pathophysiology of preeclampsia-eclampsia. It is likely that vasospasm itself exerts a damaging effect on vessels. Moreover, angiotensin II causes endothelial cells to contract. These changes likely lead to endothelial cell damage and interendothelial cell leaks. As with any other glomerulopathy, there is increased permeability to most large molecular proteins; thus abnormal albumin excretion is accompanied by other proteins, such as haemoglobin, globulins and transferrin. Normally these large protein molecules are not filtered by the glomerulus and their appearance in the urine signifies a glomerulopathic process. Renal tubular lesions are common in women with eclampsia. Acute renal failure from tubular necrosis may develop. If vasospasm is corrected, tubular necrosis is reversible. Rarely, renal cortical necrosis develops when major portion of cortex of both kidneys undergo necrosis and is irreversible (Cunningham et al., 2010). Antihypertensive agents in the present study were effective in correcting vasospasm.

**Gestational age**

Perinatal outcome is strongly influenced by gestational age and the severity of hypertension as expressed by the need of antihypertensive treatment irrespective of underlying syndromes (Van pampus et al., 1998). In the present study average gestational age at initiation of treatment was 35 to 36 weeks (> 34 weeks) in mild PIH. Antihypertensive treatment extended the gestational age significantly by almost one week in all three groups. In severe PIH, the average gestational age at initiation of treatment was 33.8 to 34.8 weeks and the gestational age advanced (< 1 week) significantly in all three treated groups. But when extension of pregnancy with respect to number of days was compared between the groups, there was no significant difference both in mild and severe PIH.

After initiation of antihypertensive therapy, most of the deliveries were late preterm (37 weeks) in mild PIH, and preterm (< 37 weeks) in severe PIH. Antihypertensive therapy may be partly responsible for extension of gestational age, since uncontrolled hypertension may lead to foetal distress resulting in termination of
pregnancy. Time of delivery is based up on gestational age, severity of preeclampsia, maternal and foetal risks (Brichant et al., 2010). Therefore indirectly time of delivery depends on the expectant management of severity of PIH, which is based partly on antihypertensive therapy and prevention of end organ dysfunction.

In the present study, antihypertensive therapy may be favouring better neonate condition and prognosis in preterm new-borns. But the criteria of the study were to determine if any difference exists with the use of these three different antihypertensive agents. All the three drugs were equally effective in prolonging gestation which indicates maternal and foetal stability.

**Perinatal outcome**

When perinatal outcome was compared between of mild and severe PIH, Apgar score of new-borns at birth was normal (7 to 10) in labetalol group compared to low scores (≤ 6) of methyldopa and nifedipine groups in mild PIH. However scores progressed to normal at 5th minute and there were no significant differences between the groups. In new-borns of severe PIH, in all three groups, low Apgar scores were recorded at birth and even though scores progressed at 5th minute, but were not normal.

In a study conducted to compare the maternal-foetal clinical intercurrences and the effectiveness of treatment in different clinical forms of hypertensive syndromes during pregnancy (HSP), lowest values for gestational age and weight of the new born and for Apgar index were observed in preeclampsia (PE) and preeclampsia superimposed chronic hypertension (PSCH). Treatment did not alter the Apgar index in relation to control and non-treated gestational hypertensive patients. Patients with PE presented the lowest gestational age and the smallest Apgar index when compared to control (Ferrao et al., 2006). The study concluded that introduction to antihypertensive therapy during gestation was fundamental importance for health improvement and pressure control of pregnant women with HSP. Nevertheless it has been of little help for prevention of perinatal intercurrences

In severe PIH of the present study, lowest gestational age and smallest Apgar index was observed when compared to mild PIH similar to above study. This may be
due to significant proteinuria in severe PIH. Therefore antihypertensive drugs are valuable in pregnancy to reduce the risk directly due to elevated blood pressure. These drugs are not expected to affect the evolution of preeclampsia or to treat other complications of this condition (Naden and Redman, 1985).

