SJIF Impact Factor: 5.464

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 7.
Issue: 6.
Page N. 01-12
Year: 2023

Review Article www.wjahr.com

PREGNANCY INDUCED HYPERTENSION (PIH): A REVIEW

Nighat Saleh[1], Rahman Gul[1,2]*, Safia Mengal[1], Kashmala Khan[3], Falsafa Jamal[1], Mir Abdul Qadir[1], Abdul Ghani Sasoli[1], Muhammad Zaman Khethran[1] and Aida durrani[4]

[1]Institute of Public Health Quetta, Balochistan, Pakistan.
[2]Faculty of Pharmacy University of Balochistan, Pakistan.
[3]Fatima Jinnah Medical University, Lahore, Pakistan.
[4]Quetta Institute of Medical Sciences.

Received date: 25 March 2023 **Revised date:** 15 April 2023 **Accepted date:** 04 May 2023

***Corresponding Author: Dr. Rahman Gul**

Institute of Public Health Quetta, Balochistan, Pakistan.

ABSTRACT

Almost 6-10% of pregnancies develop complications if mother become hypertensive during pregnancy, this is known as Pregnancy induced hypertension (PIH) in which blood pressure becomes higher than normal i.e., >140/90 mmHg. PIH classified in Mild, Moderate and Sever hypertension according to the blood pressure levels Mild BP 140–149/90–99 mmHg, Moderate BP 150–159/100–109 mmHg, and Severe BP> 160/110 mmHg are the three categories. some conditions related to pregnancy induced hypertension like chronic hypertension, pregnancy induced hypertension and pre-eclampsia, chronic hypertension with superimposed pregnancy induced hypertension plus proteinuria and unclassified hypertension. Pregnancy induced hypertension play a big role in hazards for mother, fetus and newborn morbidity and mortality. PIH have lethal effects on both the mother who have a greater risk of suffering from abruptio placentae, cerebrovascular disturbances e.g. (cerebral oedema, hyper perfusions), organ failure and disseminated intravascular coagulation And on Fetus as growth retardation (IUGR), premature and still births. after 24 h monitoring of ambulatory BP it appears as having a part in the decline from pregnancy induced hypertension to Preeclampsia. antithrombin medicines show good preventive effects in Pre-eclampsia. different Therapy is based on blood pressure readings, gestational age, symptoms, and risk factors. Consider non-drug management when blood pressure is between 140 and 149/90 and 99 mmHg. health organizations recommended different treatment line in pregnancy according to the blood pressure levels Antihypertensive therapy is recommended in accordance with the 2013 ESH/ESC guidelines. when a woman is pregnant and her blood pressure is 150/95 mmHg. treatment should start to female 140/90 mmHg BP plus pregnancy induced hypertension+/- proteinuria**,** persistent high blood pressure with superimposition of PIH or high bp with organ damage or impairment without symptoms in any trimester. The medication of choice during pregnancy is methyldopa. While labetalol has an efficacy similar to methyldopa In late pregnancy, metoprolol and atenolol seem to be both safe and helpful medications. Due to their harmful effects on the fetus, ACE inhibitors and angiotensin II antagonists are not allowed to be taken during pregnancy.

KEYWORDS: Pre-eclampsia, pregnancy-induced hypertension, antihypertensive medications, chronic hypertension and methyldopa.

INTRODUCTION

Due to the added pregnancy-induced hypertension1 >140/90 mmHg, almost 6–10% of pregnancies experience problems.[1] PIH is categorized into three degrees of hypertension based on blood pressure: Mild, Moderate, and Severe. BP are classificified in 3 levels as Mild (140-149/90-99 mmHg), Moderate (150-159/100-109 mmHg), and Severe (BP> 160/110 mmHg).[2] The Canadian Hypertension Society states that blood pressure levels during pregnancy play a role in a number of health issues, including chronic hypertension (high bp), pregnancy-induced hypertension and pre-eclampsia, chronic hypertension with superimposed pregnancy-induced hypertension and proteinuria, and unclassified hypertension, as well as the need for antihypertensive medication. as demonstrated in Table 1.[3]

Table 1: Pregnancy induced hypertension classification.

Chronic high blood pressure (1-5%)	20th gestational week, persists for more than 42 days after delivery, plus/minus proteinuria
Pregnancy induce hypertension and pre-eclampsia (PE, 2-8%)	>20th week of pregnancy, heals in 42 days after delivery, but with considerable proteinuria and poor organ perfusion
Chronic hypertension + superimposed pregnancy induced hypertension with proteinuria.	Blood pressure and protein excretion worsen in the> 20th week of pregnancy, reaching up to 3 g/24 hours.
Unclassified hypertension	>20th week of pregnancy, +/-, systems-level effects, reexamination is required up to or 42 days onward.

Epidemiology

According to an American epidemiology research conducted between 1995 and 2004, pre-eclampsia and PIH were the pregnancy-related conditions that were most frequently diagnosed[4], although persistent hypertension was far less common.[4] In Europe, preeclampsia incidence rates ranged from 2.3 to 3%, according to studies.[5,6]

Complication

The main and commonly occurring worldwide causes of maternal and neonatal morbidity and death according to WHO, are pregnancy-induced hypertension and its consequences, not the causes themselves1. In Europe, it accounts for the majority of maternal deaths.[7] The 3rd most common reason for maternal death in India between 2000 and 2009, according to a retrospective study. pregnancy induced hypertension (PIH) was the second leading factor of maternal demise in comparable research conducted in China from 1996 to 2009. 10% of maternal deaths in Africa and 25% of maternal mortality in Latin America.[1,8,9] Another study showed that hemolysis, elevated LFTs, thrombocytopenia, or partial HELLP syndrome (83.3%) were the main causes of preeclampsia-related mortality. as hemorrhagic stroke and pulmonary congestions were shown to be the causes of 60% of deaths in eclampsia patients.[10] CNS dysfunction, hepatocellular impairments, low platelet counts, acute DIC, oliguria, pulmonary congestion, cerebrovascular disturbances (cerebral oedema and hyper perfusion), and placental abruption are some other mother-related problems.[11-14] The rate of systemic problems was 6% in a study of 4,188 pre-eclamptic patients (PE). Hematologic issues and a 2.8% placental abruption rate were also mentioned.[15]In contrast to late-onset Preeclampsia.[16], the 32nd week of pregnancy is the most crucial time period for complications connected to PIH. Preeclamptic and superimposed Preeclamptic patients both have an identical likelihood of experiencing perinatal effects, according to one further comparison study published in 2016. Preeclamptic individuals, however, having a greater chance of problems from interventions, including 34-week deliveries, caesarean sections (LSCS), and newborn problems.[17] Fetal/neonatal difficulties include stillbirths, preterm birth, low birth weight newborns, and neonates who are tiny for their gestational age.[18,19] 9.2% of the 17,933 stillbirths in a study were caused by complications from pregnancy-induced hypertension.[20] According to a study from Greece, preeclamptic patients are more likely than normal patients to experience newborn complications.[21] Continuous hospital care for a preeclamptic patient lowers the risk of growth retardation and premature birth, according to retrospective research.[22] Regarding long-term health risks, numerous research shown that women with pregnancy-induced hypertension are more likely to develop additional conditions like heart disease and diabetes mellitus (DM) and renal disease later in life.[23,24] According to one study, 3,593 first-time cases of pre-eclampsia have a higher propensity to go on to develop hypertensive disorders of pregnancy in the future.[25] In comparison to pregnant women who were not hypertension, the risk of diabetes was two times higher in pregnant hypertensive women.[26] Pregnancy-induced hypertension has long-term effects on the developing fetus, including juvenile and adolescent hypertension, a tendency for reduced lipid profiles, a twofold increased risk of stroke, impaired perception, and mental disease early on.[27-31]

