

## Review Article

# Antihypertensives in Hypertensive Disorders of Pregnancy

FIROZA BEGUM<sup>1</sup>, TABASSUM PARVEEN<sup>2</sup>

### Abstract:

*Hypertension is the most common medical disorder in pregnancy. It complicates about 15% of all pregnancies and is an important cause of maternal and foetal morbidity and mortality. Hypertension is diagnosed from an absolute rise in blood pressure at or above 140/90 mm of Hg. There is general consensus that severe hypertension should receive pharmacological treatment but the value of treating mild hypertension is controversial. The threshold for treatment is 140-150 mm of Hg systolic and/ or 95-100 mm of Hg diastolic to prevent worsening complications of hypertensive mother. Opinions differ as to which is the best antihypertensive during pregnancy. All antihypertensives are either shown or assumed to cross the placenta and reach foetal circulation. While the goal of treatment is to reduce maternal risk, agents selected must be efficacious and safe for the foetus. Methyldopa and labetalol are considered as the first line antihypertensives. As second line therapy, calcium channel blocker, oral hydralazine are recommended. As third line agent, beta-adrenergic blockers are used. For immediate lowering of blood pressure sublingual Nifedipine, parenteral or oral Labetolol, parenteral Hydralazine are used. Atenolol use should probably be avoided in pregnancy because of its association with low birth weight. Both Angiotensin converting enzymes and Angiotensin receptor blockers are fetotoxic and contraindicated during pregnancy. This review article was done with the aim to update knowledge regarding indication, safety, side effects as well as impact of anti-hypertensives on the foetus.*

### Introduction

Hypertension (HTN) in pregnancy is diagnosed from an absolute rise in blood pressure (BP) i.e.  $\geq 140/90$  mmHg. Blood pressure is gestational age related. A diastolic pressure of 90 mmHg is 3 standard deviation (SD) above the mean for mid pregnancy, 2SD and 1.5SD above mean at 34 weeks and term respectively.<sup>1</sup> For diagnosis, blood pressure must be elevated at least on two occasions 6 hours apart and measurement should be made with the woman seated.

Hypertension (HTN), the most common medical disorder during pregnancy complicates about 15% of all pregnancies and accounts for one quarter of all antenatal admissions.<sup>1</sup> Despite treatment it remains as an important cause of maternal and foetal mortality and morbidity. The main risk to mother are placental abruption, accelerated hypertension leading to hospitalization, target organ damage e.g. cerebrovascular catastrophe. The foetal risk includes growth restriction and prematurity due to worsening maternal condition leading to early delivery.

Hypertensive disorder of pregnancy include-

- Chronic hypertension
- Gestational hypertension
- Pre-eclampsia (PE)
- Chr. HTN with superimposed PE

Chronic Hypertension complicates 3-5% of all pregnancies, might be higher in women who become pregnant at 30s or 40s.<sup>2</sup> The diagnosis is based on a known history of hypertension pre-pregnancy or an elevated pressure  $\geq 140/90$  mmHg before 20 weeks gestation.<sup>3</sup> The presence of even mild pre-existing hypertension almost doubles the risk of PE<sup>1</sup>. In addition, it increases the risk of placental abruption and growth restriction of the foetus with consequent increase in perinatal mortality and morbidity. The likelihood of these complications are particularly increased with long standing severe hypertension and those with pre-existing cardiovascular or renal disease.<sup>1</sup> In general when BP is controlled, these women do well and outcome is not dissimilar to normal women. The goal of treatment is to maintain BP at a

1. Professor, Feto-Maternal Medicine, Bangabandhu Sheikh Mujib Medical University

2. Assistant Professor, Feto-Maternal Medicine, Bangabandhu Sheikh Mujib Medical University

level that minimizes maternal cardiovascular and cerebrovascular risk. Prevention of preeclampsia is desirable; however, current evidence has not shown that either specific BP targets in pregnancy or specific antihypertensive agents modify the risk of superimposed preeclampsia in women with preexisting hypertension.<sup>4</sup>