When birth weight based on gestational age was assessed, 54 to 56% of neonates were appropriate for gestational age (AGA) and 40 to 44% were small for gestational age (SGA) in mild PIH. In severe PIH, 54 and 53% of neonates were AGA, similar to mild PIH in methyldopa and nifedipine groups respectively, and 64% in labetalol group. Proportion of neonates with SGA was 43 and 42% in methyldopa and nifedipine groups respectively, while in labetalol group it was 36%. Incidence of AGA and SGA did not differ in mild and severe PIH. Therefore birth weight based on gestational age was not affected with disease severity. This may be due to late onset of PIH (37 to 40 weeks) in about 50% of patients and partly due to antihypertensive therapy. There were no significant differences between the groups and between mild and severe PIH with respect to birth weights based in gestational age.

Literature states long term use of oral labetalol has been associated with an increased incidence of small for gestational age infants, a well-known side effect of the long term use of β blockers in pregnancy. Treatment induced fall in maternal BP may adversely affect foetal growth with use of oral anti-hypertensive medication to treat mild to moderate PIH. This was evidenced with birth of a higher proportion of small for gestational age infants (von Dadelszen et al., 2000). In our study use of oral labetalol was associated with lower incidence of SGA compared to methyldopa and nifedipine, may because labetalol was not used for long term.

When birth weight irrespective of gestational age was assessed, in severe PIH, neonates with normal birth weight (NBW) were 26 to 33%, much less compared to 41 to 51% of mild PIH. Whereas low birth weight (LBW) neonates were higher in severe PIH, i.e. 67 to 72% compared to 49 to 59% of mild PIH. Very low birth weight (VLBW) babies were 20 to 36% in severe PIH and 10 to 19% in mild PIH. Incidences of LBW and VLBW were high and NBW was low in severe PIH may be because of high rate of preterm deliveries (58 to 62%). Incidences of preterm and very preterm were high and term deliveries were low in severe PIH compared to mild PIH.
A study in Taiwanese women to compare the effects of disease severity on maternal complications and pregnancy outcome between severe preeclampsia and gestational hypertension concluded that proteinuria may play a role in the progression of gestational hypertension to severe forms of preeclampsia associated with subsequent maternal complications and extremely low birth weight (Liu et al., 2008). In comparison of above study incidence of LBW was associated with severe eclampsia of our study. But there was not much difference in ELBW between mild and severe PIH.

Perinatal mortality was 9 to 13%, in severe PIH, since preterm and very preterm deliveries were more compared to mild PIH. In mild PIH, incidence of perinatal mortality was absent except in 6.5% of methyldopa group. Neonatal outcome depends on the time of delivery and gestational age which can be prolonged if maternal and foetal conditions are stabilised by antihypertensive therapy.

New born infants of mothers with PIH present with intrauterine growth retardation (IUGR) (Grujic and Milasinovic, 2006; Rajan, 2005). Preeclampsia increases the risk of IUGR and LBW (Xiong et al., 1999). IUGR secondary to PIH is associated with significantly increased perinatal mortality (Xiong et al., 2007). IUGR was one of the pre-treatment risk factors (5 to 11%) in mild PIH and (9 to 14%) of present study. Therefore high rate perinatal mortality in sever PIH of our study may be attributed to significant proteinuria, gestational age and IUGR.

The incidence of perinatal mortality is 9.4-16.2% in cases of severe preeclampsia particularly in the west European countries (Rath and Bartz, 2004). Perinatal mortality rate with hypertensive disorders of pregnancy was found to be 14.4% in Turkey (Yucesoy et al., 2005). In 1986, fetal mortality rate was 32% in preeclamptic and 60% in eclamptic patients in south east Turkey. Now, these rates have been reduced because of better management options (Sumnulu et al., 1989).

In a study conducted to determine the role of proteinuria in disease severity of preeclampsia and gestational hypertension, by comparing maternal complications and pregnancy outcome, found 77 and 52% incidence of preterm labour in women of severe preeclampsia and gestational hypertension (GH) respectively. Initial drug
therapy in severe preeclampsia was with magnesium sulphate to prevent convulsions and bolus injection of hydralazine or labetalol to maintain DBP below 100 mm Hg. Oral antihypertensive drugs, such as methyldopa, hydralazine and labetalol were then given to maintain the DBP between 90 to 100 mm Hg. Gestation age at delivery was 33.7 weeks and 35.7 weeks in severe preeclampsia and gestational hypertension respectively. LBW babies were 74 and 46% in severe preeclampsia and gestational hypertension respectively. Neonatal deaths were 9% in severe preeclampsia and 4% in gestational hypertension. The study concluded that proteinuria may be responsible for progression of gestational hypertension to severe forms of preeclampsia, associated with subsequent maternal complications and extremely low birth weight babies (Liu et al., 2008).