Risk Factors

The main and prevalent risk factors for pregnancy-induced hypertension are elevated blood pressure, obesity, gestational diabetes, diabetes mellitus, collagen vascular disease, insulin resistance, being a woman of color, thrombophilia, and hypergonadism.[32,33] A study found that Asian women are less likely to experience pregnancy-related hypertension issues than non-Latino white women. Dark and Latina women is also more likely to experience these complications. Additionally, the research proves a causal link between pre-pregnancy weight gain and PIH. Despite equality and safeguards against smokers for preeclampsia.[34] The facts of parity vary; both multipara and nullipara pregnancies carry a substantial risk of pre-eclampsia.[35,36] Age greater than 30 and a higher BMI are risk factors for pregnancy-induced hypertension in Arabian women.[37] A rise in pre-pregnancy BMI increases the likelihood of twin pregnancies developing preeclampsia.[38] The risk of developing preeclampsia rises along with pregnant weight gain. Preeclamptic family and personal history are taken into account as risk factors for pregnancy-

induced hypertension in item number.[39-41].Antiphospholipid syndrome is a risk factor for hypertension brought on by pregnancy. Preeclampsia is a concern for about one-third of females with APS.[42,43] Recent formal investigations have shown a relationship between low vitamin D levels and a higher risk of preeclampsia.[44,45]

Physiology

Early in a pregnancy the mother's cardiovascular system and hemodynamics undergo several significant changes that are necessary for a steady and adequate blood flow for fetal growth. such as enhanced maternal cardiac output.[46] when the renin-angiotensin-aldosterone system stimulates the maternal plasma volume to increase. Vasodilation keeps blood pressure normal.[47] Vasodilators include prostacyclin to mention a few, the nitric oxide kallikrein-kinin system, vascular endothelial growth factor, and[48-50] A few structural changes also take place during pregnancy as a result of the maternal cardiovascular system's (CVS) functional adaptation, which causes cardiac hypertrophy and controls the needed blood supply during pregnancy. heart hypertrophy is reversible and transient.[51] In 16 to 24 weeks. The systolic, diastolic, and mean arterial blood pressure all decrease during pregnancy. which also somewhat rises starting at 28 weeks. Reduced overall vascular resistance and reduced cardiac output, typically in the second trimester.[52]

Pathophysiology

Preeclampsia, a condition caused by pregnancy-induced hypertension, involves multiple causes. There are numerous ideas that explain pathogenesis, and the placenta plays a crucial part in all of them. The two-stage model's revised hypothesis supports the idea that preeclampsia is caused by improper placenta implantation and vascularization due to maternal factors (PE).[53] Pathophysiological reasons for preeclampsia include genetic predisposition, platelet activation, cardiovascular maladaptation and vasoconstriction, immune incompatibility between maternal and fetal placenta, dysfunction of the vascular endothelium, and vasoconstriction.[54] Additionally, preeclampsia (PE) has been connected to insulin resistance and hyperlipidemia, and concomitant metabolic factors can result in endothelial dysfunction.[55-57] Reduced placental perfusion is caused by autoantibodies, oxidative stress, aberrant natural killer (NK) cells, and other immunological factors. The latter causes endothelial dysfunction and organ deficits by inducing the placenta to release anti-angiogenic and inflammatory mediators.[58] Women who have active macrophages and monocytes in their endometrium get preeclampsia.[59] In preeclamptic patients, an imbalance between pre-oxidant variables and enhanced ROS generation leads to vascular endothelium dysfunction[60] According to a study, natural killer cell's function is elevated in early-onset severe pre-eclampsia sufferers in relation to cytokine (CK) production.[61]

Angiopoietins, angiogenic agents, and their receptors are believed to be crucial for development of the vascular system and placenta regulating.[62] While angiopoietin 2 functions as an antagonistic ligand.[63,64,65] angiopoietin 1 interacts to Tie receptors. The umbilical cord from pregnancies affected by hypertension showed reduced expression of low VEGF (angiogenic factor) levels when compared to healthy pregnancies, according to research studies.[66] Preeclamptic individuals had lower levels of the angiopoietin 1/angiopoietin 2 ratio than healthy pregnant women.[67] Anti-angiogenic substances that limit angiogenesis and contribute to vascular dysfunction include soluble Flt1, tyrosine kinase 1, and soluble endoglin. By attaching to VEGF and PlGF, sFlt-1 blocks their effects.[68,69], while soluble endoglin interferes with TGF-1's ability to bind to its receptor. Both of them are supported by a healthy placenta. Numerous studies have discussed the idea of an imbalance in the amount of circulating angiogenic agents.[70,71] The sFlt-1/PlGF ratio has been anticipated as another tool for preeclampsia diagnosis.[72-74] There is no discernible difference between preeclamptic women and normal pregnant women despite the reduced VEGF level, according to a formal study that showed high levels of maternal and placental sFlt1 and soluble endoglin and low levels of PIGF in preeclamptic patients.[75] Pregnancy-induced hypertension and preeclampsia are linked, according to numerous research.[76,77] In the latter, a genetic disposition is claimed Preeclampsia is influenced by a variety of single nucleotide polymorphisms (SNPs) in candidate genes for vascular growth factors, vasoactive proteins, immunoactivity mediators, components of the renin-angiotensin-aldosterone system, coagulation factors, and components linked to oxidative stress.[78,79]

Follow-up

The evaluation of a woman with pregnancy-induced hypertension includes clinical follow-up, blood tests, and fetal ultrasounds. The nature and severity of the disorder will determine how the hypertension patients are followed up.[80,81] It comprises blood pressure values, clinical problem signs, and symptoms.[82] Urine dipstick, proteinuria, if urine dipstick has >1+, CBC, Hb%, LFTs, urea/creatinine, blood uric acid, and electrolytes are just a few of the biochemical and urine tests. Similar to that, regular fetal monitoring is required and depending on the type of hypertension condition. Pregnancies with persistent hypertension are advised to have fetal ultrasonography, alcohol analysis, and umbilical artery Doppler velocimetry at 28–30 and 32–34 weeks of pregnancy. Cardiotocography (CTG) is used to measure fetal heart activity. Fetal doppler ultrasonography is not recommended after two weeks in cases of severe pregnancy-induced hypertension or preeclampsia If aberrant fetal activity, vaginal hemorrhage, or worsening of the pre-existing ailment are noticed, cardiotocography is advised.[83] For the diagnosis, D/Ds, and assessment of pregnancy-induced hypertension, CTG monitoring appears to be a credible source. The distinction between white-coat hypertension (WCH), the diagnosis of

preeclampsia, the projection in the third trimester, and the treatment plan is very helpful.[84-88] White coat hypertension is defined as an increase in BP while in a clinic but normal outside of one. White coat hypertension has a favorable prognosis, and beta blockers or calcium channel blockers are not recommended as treatments. Despite this, Preeclampsia seldom develops in cases of WCH in early pregnancy.[89,90] In order to protect pregnant women from the negative effects of antihypertensive medications and needless C-S, it is crucial to distinguish between White Coat Hypertension and Pregnancy-Induced Hypertension. It's crucial to identify white coat hypertensive people who might develop preeclampsia. In comparison to the evaluation of treatment efficacy, ABPM contributes to the attainment of both of the aforementioned categories.[84,89,91,92]

Treatment

Medication for pregnancy-induced hypertension is based on blood pressure, signs and symptoms, gestational age, and associated risk factors.

