



Risk Factors Associated with Pregnancy Induced Hypertension and its Treatment: A Review

Dr.R.Senthil Selvi^{1*}, Greeshma Raj^{2*}, Indu. P. Vinod², Anaith Karun.K², S.Rajarajan¹

¹Professor, Department of Pharmacy Practice, The Erode College of Pharmacy, Erode, India.

²Department of Pharmacy Practice, The Erode College of Pharmacy, Erode, India.

*Corresponding author's E-mail: senthilselvi65@gmail.com

Received: 10-07-2019; Revised: 22-08-2019; Accepted: 28-08-2019.

ABSTRACT

Hypertension is the most common medical disorder encountered during pregnancy. Hypertensive disorders are one of the major causes of pregnancy-related maternal deaths. Gestational hypertension is a condition of onset of hypertension without Proteinuria after 20 weeks of gestation whereas preeclampsia is referring to the onset of hypertension and Proteinuria after 20 weeks of gestation. Maternal and fetal complications can be devastating and may include stroke, seizures, placental abruption, fetal death, and maternal death. To identify the proper drug therapy and helps to reduce the maternal & foetal complications associated with the pregnancy induced hypertension and pre-eclampsia. Treatment is a balance between managing maternal symptoms to prevent disease progression and prolonging gestation to improve fetal outcomes. The only known resolution is the delivery of the fetus and placenta. The management of PIH that depends upon the stages of the pregnancy and severity of the diseases. Pharmacologic therapies must be carefully chosen with efficacy and safety for mother and fetus in mind. This literature review explores commonly used medications to manage blood pressure during pregnancy and current study that focused on the safety and efficacy of these medications, and the risk factors associated with the disease.

Keywords: Pregnancy induced hypertension, pre- eclampsia, risk factor, classification, treatment.

INTRODUCTION

Pregnancy induced hypertension are one of the leading causes of maternal and perinatal deaths in developing countries, and many studies have been conducted in this field¹. Hypertension is a common medical problem that affects 20% - 30% of the adult population and more than 5% - 8% of all pregnancies in the world^{2,3}.

The only resolution for preeclampsia and pregnancy-induced hypertension, is delivery of the fetus and placenta^{4,5}.

When the hypertensive disorder complicate a pregnancy before full term, the risks of per-term delivery is considered and cause risk to the mother. Often medications that are used to manage the maternal blood pressure and prolong the gestation. There are many treatment options that are available to treat the hypertension in pregnant women but additional consideration must be taken before selecting the therapeutic agents in pregnancy The chosen medication is not only be safe and effective to the mother, but also it have minimal impact on the development of the fetus.

Gestational Hypertension is defined as having a blood pressure greater than 140/90mmHg without the presence of proteins in urine and diagnosed after 20th week of gestation⁶.

Pre-eclampsia is gestational hypertension (blood pressure higher than 140-90 mmHg) with Proteinuria (> 300 mg of protein in a 24 hr urine sample).

Severe pre-eclampsia involves a blood pressure higher than 160-110 mmHg, with some additional medical signs and symptoms. It referred to eclampsia when tonic clonic seizures appear in pregnant women with high blood pressure and Proteinuria⁷.

Maternal complications of preeclampsia include seizure activity, placental abruption, stroke, HELLP syndrome (hemolysis, elevated liver enzymes and low platelets), liver hemorrhage, pulmonary edema, acute renal failure, and disseminated intravascular coagulation (DIC) There could be significant mortality and morbidity associated with the mother and fetus. Fetal and neonatal complications include intrauterine growth restriction, preterm birth, low birth weight, neonatal respiratory distress syndrome, increased admission to neonatal intensive care units, and fetal or neonatal death⁸.