In the present study, incidence of preterm labour were less compared to above study, i.e. 58 to 62% and 36 to 44% in severe and mild PIH respectively. Gestation age at delivery was more i.e. 34 to 35 weeks and 37 weeks in severe and mild PIH respectively. Even though present study cannot be compared with above study, pregnancy outcome was better in our study and this may be due better maternal and foetal conditions stabilised by antihypertensive drugs chosen. Incidences of LBW babies were almost similar to our study i.e. 67 to 72% and 49 to 59% in mild and severe PIH, antihypertensive therapy can mainly stabilise maternal blood pressure but not foetal conditions such as birth weight since birth weight is affected much before treatment was initiated. Incidences of perinatal deaths in the present study were 9 to 13% in severe PIH and absent in mild PIH except 6.65% in methyldopa group. Our study results cannot be compared with the above study, since combination of antihypertensive agents were used and also conducted in a different setting.

Analysis of various population based studies suggest that PIH increases the risk of preterm delivery, SGA, LBW, neonatal death etc. and the rate of incidence increases with increased severity (Allen et al., 2004; Xiong and Fraser, 2004; Wu et al., 2010). Therefore antihypertensive therapy may not contribute much in preventing adverse neonatal outcome, since underlying disorder is responsible. Partly it may improve prognosis, if progression of severity is prevented.
In the present study, neonatal mortality or total death rate was high in severe PIH (29 to 35%) compared to mild PIH (5 to 20%). Here, total deaths included IUD before treatment and still births, perinatal deaths during treatment. 19-30% deaths were recorded excluding IUD in severe PIH and 4 to 12% in mild PIH except labetalol group after initiation of treatment.

A hospital based study conducted in India to examine the incidence and outcome of hypertension in pregnancy found 37.5% perinatal mortality rate. LBW was seen in 66.66%. The study concluded that hypertension complicated 5.38% of pregnancies (Prakash et al., 2006). Compared to this study, incidence of neonatal death rate was less and LBW was almost same in severe PIH of our study. The mortality of foetuses or new-borns was 71% in severe preeclampsia and eclampsia in a study conducted in Prague. The study concluded this may be due to major mistakes and failures in organisation of care, primary prevention, diagnosis and consequent care (Srp et al., 2002).

Neonatal mortality cannot be attributed to anti-hypertensive therapy since perinatal intercurrences are due to pre-existing placental impairment and poor fetal growth. Anti-hypertensive drugs are valuable in pregnancy to reduce the risk directly due to elevated BP. These drugs are neither expected to affect evolution of preeclampsia nor to treat other complications of this condition.

In a study conducted in Nigeria to determine factors affecting the outcome of pregnancy in hypertensive patients found 36.4% fetal mortality in preeclampsia/eclampsia group (Familoni et al., 2004). In our study fetal mortality rate was higher. This may be because of low socio-economic status of patients and illiteracy which has influenced fetal adverse outcome. In our study, treatment itself was initiated late i.e., 35-36 weeks of gestation in mild PIH and 33-34 weeks in severe PIH may be due to less regularly attended antenatal clinic (ANC). As in many cases, early diagnosis and management with antihypertensives has influenced better maternal and neonatal outcome. Therefore, in our study use of antihypertensive agents were valuable mainly to reduce risk of elevated maternal BP. These poor neonatal outcome especially, neonatal mortality rate in the present study further emphasize the need for patient education, regular ANC attendance and prompt treatment of elevated
BP at the earliest. As regular antenatal surveillance is the only way to accurately identify those who are at risk, antenatal care schedules have to be designed to detect hypertension and proteinuria. Early referral to a specialist care is indicated in high risk patients for prophylactic antihypertensive and anticonvulsant therapy, for better outcome (Chandiraman et al., 2010).