Mild to Moderate PIH

Due to a lack of information, which is nonetheless treatable, developing a treatment plan for mild to severe pregnancy-induced hypertension is challenging.[80,81,93,94] In moderate cases of pregnancy-induced hypertension, randomized controlled studies (RCTs) that included medical treatments along with palliative care or no therapy at all had mixed results. Potential controlled studies of metoprolol hydralazine, CA channel blockers, and centrally acting antihypertensives for mild pregnancy-induced hypertension. Pregnancy outcomes for women with unclassifiable hypertension or mild preeclampsia did not significantly improve when compared to the group who were not treated.[95-98] When compared to the control group, beta blockers had no influence on the onset of proteinuria, nifedipine had no impact on PE-related symptoms, hypercalciuria in a study involving 114 pregnant women with induced hypertension.[99,100] Other RCTs had treated groups that had better pregnancy outcome. In contrast to the aforementioned discoveries, beta blockers in the treatment group prevented proteinuria in comparison to the control group.[101-103] In comparison to mid-pregnancy abortions, development of severe PE, RCTs with methyldopa show superior pregnancy outcomes in cases of mild PIH and mild PE, as well as abortions in those circumstances.[104,105].One more study of methyldopa in mild pregnancy-induced hypertension showed that it was crucial to continue the pregnancy for an additional 10.3 days without any negative effects on the weight of the baby.[106] The good impact of antihypertensive medication on pregnancy outcome was validated by a randomized controlled trial (RCT) involving 100 pregnant women with moderate pregnancy-induced hypertension who received either methyldopa or labetalol treatment, and 50 controls.) Although neonatal outcomes included SGA, premature birth, and admission to NIUC, the antihypertensive medicine was intended to enhance maternal outcomes, including as the development of severe pregnancy-induced hypertension, proteinuria, hospitalization before term, and caesarean birth.[107] When compared to the untreated group, early clonidine and hydralazine treatment prevents premature delivery in the prime of pregnancy when pregnancy-induced moderate hypertension is identified.[108] Treatment with nifedipine for moderate PE improved renal function by lowering urea, creatinine, and the level of protein in the urine after 24 hours in the treated group. Isradipine treatment for.[109] females has no negative impacts on the umbilical artery blood flow or the mother's renal or liver function.[110] Neonatal glucose levels did not differ significantly among females treated with beta blockers, CA channel blockers, or decreased salt intake.[111] Beta blockers were associated with fetal growth retardation (IUGR) in Mild PIH and Mild PE, although early oxprenolol treatment did not have these effects.[112-115] An analysis of the outcomes of oral antihypertensive medications in mild to moderate PIH, fetal development retardation was linked to low blood pressure. These quantitative studies' RCTs employed beta-blockers, calcium-channel blockers, hydralazine, a-methyldopa, thiazides, ketanserin, and clonidine among other medications. Antihypertensive medication during pregnancy causes moms to deliver kids with lower birth weights than the untreated group. According to a post-hoc study, a 10 mmHg drop in mean artery pressure was connected to a 145 g drop in mean birth weight.[116]

The treated group had reduced head circumference at birth, 2 months, 6 months, and 4 years old compared to control groups as a result of RCTs of methyldopa treatment during pregnancy.[117-121] However, an RCT treating mild to moderate PIH with nifedipine found no difference between the case and control groups.[122] Due to inadequate data, a Cochrane systematic study on the control of BP in mild to moderate pregnancy-induced hypertension was unable to produce definitive results. Therefore, for pregnant women with mild to severe pregnancy-induced hypertension who do not meet the criteria for pharmaceutical care, non-pharmacological management is optional.[116,123,124,125] The relationship between fetal maternal benefit and risk states that certain lifestyle choices, such complete physical restraint and limiting sodium intake, are not mandated in PIH or PE. One advice for the pre-pregnancy Because obesity and weight growth during pregnancy are risk factors for PIH, preeclampsia, or eclampsia, BMI-dependent studies on weight gain revealed that weight gain is significant. Regular monitoring and early detection of the emergence of severe conditions are necessary.[34,36,126] It is advised that preeclampsia-prone females take calcium supplements and 75 mg of aspirin daily, especially if their intake of calcium from food is insufficient. Due to a lack of research, vitamin C, D, and E are not recommended for preventing preeclampsia. Magnesium sulphate is advised for the treatment and prevention of severe PE.

Severe hypertension

Varied health organizations have different policies about when to start antihypertensive therapy in PIH. Antihypertensive drugs are indicated when blood pressure is above 150/95 mmHg, (European Society of Cardiology/European Society of Hypertension 2013 guideline Table 2). Women who have gestational hypertension in addition to their pre-existing hypertension, proteinuria brought on by pregnancy, or hypertension with complaints or related disorders at any time during the course of the pregnancy.[127] are advised to seek antihypertensive treatment at less than140/90 mmHg. Antihypertensive medication is used to maintain a healthy pregnancy and avoid problems including eclampsia and maternal cerebral hemorrhage. The treatment strategy for severe PIH is a regular reduction of blood pressure to less than 150/90 mmHg. the management of hypertension disorders during pregnancy according to the 2010 National Institute of Clinical Excellence (NICE) guideline.[128]

Methyldopa is regarded as a safe and reliable medicine of choice during pregnancy. In an emergency, beta blockers can be administered I/V. Calcium channel blockers with minimal side effects, like nifedipine or isradipine IV, are beneficial. Hypotension may be brought on by magnesium sulphate. In late pregnancy appears that beta blockers are both secure and productive. Due to its sluggish reaction and perinatal side effects, hydralazine is no longer the preferred medication in emergency situations.[129-131] Using diuretics to avoid preeclampsia and its effects did not significantly improve pregnancy outcomes in the treated group as compared to the control groups, according to a Cochrane analysis.[132 133], Due to the substantial risk of fetotoxicity, ACE inhibitors and angiotensin II receptor blockers are not advised for use during pregnancy.[134-136] When a pregnancy is confirmed, pregnant women who were taking ACE inhibitors or Angiotensin 2 receptor blockers should be encouraged to cease taking them and transition to a different, secure antihypertensive medicine.128 Studies have linked the use of the aforementioned antihypertensive medications to an increased risk of limb contractures, intrauterine growth retardation (IUGR), fetal hypotension, impaired ossification, impaired renal tubular development, decreased glomerular perfusion pressure lung hypoplasia, decreased or no fetal urine output, oligohydramnios, cranio-facial deformity, and anuria., and decreased placental and umbilical per According to epidemiological research, Compared to the control group, pregnant women on ACE inhibitors and ARBs had a greater prevalence of fetal congenital defects.[137]