Gestational Hypertension is hypertension occurring in the second half of pregnancy in previously normotensive women, without significant proteinuria. It complicates 6-7% of all pregnancies<sup>5</sup> and resolves by six weeks postpartum. In most cases there is mild to moderate elevation of blood pressure. The risk of superimposed pre-eclampsia is 15-26%<sup>1</sup>; risk is influenced by the gestational age when hypertension develops. If hypertension develops after 36 weeks the risk falls to 10%.<sup>1</sup> Like chronic hypertension, aim of antihypertensive therapy is to prevent maternal complications of severe hypertension, there is no evidence that targeted BP control prevents preeclampsia.

Pre-eclampsia (PE), a multi-system disorder, defined as gestational hypertension associated with significant proteinuria (>300 mg/L or >500 mg/24 hours urine or on dipstick 2 + or more proteinuria), occurs usually after 20 weeks of gestation. In most cases it resolves within six weeks postpartum. PE complicates 5-6% of all pregnancies, the figure may rise up to 25% in women with pre-existing hypertension.<sup>1</sup> PE is considered severe if there is sustained elevation of BP >160/110 mm Hg on 2 occasions at least 6 hours apart, proteinuria of at least 5 gm/24 hours or multi organ involvement e.g. pulmonary oedema, seizures, oliguria, thrombocytopenia, abnormal liver enzymes and persistent severe CNS symptoms (altered maternal status, headache, blurred vision or blindness).<sup>6</sup> As currently understood, the hypertension of preeclampsia is secondary to placental under-perfusion, thus, lowering systemic BP is not believed to reverse the primary pathogenic process, and antihypertensive medication has never been demonstrated to "cure" or reverse preeclampsia. However role of anti-hypertensive is prevention of cardiovascular and cerebrovascular consequences of severe and rapid elevations of BP and requires judicious use of antihypertensive medication.

Treating hypertension during pregnancy is a real challenge. There is no general consensus about when to use anti-hypertensive agents and what level of blood

pressure (BP) control is to be achieved. There is general consensus that severe hypertension should receive pharmacological treatment but the value of treating mild hypertension is controversial. Opinions differ as to which is the best antihypertensive during pregnancy. All antihypertensives are either shown or assumed to cross the placenta and reach foetal circulation. While the goal of treatment is to reduce maternal risk, agents selected must be efficacious and safe for the foetus. Following factors should be considered and kept in mind while selecting an antihypertensive agents.

- Drugs administered during gestational days 0 to 17 (during fertilization and implantation) or days 18 to 55 (when organogenesis takes place) can critically interrupt fetal structural development. After day 55, the developing fetus is more resistant to drugs although noxious agents can cause fetal deformation by decreasing cell size and number.<sup>7</sup> So if possible drugs should be avoided in the first trimester
- Anti-hypertensives known to have minimal or no maternal or fetal adverse effects is preferred
- Episodic treatment should be avoided
- Close monitoring of the fetus of a hypertensive mother, especially when the mother is receiving antihypertensive therapy is required
- The potential long term behavioral effects of therapy should be considered.

The Food and Drug Administration reviews human and animal data to assign letter grades corresponding with risk of fetal exposure in pregnancy. Most antihypertensive agents used in pregnancy are designated as "category C," by the Food and Drug Administration. It indicates that human studies are lacking, animal studies are either positive for fetal risk or are lacking, and the drug should be used only if potential benefits justify potential risks to the fetus.<sup>8</sup> Information is, thus, based on clinical cases, small studies, and meta-analyses. This review article was done with the aim to up date knowledge regarding indication, safety, side effects as well as impact of anti-hypertensives on the foetus.