In the present study, incidences of NICU admissions in severe PIH were almost same as mild PIH i.e., 44% of neonates were admitted to NICU in all groups. Incidence of birth asphyxia was also similar i.e., 3 to 9% in mild PIH and 3 to 11% in severe PIH. In a study conducted to examine frequency of elective delivery and NICU admissions in women with stable, mild gestational hypertension delivering late pre-term (340/7-366/7), 27.3% NICU admissions were observed (Barton et al., 2011). This rate is similar to NICU admission rate in labetalol group of mild PIH of our study, even though all deliveries are not elective. This reflects better management in labetalol group. Rate of NICU admissions mainly reflects neonatal complications/morbidity.

In the present study, severe PIH was associated with increased rates of low Apgar scores, LBW, preterm deliveries and neonatal mortality, but, NICU admissions were almost similar to mild PIH. Even though rate of NICU admissions were similar in mild and severe PIH, the outcome was poor in severe PIH reflected by high rate of neonatal mortality. In a study to determine the clinical significance of proteinuria in PIH, concluded that there was a decreasing trend in gestational weeks at delivery as proteinuria became more severe and also in birth weight, 1 minute and 5th minute Apgar score. Maternal and foetal complications were common as proteinuria became more severe (Kim et al., 2000). Therefore, development of proteinuria may be attributed to the adverse maternal and foetal outcome. In our study since majority of patients in severe PIH had significant proteinuria (≥ 2+ dipstick) at presentation, the neonatal outcome was poor.
Obstetric outcome

In the present study mode of delivery was vaginal in majority of patients in both mild and severe PIH. Incidences of vaginal and caesarean sections were almost similar in mild and severe PIH. Rate of induction (70-91%) was high in vaginal deliveries of severe PIH compared to mild PIH. High induction rate indicates measures taken to prevent maternal and neonatal complications arising due to disease severity, since in cases of uncontrolled severe PIH termination of pregnancy is the treatment. Rate of spontaneous delivery was significant in labetalol group compared to nifedipine in mild PIH. Highest induction rate was found in nifedipine group and lowest in labetalol group. Induction of labour is a preventive measure to terminate pregnancy, to avoid complications due to transition from mild to severe PIH.

In the present study of mild PIH group, the rate of spontaneous labour was least and induction was highest in nifedipine group. This may be due to the inhibition of labour by nifedipine as studies indicate that nifedipine inhibits labour (Martindale, 2006). Also in the present study, there were 50% of caesarean sections in nifedipine group, mainly due to failed induction but was not significant compared to methyldopa and labetalol groups. This may be due to the tocolytic effect of nifedipine. This was not true in severe PIH, as rate of spontaneous labour was significantly high in nifedipine group compared to labetalol group.

In a study conducted to investigate whether induction of labour in women with a singleton pregnancy, complicated by gestational hypertension and mild preeclampsia reduces severe maternal morbidity, concluded that induction of labour was associated with improved maternal outcome and should be advised for women with mild hypertension disease beyond 37 weeks gestation (Koopmans et al., 2009). Even in the present study, maternal outcome was good and this may be because of high induction rate.

In a study conducted to determine the risk factors, prevalence, epidemiology and maternal-perinatal outcome in pregnant women with hypertensive disorders, found 41.2% vaginal deliveries and 58.8% caesarean sections with the most frequent indication to be fetal distress (46%). Caesarean rate was highest (63.8%) in severe
Discussion

preeclampsia patients (Yucesoy et al., 2005). In our study, caesarean section rates were low and similar in mild and severe PIH, which may be due to better management by antihypertensive agents.

Maternal outcome

Incidence of maternal mortality was absent in the present study, both in mild and severe PIH. Maternal outcome was good in mild PIH as there were no complications. While in severe PIH, complications such as DIC and intracerebral haemorrhage were absent. Incidence of eclampsia was higher (10%) in nifedipine group compared to one case (2%) each in methyldopa and labetalol groups. Incidence of eclampsia in these cases was mainly due to impending eclampsia (2 to 10%) and preeclampsia (83 to 93%). Therefore, there were no new cases of eclampsia. Eclampsia is presence of new onset grand mal seizures in a woman with preeclampsia (ACOG, 2002) not a progression from severe preeclampsia but appears to be more of a subset of preeclampsia (Katz et al., 2000). Even though 24 to 31% of partial HELLP syndrome and 3 to 9% of HELLP syndrome existed as pre-treatment risk factor, incidence of HELLP during treatment was 1.7 to 13.6%. This reflects effective management of hypertension by all three antihypertensive agents.