Table 2: ESH/ESC 2013 recommendations for pregnancy-related hypertension.[127]

values of blood pressure	hypertension medication
>160/110 mm Hg	+
>150/95 mmHg, if persistent	+
>140/90 mm a) pregnancy-related high blood pressure and/or proteinuria, or b) pre-existing hypertension with pregnancy-induced hypertension added on top of it, or c) any time during pregnancy, hypertension with asymptomatic organ damage or symptoms.	+

Various antihypertensive medications were compared in numerous RCTs during pregnancy. 24 RCTs with at least two antihypertensive drug comparisons made up a Cochrane systematic review.[138] Due to insufficient statistics, the analysis failed to reach a definitive conclusion. It has been demonstrated that nifedipine and isradipine are more successful at treating chronic high blood pressure than hydralazine. There were no distinctions between prostacyclin and hydralazine. With increasing doses of the drug, ketonserin exerts alpha-1 receptor antagonistic action as a discriminatory S2-serotoninergic antagonist. It stops serotonin's effects on platelet aggregation and vasoconstriction.[139] In comparison to ketonserin, hydralazine has a lower effect and higher negative effects on persistently high blood pressure. The alpha-1 receptor antagonist urapidil acts as an agonist at serotonin 5-HT1A receptors. Additionally, it exerts a systemic sympatholytic effect through the central nervous system's serotonin 5HT1A receptors. Through lowering peripheral vascular resistance.[140] it lowers blood pressure. Statistics from studies contrasting hydralazine and urapidil were insufficient. According Urapidil was effective in 80% of cases in a prospective study of 100 females with severe PIH.[141]. The relationship between labetalol and hydralazine, nicardipine, and methyldopa had insufficient data as well. When compared to diazoxide, labetalol was associated with a slightly lower percentage of caesarian deliveries and hypotension. Magnesium sulphate (MgSO4) showed a decreased risk of eclampsia when compared to nimodipine, but a higher risk of PPH, obstinate high blood pressure, and maternal respiratory distress. Isosorbide was linked to a lower rate of Caesarean section when compared to magnesium sulphate MgSO4.

In a randomized controlled trial, 200 pregnant women with severe pregnancy-induced hypertension received either hydralazine or labetalol intravenously. Maternal palpitations and tachycardia were noted in the group of people who took hydralazine women, while hypotension and bradycardia were noted in the labetalol-treated

group.[142] study comparing the effectiveness of hydralazine and labetalol in treating severe pregnancy-induced hypertension found that neither drug had any impact on fetal Doppler.[143] On the other hand, those who received hydralazine treatment saw an increase in uterine artery resistance. When compared to diazoxide, intravenous hydralazine causes a much higher level of persistent hypertension.[144] The latter was also discovered in a study of hypertensive emergencies treated with intravenous hydralazine or nifedipine. There is no difference.[145] in the efficacy of hydralazine and urapidil, according to a second, smaller trial. In management, Sublingual nifedipine + plasma volume expansion, magnesium sulphate (MgSO4), and intravenous nitroglycerine + plasma volume expansion was all equally effective and had no negative effects on the mother or the fetus.[146] Not to mention, a double-blind RCT comparing the effectiveness of labetalol intravenous against nifedipine revealed no discernible differences in either the amount of time needed to achieve the therapeutic goal or overall efficacy.[147]

Pregnancy-related acute severe hypertension requires hospitalization as a medical emergency. as a starting point for therapy, labetalol, nifedipine, and hydralazine are employed.[148] The effectiveness of oral nifedipine and intravenous labetalol in treating pregnant women with hypertension and blood pressure greater than 160/110 mmHg is compared in a double-blind, randomized study. Between the two groups, there were no blood pressure rules.[149] As a second line of therapy, IV nitroglycerin, oral methyldopa, or oral clonidine may be employed. It is possible to utilize magnesium sulphate (MgSO4) in conjunction with an antihypertensive medication.

Table 3: lists Treatments for Severe Hypertension (Modified by SOGC Clinical Practice Guideline 2014).[148]

Anti-hypertensive agent	**Therapeutic Dose**	**Onset**	Duration	**Comments**
Labetalol	20 mg IV stat, then repeat at a rate of 1 to 2 mg/min for a total of up to 300 mg before switching to oral.	5 min	4 h	Contra indications: asthma, cardiac failure
Nifedipine	Every 30 minutes, swallow or bite a 5 to 10 mg pill.	5-10 min	6 h	
Hydralazine	To a maximum of 20 mg IV (or 30 mg IM), administer 5 mg IV stat, followed by 5 to 10 mg IV every 30 minutes, or 0.5 to 10 mg/hr/IV.	5 min		elevated danger of maternal hypotension

CONCLUSION

Thus, it may be said that PIH is the most prevalent multifactorial obstetric condition, and that more research is required to fully describe and comprehend its pathogenesis. The mother and the fetus are more negatively impacted by pregnancy-induced hypertension. The majority of research demonstrate a strong correlation between improved medical care and improved pregnancy outcomes. In the meantime, Antihypertensive drug use is fraught with danger, particularly in cases of mild hypertension. For a more detailed assessment of the relationship between risk for harmful effects on the fetus and maternal-fetal support, additional randomized controlled studies are necessary.

REFERENCES

1. World Health Organization. WHO Recommendations for prevention and treatment of pre-eclampsia and eclampsia, 2011.
2. Visintin C, Mugglestone MA, Almerie MQ, Nherera LM, James D, Walkinshaw S, Management of hypertensive disorders during pregnancy: summary of NICE guidance. BMJ, 2010; 341: c2207.
3. 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.
4. Savitz DA, Danilack VA, Engel SM, Elston B, Lipkind HS, Descriptive epidemiology of chronic hypertension, gestational hypertension, and preeclampsia in New York State, 1995-2004. Matern Child Health J, 2013; 18: 829-838.
5. Schneider S, Freerksen N, Maul H, Roehrig S, Fischer B, Hoeft B, Risk groups and maternal-neonatal complications of preeclampsia--current results from the national German Perinatal Quality Registry. J Perinat Med, 2011; 39: 257-265.
6. Klungsoyr K, Morken NH, Irgens L, Vollset SE, Skjaerven R, Secular trends in the epidemiology of preeclampsia throughout 40 years in Norway: prevalence, risk factors and perinatal survival. Paediatr Perinat Epidemiol, 2012; 26: 190-198.
7. Wildman K, Bouvier-Colle MH, Maternal mortality as an indicator of obstetric care in Europe. BJOG, 2004; 111: 164-169.
8. Khumanthem PD, Chanam MS, Samjetshabam RD, Maternal mortality and its causes in a tertiary center. J Obstet Gynaecol India, 2012; 62: 168-171.
9. You F, Huo K, Wang R, et al, Maternal mortality in Henan Province, China: changes between 1996 and, 2009. PLoS One, 7: e47153.
10. 10 Chhabra S, Kakani A, 2007 Maternal mortality due to eclamptic and non-eclamptic hypertensive disorders: a challenge. J Obstet Gynaecol, 2012; 27: 25-29.