## Management of Hypertension in pregnancy

### Pre-pregnancy counseling:

Even in the developed countries up to 50% of pregnancies are unplanned<sup>1</sup>, so pre-pregnancy

counseling may not be feasible. In women with chronic hypertension, assessment before conception permits exclusion of secondary causes of hypertension (e.g. renal /endocrine), evaluation of target organ damage in long standing hypertension; evaluation of their hypertensive control to ensure it is optimal, discussion about increased risk of pre-eclampsia and education about drug alteration once they become pregnant as well as life style changes.

If hypertension is well controlled majority of these women under close supervision and appropriate management will have a successful outcome. Poorly controlled hypertension in the first trimester significantly increases maternal and foetal mortality and morbidity.

None of the antihypertensive agents used in routine practice have been shown to be teratogenic and women can safely conceive while taking medication. However, angiotensin converting enzyme inhibitors and angiotensin receptor blocker need to be withdrawn since they are fetotoxic.<sup>1</sup> Woman who had poor obstetric outcome in previous pregnancies because of severe pre-eclampsia, or those who are at particular risk, need to be counselled and may be offered prophylactic treatment with low dose aspirin as well as with calcium and antioxidants.

#### **Pharmacological Treatment of HTN in Pregnancy:**

Antihypertensives are agents that lower blood pressure. The results of two retrospective studies on pregnant women and randomized trial involving non-pregnant women indicate that antihypertensive therapy decreases the incidence of stroke and cardiovascular complications among pregnant women with diastolic blood pressure above 110 mmHg.<sup>9</sup> There is general agreement that pregnant women with severe hypertension should receive pharmacological treatment, but the value of treating mild essential hypertension is controversial. There seems to be less risk of developing severe HTN (risk ratio 0.50) but no difference was found in the outcome of PE, neonatal death, preterm birth and small for gestational age with treatment.<sup>4</sup>

Usually treatment is started when SBP >150 mmHg or DBP >100 mmHg. International guidelines for the treatment of hypertension in pregnancy vary with respect to thresholds for starting treatment and targeted BP goal. Therapy is recommended in the United States for BP  $\geq$  160/105 mm of Hg with no set

treatment target<sup>10</sup>; in Canada, therapy is recommended at  $\geq$  140/90 mm of Hg targeting DBP to 80 to 90 mm of Hg<sup>11</sup> and in Australia elevation  $\geq$  160/90 mm of Hg are treated to a target of SBP  $\geq$  110 mm of Hg.<sup>12</sup>

All antihypertensive drugs have been either shown or are assumed to cross the placenta and reach the foetal circulation. While the goal of treatment is to reduce maternal risk, the agents selected must be efficacious and safe for the foetus. Apart from teratogenicity, there are issues particular to hypertensive disorders of pregnancy that must be considered prior to selecting antihypertensive agents. The issues include the underlying maternal physiology and the impact of the medication on the foetus. Over zealous control may lead to placental hypoperfusion (as placental blood flow is not autoregulated) with fetal compromise.<sup>1</sup>

Women with chronic hypertension need thorough evaluation either before conception or at first prenatal visit. Depending on this evaluation, they are categorized either as 'high risk, or 'low risk' chronic hypertension. The patient is considered as 'low risk' when she has mild essential hypertension without any organ involvement. In contrast 'high risk' women are those having BP  $\geq$  180/110 mm of Hg, have target organ damage or having history of perinatal loss. High-risk women should receive aggressive antihypertensive therapy and frequent evaluations of maternal and foetal well-being, and modification of life style. In addition, these women are at increased risk for postpartum complications like pulmonary oedema, renal failure and hypertensive encephalopathy for which they should receive aggressive antihypertensive control of blood pressure as well as close monitoring. In women with low risk (essential uncomplicated) chronic hypertension, there is uncertainty regarding the benefits or risks of antihypertensive therapy.<sup>13</sup>

#### **Selection of Antihypertensive agents:**

Opinions differ as to which is the best agent for treatment of hypertension during pregnancy. The choice of drugs will differ between acute and more chronic clinical presentation.