Multiple gestations, such as twins or triplets, increase risk of pregnancy induced hypertension^{5,9}. Moreover, certain pre-existing chronic conditions increase a woman's risk, including diabetes mellitus, gestational diabetes, insulin resistance, chronic hypertension, obesity, chronic kidney disease, lupus, and vascular or connective tissue disorders^{5,8,9}. Women over the age of 35 years and women in African American race are considered at more risk for developing preeclampsia^{5,10}. Some treatment may lowers the blood pressure and minimize the adverse effects, the only known resolution of pregnancy induced hypertension is delivery of the placenta, that helps to resolving the symptoms associated with pregnancy induced hypertension³. Severe symptoms includes: headaches, visual disturbances, oliguria, non-reassuring fetal testing.

Several other symptoms indicates the hypertension in pregnancy and it require additional evaluation⁹. Persistent severe headaches, visual problem, sudden swelling of face, hands or feet, vomiting, or epigastric pain may be related to increases in blood pressure. Preeclampsia may also lead to decreased platelet count, elevated serum creatinine level, and an increase in liver enzymes^{9,11}.

Classification of PIH

The American College of Obstetricians and Gynecologists (ACOG) has classified pregnancy induced hypertension (PIH) into four groups of disorders: gestational hypertension, is defined as BP is 140/90 mmHg or higher after the 20th week of gestation; chronic hypertension, that exists before pregnancy or begins in the first 20 weeks of gestation; preeclampsia (raised BP and edema or Proteinuria) / eclampsia (preeclampsia with seizures); and preeclampsia superimposed on chronic hypertension.

Classification of Hypertensive Disorders During Pregnancy

	American College of Obstetricians and Gynecologists (ACOG)	International Society for the Study of Hypertension in Pregnancy (ISSHP)	Working Group on High Blood Pressure in Pregnancy
Chronic hypertension	BP \geq 140/90 mm Hg Present before 20 weeks	BP \geq 140/90 mm Hg Present before 20 weeks	BP \geq 140/90 mm Hg Present before 20 weeks
Gestational Hypertension	BP \geq 140/90 mm Hg Onset after 20 weeks	BP \geq 140/90 mm Hg Present after 20 weeks	BP \geq 140/90 mm Hg Onset after 20 weeks
Preeclampsia	BP \geq 140/90 mm Hg Onset after 20 weeks Proteinuria*	BP \geq 140/90 mm Hg Onset after 20 weeks Proteinuria*	BP \geq 140/90 mm Hg Onset after 20 weeks Proteinuria*
Severe Preeclampsia	BP > 160/110 mm Hg Excessive proteinuria**	BP \geq 160/110 mm Hg	DBP \geq 110 mm Hg Severe symptoms [^]
Preeclampsia Superimposed on Chronic Hypertension	BP \geq 140/90 mm Hg Present before 20 weeks New onset proteinuria	BP \geq 140/90 mm Hg Present before 20 weeks New onset proteinuria	New onset proteinuria during pregnancy in chronic hypertension

*Proteinuria is defined as > 300 mg on 24 hour urine collection or > 30 mg on a urine spot test.

RISK FACTORS

The Study by Vidyadhar B. Bangal¹² shows that incidence of PIH was higher among teenage pregnancy. Duckitt et al¹³ observed that teenage pregnancy to be one of the risk factors for PIH & eclampsia. Saha.S. et al¹⁴ concluded that eclampsia involves young primigravidas & 87.6% of eclamptic patients were below 25 years of age in his study. Contrary to this Lamminpaa et al¹⁵ mentioned higher incidence of pre-eclampsia in advanced maternal age. Jasovic Siveska E et al¹⁶ mentioned Bimodal variability i.e. PIH among young primipara & old multipara women. Among primigravida majority were having severe PIH. Study by Bhattacharya S.¹⁷ & Duckitt et al¹³ also reported that primigravida was a risk factor for preeclampsia & eclampsia. Yucesoy G. et al¹⁸ shows that PIH were high in women with lower socioeconomic status having poor access to antenatal care. The reason could be illiteracy; they come to the hospital only in case of serious problems, & in a large majority of patients preeclampsia remains asymptomatic & remits spontaneously, since diagnosis of preeclampsia is often missed. Hence these patients never come in contact with the health care system. S Ganesh Kumar wherein Past H/o PIH in previous pregnancy, family h/o PIH & obesity were risk factors of PIH¹⁹. Variable results were observed regarding route of delivery among PIH cases in different study.