11. Brichant G, Dewandre PY, Foidart JM, Brichant JF, Management of severe preeclampsia. Acta Clin Belg, 2010; 65: 163-169.
12. Duley L, The global impact of pre-eclampsia and eclampsia. Semin Perinatol, 2009; 33: 130-137.
13. Rattray DD, O'Connell CM, Baskett TF, Acute disseminated intravascular coagulation in obstetrics: a tertiary centre population review (1980 to 2009). J Obstet Gynaecol Can, 2012; 34: 341-347.
14. Matsuda Y, Hayashi K, Shiozaki A, Kawamichi Y, Satoh S, Saito S, Comparison of risk factors for placental abruption and placenta previa: case-cohort study. J Obstet Gynaecol Res, 2011; 37: 538-546.
15. Bhattacharya S, Campbell DM, The incidence of severe complications of preeclampsia. Hypertens Pregnancy, 2005; 24: 181-190.
16. Gong YH, Jia J, Lu DH, Dai L, Bai Y, Zhou R, Outcome and risk factors of early onset severe preeclampsia. Chin Med J (Engl), 2012; 125: 2623-2627.
17. Tuuli MG, Rampersad R, Stamilio D, Macones G, Odibo AO, Perinatal outcomes in women with preeclampsia and superimposed preeclampsia: do they differ? Am J Obstet Gynecol, 2011; 204: 508e1-7.
18. Bakker R, Steegers EA, Hofman A, Jaddoe VW, Blood pressure in different gestational trimesters, fetal growth, and the risk of adverse birth outcomes: the generation R study. Am J Epidemiol, 2011; 174: 797-806.
19. Yucesoy G, Ozkan S, Bodur H, et al, Maternal and perinatal outcome in pregnancies complicated with hypertensive disorder of pregnancy: a seven year experience of a tertiary care center. Arch Gynecol Obstet, 2005; 273: 43-49.
20. Ahmad AS, Samuelsen SO, Hypertensive disorders in pregnancy and fetal death at different gestational lengths: a population study of 2 121 371 pregnancies. BJOG, 2012; 119: 1521-1528.
21. Masoura S, Kalogiannidis I, Margioula-Siarkou C, et al, Neonatal outcomes of late preterm deliveries with pre-eclampsia. Minerva, 2012; 64: 109-115.
22. Liu CM, Chang SD, Cheng PJ, Relationship between prenatal care and maternal complications in women with preeclampsia: implications for continuity and discontinuity of prenatal care. Taiwan J Obstet Gynecol, 2012; 51: 576-582.
23. Mitka M, Any hypertension during pregnancy raises risk for several chronic diseases: JAMA, 2013; 309: 971-972.
24. Mannisto T, Mendola P, Vaarasmaki M, et al, Elevated blood pressure in pregnancy and subsequent chronic disease risk. Circulation, 2013; 127: 681-690.
25. Wilson BJ, Watson MS, Prescott GJ, et al, Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. BMJ, 2003; 326: 845.
26. Feig DS, Shah BR, Lipscombe LL, et al, Preeclampsia as a Risk Factor for Diabetes: A PopulationBased Cohort Study. PLoS Med, 2013; 10: e1001425.
27. Tuovinen S, Raikkonen K, Pesonen AK, et al, Hypertensive disorders in pregnancy and risk of severe mental disorders in the offspring in adulthood: the Helsinki Birth Cohort Study. J Psychiatr Res, 2012; 46: 303-310.
28. Miettola S, Hartikainen AL, Vaarasmaki M, et al, Offspring's blood pressure and metabolic phenotype after exposure to gestational hypertension in utero. Eur J Epidemiol, 2013; 28: 87-98.
29. Kajantie E, Eriksson JG, Osmond C, Thornburg K, Barker DJ, Pre-eclampsia is associated with increased risk of stroke in the adult offspring: the Helsinki birth cohort study. Stroke, 40: 1176-1180.
30. Tuovinen S, Raikkonen K, Kajantie E, et al, Hypertensive disorders in pregnancy and cognitive decline in the offspring up to old age. Neurology, 2012; 79: 1578-1582.
31. Tuovinen S, Eriksson JG, Kajantie E, et al, Maternal hypertensive disorders in pregnancy and selfreported cognitive impairment of the offspring 70 years later: the Helsinki Birth Cohort Study. Am J Obstet Gynecol, 2013; 208: 200e1-200e9.
32. Roberts JM, Pearson G, Cutler J, Lindheimer M, Summary of the NHLBI working group on research on hypertension during pregnancy. Hypertension, 2003; 41: 437-445.
33. Koual M, Abbou H, Carbonnel M, Picone O, Ayoubi JM, Short-term outcome of patients with preeclampsia. Vasc Health Risk Manag, 2013; 9: 143-148.
34. Coghill AE, Hansen S, Littman AJ, Risk factors for eclampsia: a population-based study in Washington State, 1987-2007. Am J Obstet Gynecol, 2011; 205: 553e1-7.
35. Anderson NH, Sadler LC, Stewart AW, Fyfe EM, McCowan LM, Ethnicity, body mass index and risk of pre-eclampsia in a multiethnic New Zealand population. Aust N Z J Obstet Gynaecol, 2012; 52: 552-558.
36. Schneider S, Freerksen N, Maul H, Roehrig S, Fischer B, Hoeft B, Risk groups and maternal-neonatal complications of preeclampsia--current results from the national German Perinatal Quality Registry. J Perinat Med, 2011; 39: 257-265.
37. Bener A, Saleh NM, The impact of socio-economic, lifestyle habits, and obesity in developing of pregnancyinduced hypertension in fast-growing country: global comparisons. Clin Exp Obstet Gynecol, 2013; 40: 52-57.
38. Lucovnik M, Tul N, Verdenik I, Novak Z, Blickstein I, Risk factors for preeclampsia in twin pregnancies: a population-based matched case-control study. J Perinat Med, 2012; 40: 379-382.
39. Mostello D, Catlin TK, Roman L, Holcomb WL Jr, Leet T, Preeclampsia in the parous woman: who is at risk? Am J Obstet Gynecol, 2002; 187: 425-429.
40. Dalmaz CA, Santos KG, Botton MR, Roisenberg I, Risk factors for hypertensive disorders of pregnancy