Suitable oral agents in less acute situations include – methyldopa,  $\beta$ -blockers including labetalol and calcium channel blockers (Nifedipine, Nicardipine). In more acute situations intravenous agents may be required and options include  $\beta$ -blockers (Labetolol), sublingual nifedipine and hydralazine.

### First Line Agents

The American College of Obstetrician and Gynaecologist (ACOG) currently recommends alpha Methyldopa and labetalol as appropriate first line antihypertensive therapies for women with severe hypertension.<sup>9</sup>

#### Methyldopa:

Methyldopa is a centrally acting agent ( $\alpha$ -adrenergic receptor blockers) and remains the drug of first choice for treating hypertension in pregnancy. It has been the most frequently assessed antihypertensive in randomized trial and has the longest safety track record. Treatment does not seem to have adverse effects on utero-placental or on foetal haemodynamics. Long term use has not been associated with fetal or neonatal problems<sup>9</sup> and there are safety data for children exposed in utero – up to 7.5 years follow up available, the children exhibited intelligence and cognitive development similar to control subjects.<sup>14</sup>

#### Dose

Dose of methyldopa is 250mg (thrice or four times daily), not exceeding 3 gm/day. Methyldopa may take a few days for the onset of hypotensive effect, so rapid change of dose during the first 2 or 3 days should not be undertaken. Higher dose may cause sodium and fluid retention and may need diuretic therapy to maintain the hypotensive effect.

Side effects are consequence of central  $\alpha$ -2 agonism or decrease peripheral sympathetic tone and include decreased mental alertness and impaired sleep leading to fatigue and depression in some patients, increased liver enzymes (in 5% cases) and a positive coomb's test (rare). Methyldopa should be avoided in women with a prior history of depression, because of increased risk of postnatal depression.

#### Labetalol

Is an adrenergic receptor blocking agent possessing both  $\alpha$ 1 (Post synaptic) and  $\beta$  receptor blocking activity (4 times more potent action on  $\beta$ -receptors than on  $\alpha$  receptors). It lowers blood pressure by partially blocking  $\alpha$ -adrenoceptors in the peripheral arterioles, thus causing vasodilatation and resulting reduction of peripheral resistance. At the same time, blocking of  $\beta$ -adrenoceptors in the myocardium prevents reflex tachycardia and subsequent elevation of blood pressure.

When administered orally to women with chronic hypertension, it seems as safe.<sup>15,16,17,18</sup> and effective as methyldopa, although neonatal hypoglycemia with higher doses has been reported in a study.<sup>19</sup> In a recent cochrane analysis it has been found to be more effective in lowering BP compared to methyldopa in 10 trials.<sup>4</sup> One study has shown that labetalol is better tolerated than methyldopa and controls pregnancy induced hypertension effectively without causing adverse maternal or fetal outcome. There are little data about Labetolol use and congenital malformation. A randomized double blind trial found no foetal malformation in either the treatment group exposed during the 2<sup>nd</sup> and 3<sup>rd</sup> trimester or placebo group.<sup>17</sup>

Of some concern, one placebo controlled study reported an association with fetal growth restriction in the management of preeclampsia remote from term.<sup>18</sup> Parenterally it is used to treat severe hypertension, and because of lower incidence of maternal hypotension and other adverse effects, its use now supplants that of hydralazine.<sup>2</sup>

#### Dose:

Recommended initial dose 100mg twice daily. The dose should be adjusted semi-weekly or weekly according to response. Maximal daily dose is 1200mg (total).

Adverse effects are consequence of  $\alpha$  receptor block and include fatigue, lethargy, exercise intolerance due to  $\alpha$ 2 blocking effect in skeletal muscle vasculature, peripheral vasoconstriction, sleep disturbances and bronchospasm. Labetalol should not be used in women with asthma or having history of obstructive airway diseases, uncontrolled CCF, 2<sup>nd</sup> or 3<sup>rd</sup> degree AV block, severe peripheral arterial disease and hepatic impairment. Severe hepatocellular damage has been reported after both short and long term treatment.