TREATMENT FOR PREGNANCY INDUCED HYPERTENSION

The only known resolution of pregnancy induced hypertension is delivery of the fetus and placenta. The focus of pharmacological treatment helps to reduce the maternal signs and symptoms so gestation may be prolonged and improved the fetal outcomes⁸. Treatment that provide maternal and fetal safety. An increased gestation that helps to decreased morbidity and mortality for the fetus, but this should be weighed against maternal condition, as preeclampsia may quickly progress to eclampsia, HELLP syndrome, or other morbidities^{4,5,23}.

According to NHBPEP methyldopa, labetalol, beta blockers (other than atenolol), slow release nifedipine, and a diuretic are considered as appropriate treatment for pregnancy induced hypertension²⁰.

If a woman's blood pressure is well controlled on an agent in pre-pregnancy she may continue it during pregnancy, with the exception of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. If restarting drug therapy in women with chronic hypertension, methyldopa is recommended as first line therapy. For emergency treatment in preeclampsia, IV hydralazine, labetalol and oral nifedipine can be used²¹.

The ACOG Practice Bulletins also recommend that methyldopa and labetalol are appropriate first-line agents



and beta-blockers and angiotensin-converting enzyme inhibitors are not recommended during pregnancy²².

ACEIs and ARBs have been associated with unwanted effects on fetal growth and development, including renal failure and death of the fetus^{23,24}. When studies during the first trimester of pregnancy, ACEIs such as lisinopril have been associated with an increased risk of major fetal malformations, including cardiovascular and central nervous system defects^{8,23}.

When ACEIs are used in second and third trimesters of pregnancy Oligohydramnios, cardiovascular system malformation, central nervous system malformations, hypotension, reversible or irreversible renal failure, and death have been reported^{8,23}. ARBs have limited safety profile data during pregnancy, but as ARBs act on the renin-angiotensin-aldosterone system in a similar way to ACEIs, the risks are thought to be comparable to that of ACEIs^{8,24}.

Hydralazine

Hydralazine is a direct arterial smooth muscle dilator, has been the drug of choice for the acute treatment of severe hypertension in pregnancy. This drug induces a baroreceptor – mediated tachycardia and increases cardiac output, which increases uterine flow and lowering the BP²⁵. According to the studies of Marko Folic et al. acute severe hypertension in pregnancy exhibited that labetalol has less maternal hypotension than hydralazine. According to the studies of Widerlov et al. Generally, hydralazine has been used in all trimesters of pregnancy and it doesn't show any teratogenicity, although Widerlov et al. reported neonatal thrombocytopenia and Yemini et al. a case of maternal, and possibly neonatal, lupus after six days of parenteral hydralazine therapy for severe hypertension^{26,27}.

Side effect of hydralazine includes nausea, vomiting, tachycardia, flushing, headache and tremor. Some of the hydralazine induced adverse effects mimic symptoms associated with severe pre-eclampsia and imminent eclampsia making it difficult for a clinician to differentiate between drug associated and disease related problems²⁵.

In Magee et al study, Increased incidence of certain maternal and fetal outcome should be observed when hydralazine is compared with other anti hypertensive drugs, including maternal hypotension, increased number of cesarean sections, and lower Apgar scores at one minute. For a Women taking hydralazine also had more headaches and tachycardia than with other antihypertensive agents²⁸. The studies concluded that the hydralazine have increased adverse effect than other drugs so it couldn't be used as a first line for PIH.