in southern Brazil. Rev Assoc Med Bras, 2011; 57: 692-696.
41. Melamed N, Hadar E, Peled Y, Hod M, Wiznitzer A, Yogev Y, Risk for recurrence of preeclampsia and outcome of subsequent pregnancy in women with preeclampsia in their first pregnancy. J Matern Fetal Neonatal Med, 2012; 25: 2248-2251.
42. Danza A, Ruiz-Irastorza G, Khamashta M, Antiphospohlipid syndrome in obstetrics. Best Pract Res Clin Obstet Gynaecol, 2012; 26: 65-76.
43. Clark EA, Silver RM, Branch DW, Do antiphospholipid antibodies cause preeclampsia and HELLP syndrome? Curr Rheumatol Rep, 2007; 9: 219-925.
44. Wei SQ, Qi HP, Luo ZC, Fraser WD, Maternal vitamin D status and adverse pregnancy outcomes: a systematic review and meta-analysis. J Matern Fetal Neonatal Med, 26: 889-899.
45. Tabesh M, Salehi-Abargouei A, Tabesh M, Esmaillzadeh A, Maternal Vitamin D Status and Risk of Pre- Eclampsia: A Systematic Review and Meta-Analysis. J Clin Endocrinol Metab, 2013; 98: 3165-173.
46. Ouzounian JG, Elkayam U, Physiologic changes during normal pregnancy and delivery. Cardiol Clin, 2012; 30: 317-329.
47. Valdes G, Corthorn J, Challenges posed to the maternal circulation by pregnancy. Integr Blood Press Control, 2011; 4: 45-53.
48. Valdes G, Kaufmann P, Corthorn J, Erices R, Brosnihan KB, Joyner-Grantham J, 2009 Vasodilator factors in the systemic and local adaptations to pregnancy. Reprod Biol Endocrinol 7: 79.
49. Seeliger C, Brueckmann A, Schleussner E, Maternal endothelial function in the course of pregnancy and postpartum - ultrasound-based longitudinal assessment using flow-mediated dilatation (FMD). Ultraschall Med, 2012; 33: E126-131.
50. van Drongelen J, Hooijmans CR, Lotgering FK, Smits P, Spaanderman ME, Adaptive changes of mesenteric arteries in pregnancy: a meta-analysis. Am J Physiol Heart Circ Physiol, 2012; 303: H639-657.
51. Hunter S, Robson SC, Adaptation of the maternal heart in pregnancy. Br Heart J, 1992; 68: 540-543.
52. Savu O, Jurcut R, Giusca S, et al, Morphological and functional adaptation of the maternal heart during pregnancy. Circ Cardiovasc Imaging, 2012; 5: 289-297.
53. Roberts JM, Hubel CA, The two stage model of preeclampsia: variations on the theme. Placenta, 2009; 30: Suppl A: S32-37.
54. Santillan MK, Santillan DA, Sigmund CD, Hunter SK, From molecules to medicine: a future cure for preeclampsia? Drug News Perspect, 2009; 22: 531-541.
55. Al-Nasiry S, Ghossein-Doha C, Polman S, et al, Metabolic syndrome after pregnancies complicated by pre-eclampsia or small for gestational age: a retrospective cohort. BJOG, 2014; DOI: 10.1111/1471-0528.13117.
56. Abhari FR, Ghanbari Andarieh M, Farokhfar A, Ahmady S, Estimating rate of insulin resistance in patients with preeclampsia using HOMA-IR index and comparison with non preeclampsia pregnant women. Biomed Res Int, 2014; 140851.
57. Spracklen CN, Smith CJ, Saftlas AF, Robinson JG, Ryckman KK, Maternal hyperlipidemia and the risk of preeclampsia: a meta-analysis. Am J Epidemiol, 2014; 180: 346-358.
58. Wang A, Rana S, Karumanchi SA, Preeclampsia: the role of angiogenic factors in its pathogenesis. Physiology (Bethesda), 2009; 24: 147-158.
59. Faas MM, Spaans F, De Vos P, Monocytes and macrophages in pregnancy and pre-eclampsia. Front Immunol, 2014; 5: 298.
60. Sanchez-Aranguren LC, Prada CE, Riano-Medina CE, Lopez M, Endothelial dysfunction and preeclampsia: role of oxidative stress. Front Immunol 5: 372.
61. Bueno-Sanchez JC, Agudelo-Jaramillo B, EscobarAguilerae LF, et al, 2013 Cytokine production by non- stimulated peripheral blood NK cells and lymphocytes in early-onset severe pre-eclampsia without HELLP. J Reprod Immunol, 2014; 97: 223-231.
62. Burton GJ, Charnock-Jones DS, Jauniaux E, Regulation of vascular growth and function in the human placenta. Reproduction, 2009; 138: 895-902.
63. Fagiani E, Christofori G, Angiopoietins in angiogenesis. Cancer Lett, 2013; 328: 18-26.
64. Baker PN, Krasnow J, Roberts JM, Yeo KT, Elevated serum levels of vascular endothelial growth factor in patients with preeclampsia. Obstet Gynecol, 1995; 86: 815-821.
65. Aref S, Goda H, Abdelaal E, Circulating vascular growth factor (VEGF) angiopoietin-1 (Angi-1) and soluble tie-2 receptor in pregnancy complicated with pre-eclampsia: A prospective study. J Obstet Gynaecol India, 2013; 63: 316-320.
66. Bhavina K, Radhika J, Pandian SS, VEGF and eNOS expression in umbilical cord from pregnancy complicated by hypertensive disorder with different severity. Biomed Res Int, 2014; 982159.
67. Bolin M, Wiberg-Itzel E, Wikstrom AK, et al, Angiopoietin-1/angiopoietin-2 ratio for prediction of preeclampsia. Am J Hypertens, 2009; 22: 891-895.
68. Park JE, Chen HH, Winer J, Houck KA, Ferrara N, Placenta growth factor. Potentiation of vascular endothelial growth factor bioactivity, in vitro and in vivo, and high affinity binding to Flt-1 but not to Flk-1/ KDR. J Biol Chem, 1994; 269: 25646-25654.
69. Jang YS, Choi IH, Contrasting roles of different endoglin forms in atherosclerosis. Immune,2014; 14: 237-240.
70. Clark DE, Smith SK, He Y, et al, A vascular endothelial growth factor antagonist is produced by the human placenta and released into the maternal circulation. Biol Reprod, 1998; 59: 1540-1548.