### Second Line Agents

These agents should be used when monotherapy is insufficient or when women can not tolerate it.

#### Calcium channel blockers :

Nifedipine is the most widely used calcium channel blocker and is safe at any gestation.<sup>2</sup> It reduces vascular resistance by inhibiting transmembrane calcium influx into vascular smooth muscle. Nifedipine does not seem to cause a detectable decrease in

uterine blood flow. Oral administration lowers BP within 10-15 minutes, slow release tablet has slower onset of action (60 min); long acting nifedipine given once daily is usually preferred. Use of sublingual form should be avoided to minimize the risk of sudden hypotension and foetal distress.

Concomitant use with MgSo<sub>4</sub> (as in severe PE or eclampsia) should be avoided. There have been reports that the combination causes neuromuscular blockade and severe hypotension<sup>9</sup>. Action of calcium channel blockers is potentiated by MgSo<sub>4</sub> and sometimes it may appear as cardiotoxic.<sup>20</sup> Maternal adverse effects of calcium channel blockers include – headache, tachycardia, lower extremity oedema and allergic hepatitis.

### **Hydralazine:**

Hydralazine selectively relaxes arteriolar smooth muscle by an as yet unknown mechanism. Its greatest use is in the urgent control of severe hypertension or as a third line agent for multi drug control of refractory hypertension. It is effective orally, intravenously or intramuscularly. Hydralazine previously used as an infusion in the treatment of acute severe hypertension is no longer advocated because of the risk of sudden hypotension with concomitant placental hypoperfusion.

Oral hydralazine is safe throughout pregnancy although occurrence of maternal and neonatal lupus like syndromes have been reported following chronic use<sup>1</sup>. Taken orally as monotherapy hydralazine is not tolerated well because of adverse effects e.g. palpitation, headaches and dizziness. It is therefore combined with methyldopa or labetalol.

### **Third line Agent**

**β adrenergic blockers:** This group of drugs act by competitive inhibition of catecholamines at β<sub>1</sub> and β<sub>2</sub> adrenoceptors. In the past β adrenergic blocker have been highlighted as a class of antihypertensives associated with an increased risk of intrauterine growth retardation (IUGR), in particular atenolol have been signed out. Recent meta-analysis of published data from randomized trial reveals that IUGR appeared not to be related to antihypertensive used.<sup>1</sup> β blockers are still avoided in the first half of pregnancy, because of concern about growth restriction and risks of neonatal β-blockade causing neonatal hypotension and hypoglycaemia.<sup>14</sup> Use of β blockers should be limited to women with chronic hypertension, in whom methyldopa and nifedipine have unsatisfactory control.

Lipid soluble oxprenalol, metoprolol, propynolol have short half life compared to atenolol. The safety and efficacy of parazocine have also been demonstrated.

### **Diuretics**

Although not a teratogenic drug but it is used infrequently in pregnancy because it interferes with plasma volume expansion associated with pregnancy<sup>1</sup>. Many women with chronic hypertension are treated with diuretics, whether therapy should be continued during pregnancy is controversial.<sup>18</sup>

The National High Blood Pressure Education Program working group (USA) concluded that therapy to control blood pressure should be continued in women who are already on it. Diuretic therapy is particularly useful in pregnant women with salt sensitive hypertension or with left ventricular diastolic dysfunction, however it should be discontinued if the women develops superimposed preeclampsia or there is evidence of reduced fetal growth.<sup>1</sup>

Hydrochlorothiazide in dose of 12.5 to 25 mg daily may minimize the untoward side effects e.g. impaired glucose tolerance, hypokalemia and therefore may be used<sup>21</sup>. Spironolactone is not recommended because of its antiandrogenic effects during foetal development<sup>22</sup>.