HELLP syndrome is one of the most sever variants of liver failure in pregnancy characterized by haemolysis, elevated liver enzymes and low platelet count (Anon, 2010). HELLP syndrome is 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. Laboratory parameters are not efficient in detecting perinatal results, but can be used as risk denominators in evaluating maternal complications (Erdemoglu et al., 2010). The only radical and efficient method of HELLP syndrome treatment available is a timely delivery (Anon, 2010). The altered biochemical parameters of HELLP syndrome were effectively controlled by all three antihypertensive agents in our study, since progression of partial HELLP syndrome to HELLP syndrome was prevented.
Incidence of abruption placentae was 2-5%. One case of ARF was recorded in nifedipine group. In the present study, maternal complications were almost absent in mild PIH, reflecting good management of PIH with antihypertensive agents since progression of mild PIH to severe has been prevented. Even in severe PIH, 80-90% of patients did not have any incidence of maternal complications, since, incidence of eclampsia and HELLP syndrome were controlled by antihypertensive therapy. All the three drugs were effective in preventing maternal complications.

In a study to determine maternal and perinatal outcome in pregnancies complicated with hypertensive disorders, observed maternal mortality of 1.2% and all the cases were complicated with HELLP syndrome. Intracranial bleeding was the cause of maternal death in one case while the other two cases were due to ARF and disseminated intravascular coagulation respectively (Yucesoy et al., 2005). In our study in severe PIH, though the incidence of HELLP syndrome was 1.7-13.6% and one case of ARF existed, no maternal mortality occurred. Therefore, the antihypertensive agents used were effective in preventing maternal morbidity and mortality compared to neonatal outcome. Neonatal morbidity and mortality in PIH is often related to IUGR occurring as a result of placental insufficiency. Hypertension during pregnancy is responsible for high fetal mortality rate and LBW. Even though fetal growth retardation (FGR) is an independent entity, FGR in pregnancies complicated by hypertension had poorer perinatal outcome than FGR in normotensive women (Piper et al, 1996).

In the present study, most cases of PIH were admitted by the end of third trimester by which much damage has already occurred to the foetus, antihypertensive treatment at that point could not reverse the underlying syndrome immediately to improve the perinatal outcome. Since antihypertensive agents in the study were effective in controlling hypertension to prolong gestation.
Side effects

In the present study, adverse effects occurred during treatment with antihypertensive agents, were transient and tolerable. There were no maternal adverse events, which resulted in need for discontinuation of medication. Side effects were milder and infrequent in labetalol treated patients as majority of the patients did not have (82%) any side effects in mild PIH. With higher doses of labetalol, although frequency of side effects increased but were tolerable and 24% of patients did not have any side effects. Lower incidence of side effects observed in labetalol group was significant compared to methyldopa and nifedipine groups. Palpitation was the most frequent adverse effect followed by headache, fatigue, weakness, dizziness and flushing with higher doses.

In nifedipine treated patients, both mild and severe (84% and 86%) PIH, experienced headache as the major side effect, but was tolerable, since it did not result in need for discontinuation of therapy. The side effects of nifedipine are due to its vasodilation action. The most common side effects i.e. severe headache can mimic impending eclampsia (Bolte et al., 2001).

In a randomised double blind trial of oral nifedipine and intravenous labetalol in hypertensive emergencies of pregnancy, minor side effects such as headache, cutaneous flushing and nausea were infrequent, transient and did not result in need for discontinuation of either study medication. Patients receiving nifedipine experienced a significant increase in urine output compared with women receiving labetalol. The ability of nifedipine to enhance urine output has been attributed to a selective renal vasodilation. Urinary output in context of preeclampsia would appear to be beneficial (Vermillion et al., 1999). In our study results, incidences of adverse effects were less in labetalol group, headache was more frequent in nifedipine group, but were tolerable. However in our study urine output was not determined.