71. Guller S, Tang Z, Ma YY, Di Santo S, Sager R, Schneider H, Protein composition of microparticles shed from human placenta during placental perfusion: Potential role in angiogenesis and fibrinolysis in preeclampsia. Placenta, 2011; 32: 63-69.
72. Conti E, Zezza L, Ralli E, et al, Growth factors in preeclampsia: a vascular disease model. A failed vasodilation and angiogenic challenge from pregnancy onwards? Cytokine Growth Factor Rev,2013; 24: 411-425.
73. Stubert J, Ullmann S, Bolz M, et al, Prediction of preeclampsia and induced delivery at <35 weeks gestation by sFLT-1 and PlGF in patients with abnormal midtrimester uterine Doppler velocimetry: a prospective cohort analysis. BMC Pregnancy Childbirth, 2014; 14: 292.
74. Forest JC, Theriault S, Masse J, Bujold E, Giguere Y, Soluble Fms-like tyrosine kinase-1 to placental growth factor ratio in mid-pregnancy as a predictor of preterm preeclampsia in asymptomatic pregnant women. Clin Chem Lab Med, 2014; 52: 1169-1178.
75. Kleinrouweler CE, Wiegerinck MM, Ris-Stalpers C, et al, Accuracy of circulating placental growth factor, vascular endothelial growth factor, soluble fms-like tyrosine kinase 1 and soluble endoglin in the prediction of pre-eclampsia: a systematic review and meta-analysis. BJOG, 2012; 119: 778-787.
76. Bezerra PC, Leao MD, Queiroz JW, et al, Family history of hypertension as an important risk factor for the development of severe preeclampsia. Acta Obstet Gynecol Scand, 2010; 89: 612-617.
77. Esplin MS, Fausett MB, Fraser A, et al, Paternal and maternal components of the predisposition to preeclampsia. N Engl J Med, 2001; 344: 867-872.
78. Williams PJ, Broughton Pipkin F, The genetics of pre-eclampsia and other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecol, 2011; 25: 405-417.
79. Yang J, Shang J, Zhang S, Li H, Liu H, The role of the renin-angiotensin-aldosterone system in preeclampsia: genetic polymorphisms and microRNA. J Mol Endocrinol, 2013; 50: R53-66.
80. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al, ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J, 2011; 32: 3147-3197.
81. Lowe SA, Brown MA, Dekker GA, et al, Guidelines for the management of hypertensive disorders of pregnancy 2008. Aust N Z J Obstet Gynaecol, 2009; 49: 242-246.
82. Mancia G, De Backer G, Dominiczak A, et al, Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J, 2007; 28: 1462-1536.
83. National Collaborating Centre for Women's and Children's Health (UK), NICE Clinical Guidelines, No. 107. In: Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. London: RCOG Press, 2010;
84. Kazimierak W, Kowalska-Koprek U, Karowicz-Bilinska A, et al, 24-hour Holter measurement of blood pressure in pregnant women and effectiveness of the treatment. Ginekol Pol, 2008; 79: 174-176.
85. Davis GK, Mackenzie C, Brown MA, et al, Predicting transformation from gestational hypertension to preeclampsia in clinical practice: a possible role for 24 hour ambulatory blood pressure monitoring. Hypertens Pregnancy, 2007; 26: 77-87.
86. Giannubilo SR, Dell'Uomo B, Tranquilli AL, Perinatal outcomes, blood pressure patterns and risk assessment of superimposed preeclampsia in mild chronic hypertensive pregnancy. Eur J Obstet Gynecol Reprod Biol, 2006; 126: 63-67.
87. Biswas A, Choolani MA, Anandakumar C, Arulkumaran S, Ambulatory blood pressure monitoring pregnancy induced hypertension. Acta Obstet Gynecol Scand, 1997; 76: 829-833.
88. Hermida RC, Ayala DE, Iglesias M, Circadian rhythm of blood pressure challenges office values as the "gold standard" in the diagnosis of gestational hypertension. Chronobiol Int, 2003; 20: 135-156.
89. Brown MA, Mangos G, Davis G, Homer C, The natural history of white coat hypertension during pregnancy. BJOG, 2005; 112: 601-606.
90. Brown M, Is there a role for ambulatory blood pressure monitoring in pregnancy? Clin Exp Pharmacol Physiol, 2013; 41: 16-21.
91. Benedetto C, Zonca M, Giarola M, Maula V, Chiarolini L, Carandente F, 24-hour blood pressure monitoring to evaluate the effects of nifedipine in pre-eclampsia and in chronic hypertension in pregnancy. Br J Obstet Gynaecol, 1997; 104: 682-688.
92. Staessen JA, Asmar R, De Buyzere M, et al, Task Force II: blood pressure measurement and cardiovascular outcome. Blood Press Monit, 2001; 6: 355-370.
93. Magee LA, Abalos E, von Dadelszen P, Sibai B, Easterling T, Walkinshaw S, How to manage hypertension in pregnancy effectively. Br J Clin Pharmacol, 2011; 72: 394-401.
94. Szczepaniak-Chichel L, Tykarski A, Treatment of arterial hypertension in pregnancy in relation to current guidelines of the Polish Society of Arterial Hypertension from 2011. Ginekol Pol, 2012; 83: 778-783.
95. Hogstedt S, Lindeberg S, Axelsson O, et al, A prospective controlled trial of metoprolol-hydralazine treatment in hypertension during pregnancy. Acta Obstet Gynecol Scand, 1985; 64: 505-510.

96. Gruppo di Studio Ipertensione in Gravidanza, Nifedipine versus expectant management in mild to moderate hypertension in pregnancy. Gruppo di Studio Ipertensione in Gravidanza. Br J Obstet Gynaecol, 1998; 105: 718-722.
97. Sibai BM, Barton JR, Akl S, Sarinoglu C, Mercer BM, A randomized prospective comparison of nifedipine and bed rest versus bed rest alone in the management of preeclampsia remote from term. Am J Obstet Gynecol, 1992; 167: 879-884.
98. 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: 960-966.
99. Cruickshank DJ, Robertson AA, Campbell DM, MacGillivray I, Does labetalol influence the development of proteinuria in pregnancy hypertension? A randomised controlled study. Eur J Obstet Gynecol Reprod Biol, 1992; 45: 47-51.
100. Barton JR, Mercer BM, Sibai BM, The effect of nifedipine on urinary excretion of calcium in preeclampsia. Am J Perinatol, 1997; 14: 609-612.
101. Rubin PC, Butters L, Clark DM, et al, Placebocontrolled trial of atenolol in treatment of pregnancyin associated hypertension. Lancet, 1983; 1: 431-434.
102. Pickles CJ, Symonds EM, Broughton Pipkin F, 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.
103. Pickles CJ, Broughton Pipkin F, Symonds EM, A randomised placebo controlled trial of labetalol in the treatment of mild to moderate pregnancy induced hypertension. Br J Obstet Gynaecol, 1992; 99: 964-968.
104. Redman CW, Fetal outcome in trial of antihypertensive treatment in pregnancy. Lancet, 1976; 2: 753-756.
105. Elhassan EM, Mirghani OA, Habour AB, Adam I, Methyldopa versus no drug treatment in the management of mild pre-eclampsia. East Afr Med J 79: 172-175.
106. Weitz C, Khouzami V, Maxwell K, Johnson JW, Treatment of hypertension in pregnancy with methyldopa: a randomized double blind study. Int J Gynaecol Obstet, 2002; 25: 35-40.
107. Molvi SN, Mir S, Rana VS, Jabeen F, Malik AR, 2012 Role of antihypertensive therapy in mild to moderate pregnancy-induced hypertension: a prospective randomized study comparing labetalol with alpha methyldopa. Arch Gynecol Obstet, 1987; 285: 1553-1562.
108. Phippard AF, Fischer WE, Horvath JS, et al, Early blood pressure control improves pregnancy outcome in primigravid women with mild hypertension. Med J Aust, 1991; 154: 378-382.
109. Ismail AA, Medhat I, Tawfic TA, Kholeif A, Evaluation of calcium-antagonist (Nifedipine) in the treatment of pre-eclampsia. Int J Gynaecol Obstet, 1993; 40: 39-43.
110. Wide-Swensson DH, Ingemarsson I, Lunell NO, et al, Calcium channel blockade (isradipine) in treatment of hypertension in pregnancy: a randomized placebo-controlled study. Am J Obstet Gynecol,1995; 173: 872-878.
111. Darcie S, Leone CR, Calil VM, Prescinotti EP, Kahhale S, Zugaib M, Glycemia in newborns of hypertensive mothers according to maternal treatment. Rev Hosp Clin Fac Med Sao Paulo, 2004; 59: 244-250.
112. Butters L, Kennedy S, Rubin PC, Atenolol in essential hypertension during pregnancy. BMJ, 1990; 301: 587-589.
113. 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.
114. Plouin PF, Breart G, Llado J, et al, A randomized comparison of early with conservative use of antihypertensive drugs in the management of pregnancy-induced hypertension. Br J Obstet Gynaecol, 1990; 97: 134-141.
115. Cruickshank DJ, Campbell DM, Atenolol in essential hypertension during pregnancy. BMJ, 1990; 301: 1103.
116. von Dadelszen P, Ornstein MP, Bull SB, Logan AG, Koren G, Magee LA, Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: a meta-analysis. Lancet, 2000; 355: 87-92.
117. Cockburn J, Moar VA, Ounsted M, Redman CW, Final report of study on hypertension during pregnancy: the effects of specific treatment on the growth and development of the children. Lancet, 1982; 1: 647-649.
118. Moar VA, Jefferies MA, Mutch LM, Ounsted MK, Redman CW, Neonatal head circumference and the treatment of maternal hypertension. Br J Obstet Gynaecol, 1978; 85: 933-937.
119. Mutch LM, Moar VA, Ounsted MK, Redman CW, Hypertension during pregnancy, with and without specific hypotensive treatment. I. Perinatal factors and neonatal morbidity. Early Hum Dev, 1977; 1: 47-57.
120. Mutch LM, Moar VA, Ounsted MK, Redman CW, Hypertension during pregnancy, with and without specific hypotensive treatment. II. The growth and development of the infant in the first year of life. Early Hum Dev, 1977; 1: 59-67.
121. Ounsted MK, Moar VA, Good FJ, Redman CW, Hypertension during pregnancy with and without specific treatment; the development of the children at the age of four years. Br J Obstet Gynaecol, 1980; 87: 19-24.
122. Bortolus R, Ricci E, Chatenoud L, Parazzini F, Nifedipine administered in pregnancy: effect on the