### **Drug treatment of severe hypertension**

A rise of BP  $\geq 170/110$  mmHg is called severe hypertension<sup>1</sup>. The primary objective of treatment in women with severe hypertension and preeclampsia is to prevent cerebral complications eg. encephalopathy and haemorrhage. The threshold for treatment is usually a sustained DBP  $\geq 110$  mmHg, some experts use mean pressure  $>125$  mmHg as threshold. The aim of therapy is to keep mean arteriolar pressure (MAP) below 126 mmHg (but not below 90 mmHg).

Antihypertensives commonly used include nifedipine (oral or sublingual gel), parenteral labetalol or hydralazine and sodium nitroprusside.

First choice agent: Calcium Channel blocker

Nifedipine (5 mg capsule) – can be given either in first instance or be repeated if satisfactory BP control has not occurred by 30 minutes. If BP control has occurred, then it can be changed to a slow release preparation, the action of which lasts for 12-24 hours, BP should be measured every ½ hour as there may be marked drop in blood pressure. Nifedipine should not be used

in women with atherosclerotic CVD or who are at risk of atherosclerotic disease

### Second choice agent

Labetalol: Can be given in different ways – orally as 200 mg tablet which will lower blood pressure within half an hour, a second dose may be given if needed. Instead of oral preparation, a 20 mg bolus infusion can be given over 1 minute, which will have onset of action in 5 minutes. The dose may be repeated if DBP has not reduced by 30 minutes (up to a maximum of 200 mg). Labetalol also can be given through an infusion pump 5 mg/ml at a rate of 4 ml/hr, infusion rate should be doubled every ½ hr to a maximum of 32 ml (160 mg)/hr until BP has dropped and then stabilized to an acceptable level. Although in a systematic review of trials labetalol (along with methyl dopa, nifedipine or hydralazine) does not seem to cause neonatal heart rate effects but parenteral therapy has been found to increase the risk of neonatal bradycardia, requiring intervention in 1 of 6 newborn.<sup>2</sup>

### Parenteral Hydralazine

Hydralazine is an arteriolar vasodilator. It has a very rapid onset of action and cause profound and rapid hypotension. It also causes increased sympathetic discharge resulting in tachycardia and increased cardiac output. Intravenous hydralazine is no longer the drug of choice, because of adverse perinatal outcome. Foetal distress due to maternal hypotension leading to emergency caesarean section and thrombocytopenia (a rare side effect in adult) has been reported in neonates in women with this drugs.<sup>14</sup>

Initial dose is 5 - 10 mg as intra-venous bolus. If blood pressure is not controlled in 20 minutes, then to repeat initial dose as needed (usually about every 3 hours; maximum, 400 mg per day). The goal of therapy is to decrease diastolic blood pressure to 90-100 mmHg.

Recently a meta-analysis was done by Laura and colleagues on hydralazine for treatment of severe hypertension in pregnancy. Of 21 trials (893 women), eight compared hydralazine with nifedipine and five with labetalol. In this meta-analysis Hydralazine was found to be associated with more maternal hypotension(13 trial); more caesarean section(14 trials); more placental abruption (5 trials); more maternal oligourea (3 trials); more adverse effects on foetal heart rate (12 trials) and more low Apgar score at one minute(3

trials). The results of this review support the use of antihypertensive agents other than hydralazine for the acute management of severe hypertension in pregnancy.<sup>23</sup>

Sodium Nitroprusside (Nitropress) – is an arteriolar and venular vasodilator. It is a potent antihypertensive that acts by forming nitrous oxide. It is rarely needed in obstetrics except in cases of severe HTN with acute CCF and pulmonary oedema. It reduces peripheral resistances and left ventricular preload, leading to reduction of pulmonary congestion.

Because of the concern about foetal toxicity (foetal accumulation of cyanide) this agent should be reserved for situations when other antihypertensive agents are not available or do not work.