Methyldopa

Methyldopa, a centrally acting α agonist that decreases sympathetic outflow to decrease BP, is the most commonly used antihypertensive agent for chronic treatment of hypertension in pregnancy. The usual starting dose of 750-1000mg/day, to be administered in 3-4 daily divided doses, can be increased 2 or 3gm/day if needed.

This medication may be administered by either intravenous or oral routes.²⁹ Higher dose maybe needed to control BP in pregnancy.

According to the study of Deb et al Methyldopa is most commonly prescribed anti hypertensive drug and it is safe during pregnancy. No adverse effect on development and growth of the foetus. The adverse effect that occurs in pregnant women are dizziness, sedation accompanied by loss of energy.

Labetalol

Labetalol a non-selective β -blocking agent with vascular α -1-receptor blocking capabilities is widely used in pregnancy³⁰. Labetalol may be preferred over other beta blockers because it dilates arterioles and decreases vascular resistance without significantly decrease cardiac output³². Fetal growth restriction and low placental weight in patients (with essential hypertension) have been associated with the use of atenolol during the second trimester³⁰. Side effects include fatigue, lethargy, exercise intolerance, sleep disturbance and bronchoconstriction. In a review of antihypertensive drug therapy for mild-to-moderate hypertension during pregnancy, β -blockers appear to be more effective than methyldopa in limiting episodes of severe hypertension in women with hypertensive disorders of pregnancy. It may be associated with a risk of fetal bradycardia and neonatal hypoglycemia³¹.

According to the Odigboegwu et al. the use of methyldopa is compared with the use of labetalol, it indicates that labetalol is more safe during the time of pregnancy. Subhedar V et al. indicated that Labetalol is more advantageous than methyldopa.

Nifedipine/Nicardipine

Calcium channel blockers inhibit the L-type calcium channels in the cardiac and vascular smooth muscle cells, which exerts negative inotropic effects on the heart and causes vasodilation, and thereby decreases the systemic vascular resistance³³. The use of both nifedipine and nifedipine have been studied during pregnancy. In a study by Aya et al, an intravenous loading dose of nicardipine demonstrated a 15-30% decrease in maternal mean arterial pressure in all twenty patients with severe preeclampsia within 15 to 20 minutes of initiation of intravenous nicardipine³⁴. An open, prospective study published in the Journal of Hypertension in 2005 investigated the use of nicardipine as a second line agent in preeclampsia³⁵.

In 2010, the Obstetrical and Gynecological Survey published a review that analyzed data about five studies of nicardipine use in preeclampsia. The most common maternal side effects are transient hypotension, nausea, headache, and flushing. The most common adverse effects for the fetus/neonate included preterm delivery and being small for gestational age. However, the incidence was comparable to other studies of antihypertensives used during pregnancy³³. Short acting nifedipine has been



reported to be as safe and effective as intravenous hydralazine for the acute treatment of severe hypertension in pregnancy.

Medication	Maternal adverse effect	Foetal adverse effect
Hydralazine	Nausea, vomiting, hypotension, tachycardia, headaches, palpitations, flushing, fluid retention	Neonatal thrombocytopenia
Labetalol	Hypotension, headache, bradycardia	Intrauterine growth restriction, neonatal bradycardia, neonatal hypotension
Methyldopa	Drowsiness, dizziness, dry mouth, nausea	No risk found in long term use
Nicardipine	Headache (most common), tachycardia, nausea, flushing, dizziness	Neonatal hypotension
Nifedipine	Rebound tachycardia, nausea, flushing, dizziness	Neonatal hypotension

CONCLUSION

Hypertension is the one of the most important complication during the time of pregnancy. All the hypertensive disorders are associated with increased maternal mortality and morbidity. The major risk factors associated with pregnancy induced hypertension are teenage pregnancy, obesity, age more than 35 years, family history of PIH and PIH on last pregnancies. There are many type of antihypertensive drugs used in PIH such as Methyldopa, Hydralazine, Labetalol, Nifedipine and Nicardipine. Hydralazine have more adverse effect so, it couldn't be used as a first line drug for PIH. In case of methyldopa, it doesn't produce any adverse effect in foetus but there are minor complication's in mother. Labetalol is more safe and advantageous during pregnancy. Short acting nifedipine is safe and effective for the acute treatment of severe hypertension in pregnancy.

Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers are contraindicated during the time of pregnancy due to its serious adverse effect like, fetal malformations, cardiovascular and central nervous system defects, reversible or irreversible renal failure, and death.

Before selection of drug both the benefits and risk associated with the drug should be assessed. By following proper drug therapy will help to reduce the both maternal and foetal complication associated with pregnancy induced hypertension.

REFERENCES

- Henry, C.S, Biedermann, S.A., Campbell, M.F. and Guntupalli, J.S. Spectrum of Hypertensive Emergencies in Pregnancy. *Critical Care Clinics*, 20, 2004, 607-712.
- De Cherney, A.H., Nathan, L., Laufer, N. and Roman, A.S. *Current Diagnosis & Treatment: Obstetrics & Gynecology*. 11th Edition, Chapter 26: Hypertension in Pregnancy. 2012.
- Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *American Journal of Obstetrics and Gynecology*, 183, 2000, S1-S22. <http://dx.doi.org/10.1067/mob.2000.107928>
- McCoy S, Baldwin K. Pharmacotherapeutic options for the treatment of preeclampsia. *Am J Health Syst Pharm*. 66, 2009, 337- 344.
- Dattel BJ, Chescheir N, Lockwood C. *Your pregnancy & birth*. Fourth Edition ed. Washington, D.C.: The American College of Obstetricians and Gynecologists. 2005.
- Singhal SR, Deepika, Anshu, Nanda S. Maternal and perinatal outcome in severe Preeclampsia and eclampsia. *JSAFOG*. 1(3), 2009, 25-8.
- Walker JJ. Preeclampsia. *Lancet*. 2000, 356, 1260-5.
- Vest AR, Cho LS. Hypertension in pregnancy. *Cardiol Clin*. 30, 2012, 407- 423
- Barss V, Repke J. *Preeclampsia (beyond the basics)*. South Holland: Up-to-date, 2012.
- ACOG Committee on Practice Bulletins--Obstetrics. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. *Obstet Gynecol*. 99, 2002, 159-167.
- Joseph T. DiPiro, Robert L. Talbert, Gary C. Yee, Gary R. Matzke, Barbara G. Wells, L. Michael Posey editors. *Pharmacotherapy: A pathophysiologic approach*. Eighth ed. McGraw Hill, 2011.
- Bangal V, Giri P, Mahajan A. Maternal and foetal outcome in pregnancy induced hypertension: a study from rural tertiary care teaching hospital in India. *International Journal of Biomedical Research IJBR* 2(12), 2011, 595-599.
- Duckitt K, Harrington D. Risk factors for preeclampsia at antenatal booking: systematic review of controlled studies. *BMJ*, 330, 2005, 565-577.
- Saha S, Ghosh S, Ganguly RP, Das A. Comparative study of efficacy of magnesium sulphate and diazepam in the management of eclampsia in a peripheral rural medical college (A cross over study of 440 cases). *J Obstet Gynecol Ind*, 52, 2002, 69-72.
- Lamminpää R, Vehviläinen-Julkunen K, Gissler M, Heinonen S. Preeclampsia complicated by advanced maternal age: a registry-based study on primiparous women in Finland 1997-2008. *BMC Pregnancy Childbirth*, 12(1), 2012, 47.
- Jasovic Siveska, Jasovic V, Stoilova S. Previous Pregnancy History, Parity, Maternal age & risk of PIH. *Bratisl Lek Lysti*, 112(4), 2011, 188-91
- Yücesoy G, Ozkan S, Bodur H, Tan T, Calişkan E, Vural B, Corakçi A. Maternal and perinatal outcome in pregnancies complicated with hypertensive disorder of pregnancy: a seven year experience of a tertiary care center. *Arch Gynecol Obstet*., 273(1), 2005, 43-9.