In methyl dopa treated patients, dizziness was frequent with lower doses and weakness in higher doses. Almost all patients treated with higher doses experienced side effects, whereas with lower doses 41% of patients did not have any side effects. The side effects of methyldopa are consequences of its pharmacological action.
As per the literature, labetalol administered intravenously or orally appears to be as effective and as safe and causes fewer side effects (Naden and Redman, 1985; Tarek et al., 1993). In the present study oral labetalol was effective and safe. Nifedipine is also stated to be safe since there were any serious adverse effects in mother or foetus (Aali and Nejad, 2002). Our study results substantiate this statement. In a study to find the effect of nifedipine on postpartum blood loss in patients with PIH observed increase in the amount of blood loss and rate of postpartum haemorrhage (PPH) (Yang and Liu, 2000). But in our study, we did not find any such effect as there were no incidences of PPH in any of the study groups. In a comparative study to assess the efficacy and safety of labetalol compared with methyldopa in the management of mild and moderate cases of PIH, stated that labetalol was quicker and more efficient at controlling BP having a beneficial effect on renal function and causing fewer side effects compared with methyldopa (El-qarmalawi et al., 1995). This is supported by our study results, since labetalol had fewer side effects compared to methyldopa in both mild and severe PIH groups.

**Biochemical parameters**

Biochemical parameters such as blood urea, serum creatinine serum uric acid, liver function tests (estimation of liver enzymes for liver damage) and blood platelets were estimated on alternate days during treatment. These biochemical parameters were investigated for diagnosis and prognosis of PIH. Since very few cases of altered biochemical parameters were present in mild PIH, assessment was done for these parameters in severe PIH.

In the present study elevated levels of blood urea (more than 35 mg/dl), serum creatinine (more than 1.1 mg/dl) and serum uric acid (more than 6 mg/dl) were significant in severe PIH. The most common cause of an elevated blood urea is poor kidney function although serum creatinine level is the specific measure of renal function. Causes of high blood urea and serum creatinine in PIH are due to renal arteriolar vasospasm and glomerular endotheliosis resulting in decreased renal perfusion. This result in decreased glomerular filtration rate (GRF) and increased levels of urea and creatinine (Strevens et al., 2003; Thangaratinam et al., 2006; 2011a). Pathophysiologic mechanisms of preeclampsia comprising increased
trophoblastic tissue shedding, endothelial dysfunction and reduced blood flow in the fetomaternal unit have also been hypothesised as the underlying cause of hyperuricemia in this condition (Romero et al., 1988).

Even though serum uric acid, serum creatinine and lactic dehydrogenase are useful for diagnosis and severity classification of preeclampsia (Peralta Pedrero et al., 2004), serum uric acid is a poor predictor of maternal and foetal complications in women with preeclampsia (Williams and Galemeau, 2002; Thangaratinam et al., 2006).

Significant reduction in blood urea, serum creatinine and serum uric acid were observed on day 4 of treatment, compared baseline values and reduction progressed further on day 8 to normal levels in all the three treatment groups. Reduction in the above biochemical parameters were may be due to improved renal function i.e. increasing in GFR as a result of reduced vasospasm. This indicates, reduced disease severity and reversal of renal vasospasm. This effect cannot be attributed directly to antihypertensive therapy since termination of pregnancy (delivery) can result in recovery of renal function in the absence of chronic renovascular disease.

Liver function tests are routinely performed with preeclampsia as part of a battery of investigations to assess severity at admission and later to guide appropriate management.

Hepatic dysfunction is one of the frequent manifestations of multisystem involvement in preeclampsia. The prevalence of liver dysfunctions as determined by an elevated serum glutamic oxalic transaminase (SGOT), serum alanine glutamic transaminase (SGPT) concentration was 21% in a population with PIH. With severe preeclampsia at times there are alterations in tests of hepatic function and integrity. Increased hepatic artery resistance was described in preeclamptic women using Doppler sonography (Cunningham et al., 2010). Periportal haemorrhagic necrosis in the periphery of the liver lobule is the most likely reason for increased serum liver enzymes. Liver function tests was considered elevated when SGPT is more than 40 IU/L and SGOT is more than 40 IU/L, total bilirubin more than 1.0 mg/dl, lactic dehydrogenase (LDH) more than 350 IU/L.
At admission markedly elevated biomarkers of liver injury were recorded in 60 to 73% of patients in severe PIH. After 8 days of treatment in 33 to 63% of these patients, there was an improvement status of liver as indicated by decrease in biomarkers of liver injury to normal range. Reversal of liver dysfunction was may be due to reduced hepatic artery resistant as a result of reversal of vasospasm.