### Antihypertensive drugs to be avoided in pregnancy:

Both Angiotensin converting enzyme (ACE) inhibitors and Angiotensin receptor blockers (ARBs) are fetotoxic<sup>1</sup>, therefore all women of childbearing age treated with these drugs must be informed of the need for drug discontinuation, should they become pregnant. Used in the 1<sup>st</sup> trimester, the babies are 4 times likely to develop cardiovascular problem and 5 times likely to develop CNS malformation (hypocalveria).<sup>24</sup>

ACE inhibitors are also contraindicated in the 2<sup>nd</sup> and 3<sup>rd</sup> trimester because of risk of ACE inhibitor fetopathy – including IUGR, pulmonary hypoplasia, foetal renal tubular dysplasia, neonatal renal failure and death.<sup>1</sup>

### Antihypertensive treatment in the postpartum period and during breast feeding:

Immediately after delivery BP falls but rises typically over the first five days, perhaps reflecting vasomotor instability. Recent Cochrane analysis shows that the need for treatment, the management of antihypertensive medication, and patient counseling have been unguided by the literature.<sup>25</sup> Tan and de Swiet<sup>26</sup> have suggested that antihypertensive drugs should be given if the BP exceeds 150 mm Hg systolic or 100 mm Hg diastolic in the first 4 days of the puerperium. Choice of antihypertensive agent in the postpartum period is often influenced by breast feeding.<sup>27</sup> Most antihypertensive drugs are present in very low concentration in the breast milk except atenolol and metoprolol whose concentration is similar to that of maternal plasma, possibly to levels that could affect the infant; by contrast, exposure to labetalol and propranolol seems low.<sup>28</sup>

Methyldopa should be avoided during postpartum period because of the risk of postnatal depression. Diuretics should also be avoided as it may reduce milk volume by suppressing lactation. Therefore  $\beta$ -blocker plus nifedipine may be used if another agent is required. Women with gestational hypertension or preeclampsia are usually able to stop all antihypertensives within six weeks postpartum. Those with chronic hypertension can resume their pre-pregnancy drugs. ACE inhibitor and ARBs should be avoided because of their side effect on neonatal renal function<sup>9</sup>.

### Conclusion:

Hypertensive disorders are an important cause of maternal and perinatal mortality and morbidity worldwide. Pre-pregnancy counseling is essential in women with chronic hypertension as well as those with history of pre-eclampsia. Opinions differ as to which is the best antihypertensive during pregnancy. It is important to balance the risk to the fetus associated with treating the illness against risk to both the mother and the fetus in failing to treat the mother. Maternal and neonatal outcomes are generally good in women who have mild chronic hypertension or gestational hypertension. Antihypertensive therapy may permit these women to continue their pregnancies to term.

In contrast, pre-eclampsia is a unique syndrome of pregnancy that is potentially dangerous for both mother and fetus; it does not respond well to conventional antihypertensive therapy used in non pregnant women. Close medical supervision and timely delivery are the keys to the treatment of pre-eclampsia.