development of children at 18 months. BJOG, 2000; 107: 792-794.
123. Abalos E DL, Steyn DW, Henderson-Smart DJ, Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cohrane Database Syst Rev, 2007; 1: CD002252.
124. Magee LA, Elran E, Bull SB, Logan A, Koren G, Risks and benefits of beta-receptor blockers for pregnancy hypertension: overview of the randomized trials. Eur J Obstet Gynecol Reprod Biol, 2000; 88: 15-26.
125. Nabhan AF, Elsedawy MM, Tight control of mildmoderate pre-existing or non-proteinuric gestational hypertension. Cochrane Database Syst Rev, 2011: 7; CD006907.
126. Gaillard R, Steegers EA, Hofman A, Jaddoe VW, Associations of maternal obesity with blood pressure and the risks of gestational hypertensive disorders. The Generation R Study. J Hypertens, 2011; 29: 937-944.
127. Task Force Members, ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J, 2013; 34: 2159-2219.
128. Hypertension in Pregnancy: The Management of Hypertensive Disorders During Pregnancy. National Collaborating Centre for Women's and Children's Health. London: RCOG Press, 2010;
129. Magee LA, Cham C, Waterman EJ, Ohlsson A, von Dadelszen P, Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. BMJ, 2003; 327: 955-960.
130. 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: 419-436.
131. Solomon CG, Seely EW, Hypertension in pregnancy. Endocrinol Metab Clin North Am, 2011; 40: 847-863.
132. Folic M, Folic N, Varjacic M, Jakovljevic M, Jankovic S, Antihypertensive drug for therapy for hypertensive disorders in pregnancy. Acta Medica Medianae, 2008; 47: 65-72.
133. Churchill D, Beevers GD, Meher S, Rhodes C, Diuretics for preventing pre-eclampsia. Cochrane Database Syst Rev, 2007; 1: CD004451.
134. Cooper WO, Hernandez-Diaz S, Arbogast PG, et al, Major congenital malformations after first trimester exposure to ACE inhibitors. N Engl J Med, 2006; 354: 2443-2451.
135. Deva M, Kara T, ACE inhibitor fetopathy: a case series and survey of opinion amongst New Zealand paediatricians, obstetricians, neonatologists, and nephrologists. N Z Med J, 2012; 125: 51-61.
136. Bullo M, Tschumi S, Bucher BS, Bianchetti MG, Simonetti GD, Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists: a systematic review. Hypertension,2012; 60: 444-450.
137. Polifka JE, Is there an embryopathy associated with first-trimester exposure to angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists? A critical review of the evidence. Birth Defects Res A Clin Mol Teratol, 2012; 94: 576-598.
138. Duley L, Henderson-Smart DJ, Meher S, Drugs for treatment of very high blood pressure during pregnancy. Cochrane Database Syst Rev, 2006; 3: CD001449.
139. Brogden RN, Sorkin EM, Ketanserin. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in hypertension and peripheral vascular disease. Drugs, 1990; 40: 903-949.
140. Buch J, Urapidil, a dual-acting antihypertensive agent: Current usage considerations. Adv Ther, 2010; 27: 426-443.
141. Carles G, Helou J, Dallah F, Ibrahim N, Alassas N, Youssef M, Use of injectable urapidil in pregnancy-induced hypertension and preeclamp Obstet Biol Reprod, 2012; 41: 645-649.
142. Vigil-De Gracia P, Lasso M, Ruiz E, Vega-Malek JC, de Mena FT, Lopez JC, Severe hypertension in pregnancy: hydralazine or labetalol. A randomized clinical trial. Eur J Obstet Gynecol Reprod Biol, 2006; 128: 157-162.
143. Baggio MR, Martins WP, Calderon AC, et al, Changes in fetal and maternal Doppler parameters observed during acute severe hypertension treatment with hydralazine or labetalol: a randomized controlled trial. Ultrasound Med Biol, 2011; 37: 53-85.
144. Hennessy A, Thornton CE, Makris A, et al, A randomised comparison of hydralazine and mini-bolus diazoxide for hypertensive emergencies in pregnancy: the PIVOT trial. Aust N Z J Obstet Gynaecol, 2007; 47: 279-285.
145. Wacker JR, Wagner BK, Briese V, et al, Antihypertensive therapy in patients with pre-eclampsia: A prospective randomised multicentre study comparing dihydralazine with urapidil. Eur J Obstet Gynecol Reprod Biol, 2006; 127: 160-165.
146. Manzur-Verastegui S, Mandeville PB, Gordillo-Moscoso A, Hernandez-Sierra JF, Rodriguez-Martinez M, Efficacy of nitroglycerine infusion versus sublingual nifedipine in severe pre-eclampsia: a randomized, triple-blind, controlled trial. Clin Exp Pharmacol Physiol, 2008; 35: 580-585.
147. Raheem IA, Saaid R, Omar SZ, Tan PC, Oral nifedipine versus intravenous labetalol for acute blood pressure control in hypertensive emergencies of pregnancy: a randomised trial. BJOG, 2012; 119: 78-85.
148. Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P, SOGC Hypertension Guideline Committee, 2014 Diagnosis, Evaluation, and Management of the Hypertensive Disorders of

Pregnancy: executive Summary. J Obstet Gynaecol Can, 2014; 36: 575-576.
149. Raheem IA, Saaid R, Omar SZ, Tan PC, Oral nifedipine versus intravenous labetalol for acute blood pressure control in hypertensive emergencies of pregnancy: a randomised trial. BJOG, 2012; 119: 78-85.