A systematic review done to determine the accuracy with which liver function tests predicts complications in women with preeclampsia, stated that liver function tests performed better in predicting adverse maternal than foetal outcomes in women with preeclampsia. Presence of increased liver enzymes was associated with an increased probability of maternal and foetal complications, but normal liver enzymes did not rule out the disease, as specificity was often higher than sensitivity (Thangarathanam et al., 2011b).

In the present study, adverse maternal outcome was absent in mild PIH, except 2 cases in nifedipine group, as liver dysfunction was present only in 2.33 to 3.39% patients at presentation. Where as in severe PIH, adverse maternal outcome was absent in 80 to 90% of patients even though, liver dysfunction existed in 60 to 73% of patients before treatment. This may be attributed to better management of severity of PIH, by antihypertensive therapy. Improvement in status of liver cannot be completely attributed antihypertensive therapy to since termination of pregnancy can reverse liver injury in majority of cases in severe PIH.

Thrombocytopenia is an associated phenomenon of PIH. Cause for decreased platelets in PIH (thrombocytopenia) is due to entrapment in injured endothelium of arteries. This causes platelet aggregation resulting in decreased platelet count. The injured endothelium along with platelet aggregation also causes damage to RBC’s resulting in micro-angiopathic haemolytic anaemia (Cunningham et al., 2010). Platelet count significantly increased on day 8 in all three groups compared to baseline values at admission. Blood platelets regained to normal values in labetalol group where as it was almost normal in methyldopa and nifedipine groups and this progress in count, was may be due to antihypertensive therapy. At admission 62 to 66% of patients in severe PIH group had low platelet count (less than 2,00,000/mm³).
A study conducted to see the platelet count in 100 cases of PIH, found that 47% had low platelet count (less than 1,50,000/mm$^3$). Among eclampsia group 60% had low platelet count. 12% cases developed postpartum haemorrhage and among them 66.67% had low platelet count. 74.28% of patients with low platelet count had low birth weight babies. The study concluded that platelet count is a very important investigation for antenatal mother having PIH as it directly related to maternal and perinatal outcome (Rahim et al., 2010).

Platelet count is not useful for diagnosis, but useful for severity classification. There is an inverse relationship between the severity of PIH and platelet number (Mohapatra et al., 2007). In the present study there was an improvement in platelet count during antihypertensive therapy, which substantiates reduction in severity of the disease. Monitoring the course of platelet function in HELLP syndrome is important for clinical decision making (Kuiper et al., 2011).

In the present study, additional drugs like magnesium sulphate and phenobarbitone were used in less than 15% of severe PIH patients as a prophylaxis or treatment of eclampsia. Since incidence of eclampsia and HELLP syndrome was low in the present study, use of above drugs was limited. This indirectly reflects better maternal conditions may be due to antihypertensive therapy. There were no significant differences with respect to maternal, perinatal and obstetric outcome between treatment groups of mild and severe PIH except for side effects.

In comparative trials of β-blockers (usually of β-blockers compared with methyldopa), labetalol was found to be more effective anti-hypertensive than methyldopa, but no other differences in maternal or perinatal outcomes have been demonstrated (Magee et al., 2008). Even in the present study, although labetalol was effective in controlling hypertension with low incidence of adverse effects, there were no differences in maternal and perinatal outcomes compared to methyldopa.

Adverse perinatal outcome and neonatal effects of β-blockers therapy appears to be most often reported if there is evidence of pre-existing fetal compromise (IUGR). Adrenergic blockade in the fetus may interfere with its ability to handle the stress of delivery. Labetalol could overcome some of these concerns by its partial
adrenoceptor agonist activity which may have favourable effects on pulmonary surfactant production on lung maturation (Tarek et al., 1993). In the present study there was no difference in the rate of NICU admissions due to birth asphyxia between groups, indicating ability of infants to handle stress during delivery was similar in all three treatment groups in contrast to other studies, labetalol effectively decreases maternal BP, occurrence of proteinuria and also foetal and neonatal complications (Bolte et al., 2000). Present study results substantiate these effects of labetalol.