### References:

1. James PR, Nelson CP. Management of hypertension before, during and after pregnancy. *Heart* 2004; 90: 1499-1504.
2. Magee LA, Omstein MP, von Dadelszen P. Management of hypertension in pregnancy. *BMJ* 1999; 318: 1332-6.
3. Brown MA, Haque WM, Higgins J et al. The detection, investigation and management of hypertension in pregnancy. Full consensus statement. *Aus N Z J Obstet Gynaecol* 2000; 40:139-55.
4. Abalos E, Duley L, Steyn D, Henderson-Smart D. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2007; CD002252.
5. Walker JJ. Pre eclampsia. *Lancet* 2000; 356: 1260-5.
6. Sibai BM. Diagnosis and management of gestational hypertension and pre-eclampsia. *Obstet Gynaecol* 2003; 102: 181-92.
7. Khedun SM, Maharaj B, Moodley J. Effects of antihypertensive drugs on the unborn child. What is known, and how should this influence prescribing? *Paediatr Drugs* 2000; 2 (6): 419-36.
8. Lindheimer MD, Barron WM. *Medical Disorders in Pregnancy*, 3rd ed. St. Louis: Mosby; 2000.
9. Sibai BM. Treatment on hypertension in pregnant women. *N Engl J Med* 1996; 335(4): 257-65.
10. Report of the National High Blood Pressure Education Program working group on High Blood Pressure in Pregnancy. *Am J Obstet Gynaecol* 2000; 183: S<sub>1-22</sub>.
11. Helewa ME, Burrows RF, Smith J, Williams K, Brain P, Rabkin SW. Report of the Canadian Hypertension Society Consensus Conference: 1. Definitions, evaluation and classification of hypertensive disorders in pregnancy. *CMAJ*. 1997; 157: 715–725.
12. Brown MA, Hague WM, Higgins J, Lowe S, McCowan L, Oats J, Peek MJ, Rowan JA, Walters BN. The detection, investigation and management of hypertension in pregnancy: full consensus statement. *Aust N Z J Obstet Gynaecol* 2000; 40: 139–155.
13. Sibai BM. Chronic Hypertension in Pregnancy. *Obstetrics & Gynaecology* 2002; 100: 369-377.
14. Yankowitz J. Pharmacologic Treatment of hypertensive disorders during pregnancy. *J perinatal neonatal nursing* 2004; 18: 230-40.
15. Sibai BM, Mabie WC, Shamsa F, Villar MA, Anderson GD. A comparison of no medication versus methyldopa or labetalol in chronic hypertension during pregnancy. *Am J Obstet Gynecol* 1990; 162: 960–967.
16. Plouin PF, Breart G, Maillard F, Papiernik E, Relier JP. Comparison of antihypertensive efficacy and perinatal safety of labetalol and methyldopa in the treatment of hypertension in pregnancy: a randomized controlled trial. *Br J*

- Obstet Gynaecol 1988; 95: 868–876.
17. Pickles CJ, Symonds EM, Pipkin FB. The fetal outcome in a randomized double-blind controlled trial of labetalol versus placebo in pregnancy-induced hypertension. *Br J Obstet Gynaecol* 1989; 96: 38–43.
  18. Sibai BM, Gonzalez AR, Mabie WC, Moretti M. A comparison of labetalol plus hospitalization versus hospitalization alone in the management of preeclampsia remote from term. *Obstet Gynecol* 1987; 70: 323–327.
  19. Munshi UK, Deorari AK, Paul VK, Singh M. Effects of maternal labetalol on the newborn infant. *Indian Pediatr* 1992; 29: 1507–1512.
  20. mag-Ales K. Magnesium plus nifedipine. *Am J Obstet Gynecol* 1990; 162: 288
  21. Magee LA. Drugs in pregnancy. Antihypertensives. *Best Pract Res Clin Obstet Gynaecol* 2001; 15: 827–845.
  22. Groves TD, Corenblum B. Spironolactone therapy during human pregnancy. *Am J Obstet Gynecol* 1995; 172: 1655–1656.
  23. LauraA Magee, Chris Cham, Elizabeth J Waterman, Arne Ohisson, Peter von Dadeiszen. Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. *BMJ* 2003; 327: 955-65.
  24. Coopeer WO, Hernandez-Diaz S, Arbogast PG et al. Major congenital malformations after first trimester exposure to ACE inhibitors. *N Engl J Med* 2006; 354: 2443-51.
  25. Magee L, Sadeghi S. Prevention and treatment of postpartum hypertension. *Cochrane Database Syst Rev* 2005; CD004351.
  26. Tan LK, de Swiet M. The management of postpartum hypertension. *bjog* 2002; 109: 733–736.
  27. Beardmore KS, Morris JM, Gallery ED. Excretion of antihypertensive medication into human breast milk: a systematic review *Hypertens Pregnancy* 2002; 21: 85–95.
  28. Atkinson H, Begg EJ. Concentrations of beta-blocking drugs in human milk. *J Pediatr* 1990; 116: 156.