18. Bhattacharya M. Pregnancy induced hypertension and prior trophoblastic exposure. *Ind J Obstet Gynecol*, 54 (6), 2004, 568-70.
19. S Ganesh Kumar, B Unnikrishnan, K Nagaraj, S Jayaram. Determinants of pre-eclampsia: A case-control study in a district hospital in South India. *Indian J of Community Medicine*, 35(4), 2010, 502-505.
20. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *American journal of obstetrics and gynecology*. 183(1), 2000, S1–S22.
21. ACOG Practice Bulletin. Chronic hypertension in pregnancy. ACOG Committee on Practice Bulletins. *Obstetrics and gynecology*. 98 suppl(1), 2001, 177–185. [PubMed: 11508256]
22. Borgelt LM, O'Connell MB, Smith JA, Calis KA. *Women's health across the lifespan*. Maryland: American Society of Health-System Pharmacists, 2010.
23. Lisinopril. Lexi-Drugs. In: LexiComp 1.6.4(140). Philadelphia, PA: Wolters Kluwer Health. c2010.
24. Hydralazine. Lexi-Drugs. In: LexiComp 1.6.4(140). Philadelphia, PA: Wolters Kluwer Health. c2010.
25. ACOG committee on practice bulletin. ACOG practice bulletin. chronic hypertension in pregnancy. ACOG committee on practice bulletin. *obstet gynecol*. 2001, 98suppl 177.
26. Widerlov E, Karlman I, Storsater J. Hydralazine induced neonatal thrombocytopenia. *N Engl J Med*. 303, 1980, 1235.
27. Yemini M, Shoham (Schwartz) Z, Dgani R. Lupus-like syndrome in a mother and newborn following administration of hydralazine: a case report. *European Journal of Obstetrics, Gynecology and Reproductive Biology* 30, 1989, 193-7.
28. Magee LA, Cham C, Waterman EJ, Ohlsson A, von Dadelszen P. Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. *BMJ*. 327, 2003, 955-960.
29. Applied therapeutics Koda-Kimble and Young's the clinical use of drugs page no:1127
30. Podymow T, August P. Antihypertensive drugs in pregnancy. *Seminars in nephrology*. 31(1), 2011, 70–85.
31. Butters L, Kennedy S, Rubin PC. Atenolol in essential hypertension during pregnancy. *Bmj*. 1990, 301(6752),587–589.
32. Molvi SN, Mir S, Rana VS, Jabeen F, Malik AR. Role of antihypertensive therapy in mild to moderate pregnancy-induced hypertension: a prospective randomized study comparing labetalol with alpha methyldopa. *Arch Gynecol Obstet*. 285, 2012, 1553-1562.
33. Nij Bijvank SW, Duvekot JJ. Nicardipine for the treatment of severe hypertension in pregnancy: a review of the literature. *Obstet Gynecol Surv*. 65, 2010, 341-347.
34. Aya AG, Mangin R, Hoffet M, Eledjam JJ. Intravenous nicardipine for severe hypertension in pre-eclampsia--effects of an acute treatment on mother and foetus. *Intensive Care Med*. 25, 1999, 1277-1281.
35. Hanff LM, Vulto AG, Bartels PA, Roofthoof DW, Bijvank BN. Intravenous use of the calcium-channel blocker nicardipine as second-line treatment in severe, early-onset pre-eclamptic patients. *J Hypertens*. 23, 2005, 2319- 2326.
36. American Society of Nephrology; News release, nov.8, 2008. Available from 621138.pregnant-rural-womenmore-at-risk.htm.

Source of Support: Nil, Conflict of Interest: None.