Labetalol has been used both intravenously and orally for rapid BP reduction. A major drawback of labetalol use is that intravenous administration of this drug has been associated with severe and sometimes lethal symptoms of β-adrenergic blockade, such a hypotension, bradycardia and hypoglycaemia in new born. Several cases of fatal early neonatal cardiogenic shock due to administration of high doses of labetalol (100/200 ng/hr) have been registered in Netherlands (Bolte et al., 2000). Therefore, in the present study oral labetalol was used and found to be effective.

In an effort to assess benefit to risk ratio with use of antihypertensive agents in mild to moderate PIH compared to no antihypertensive treatment, historical cohort study was conducted. The objective of the study was to determine the functional development of children born after treatment of mild to moderate gestational hypertension with labetalol versus methyldopa and no anti-hypertensive treatment. In this hypothesis generating study, labetalol exposure in utero seemed to increase the risk of attention deficit hyperactivity disorder (ADHD) among children of primary school age, whereas prenatal methyldopa exposure might influence sleep. Further studies with appropriate sample sizes are warranted to determine the long term effects of anti-hypertensive medication (Pasker-de Jong et al., 2010).

Alpha methyldopa is one of the most widely prescribed antihypertensive agents during pregnancy. Despite its known potential hepatotoxicity, there have been only a few reports describing hepatotoxicity with the use of this drug during pregnancy (Furroff, 1978). Recently there was a report of new case of acute hepatitis in a pregnant women related to use of methyldopa. The authors reporting the case suggested to briefly reviewing the literature on methyldopa induced hepatotoxicity in pregnancy (Slim et al., 2010).
Concern with use of nifedipine as per literature is that it may inhibit labour and have synergistic action with magnesium sulphate in blood pressure lowering. In the present study magnesium sulphate was mainly used to prevent or treat eclampsia and not as an antihypertensive agent. 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; Khedum et al., 2000). In practice and in a recent evaluation, these medications are commonly used together without increased risk (Magee et al., 2005; Podymow and August, 2008). Even in our study nifedipine and magnesium sulphate were used concomitantly, without increased risk as there were no significant differences with respect to obstetric outcome between the groups in mild and severe PIH. The magnitude of risk is presumably small given how commonly nifedipine and magnesium sulphate are used together, however clinicians who prefer to use magnesium sulphate for prophylaxis against eclampsia may like to have other agents such as labetalol at their disposal (Magee et al., 1999). A clinical advantage of nifedipine is that it can be given orally, easily/widely available and cheap (Aali and Nejad, 2002).

The decision to treat elevated arterial pressure in pregnancy depends on the risk and benefits imposed on the mother and foetus. In our study treatment of mild PIH during pregnancy may have reduced maternal or foetal risk by preventing progression to severe PIH. From results of present study labetalol was found to be the most effective drug in the treatment of mild and severe PIH may be because of rapid onset of action, reduction of BP to normotensive values with fewer side effects. Even though nifedipine and methyldopa were equally effective in mild PIH, methyldopa may be preferred because of lower incidence of side effects. In severe PIH, nifedipine is preferred over methyldopa since antihypertensive efficacy was greater, widely available and cheap.

In the present study there were no adverse maternal outcome, but neonatal outcome was poor, since neonatal outcome is strongly influenced by gestational age and severity of PIH. Poor neonatal outcome especially, neonatal mortality rate further emphasize the need for patient education, education of primary health care personal, prompt diagnosis of high risk patients, timely referral to tertiary care centre, regular
ANC attendance, improved prenatal care, prompt treatment of elevated BP at the earliest.

The baseline characters and pre-treatment risk factors of the study may be useful in diagnosing high risk patients. Outcome of this study is useful to the practicing obstetricians in choosing an appropriate antihypertensive agent as well as in formulating the guidelines for treatment of hypertensive disorders in pregnancy for India. Further, well designed randomized control trials are desired to identify long term effects of these agents in prenatally exposed children.