Review Article

Pregnancy-Induced Hypertension and Preeclampsia: A Review of Current Antihypertensive Pharmacologic Treatment Options

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Abstract

Hypertensive emergencies are the second leading cause of maternal mortality during pregnancy, affecting one out of ten pregnancies. Maternal and fetal complications can be devastating and may include stroke, seizures, placental abruption, fetal death, and maternal death. Although prompt recognition and treatment can greatly reduce the morbidity and mortality associated with pregnancy-induced hypertension and preeclampsia, the only known resolution is delivery of the fetus and placenta. Treatment is a balance between managing maternal symptoms to prevent disease progression and prolonging gestation to improve fetal outcomes. Management of pregnancy- induced hypertension and preeclampsia depends on the gestational stage at presentation, severity of disease, and the condition of the woman and fetus. Most common options may include medication therapies and induction of labor. 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, the current research that supports the safety and efficacy of these agents, and the factors that may play a role in deciding between medication therapy versus induction of labor.

Introduction

Hypertensive conditions during pregnancy contribute greatly to maternal morbidity and mortality around the world [1]. In the United States, preeclampsia accounts for 15% to 17.6% of maternal deaths [1,2] Hypertension complicates approximately one out of every ten pregnancies [1]. The only resolution for preeclampsia and pregnancy-induced hypertension, also known as gestational hypertension, is delivery of the fetus and placenta [1,3] When hypertensive disorders complicate a pregnancy before full term, the risks of preterm delivery must be considered in addition to the risks to the mother. Often medications are used to manage maternal blood pressure and prolong gestation. Although many treatment options exist for hypertension in the general population, additional consideration must be utilized when selecting a pharmacotherapeutic agent in pregnancy. The chosen medication must not only be effective and safe for the mother, but also have minimal impact on the development of the fetus.

The complications of uncontrolled high blood pressure during pregnancy affect multiple organ systems and can be detrimental to both mother and fetus [1,3,4] 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 morbidity and mortality for the fetus as well. 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 death [5].

While the exact causes of preeclampsia are not well understood, certain factors may increase a woman's risk of developing pregnancy-induced hypertension or preeclampsia. It is widely known that preeclampsia occurs most often during a woman's first pregnancy [3,5,6,7]. Additionally, women with a history of preeclampsia are more likely to have recurrence in a subsequent pregnancy [3,5,6]. Multiple gestations, such as twins or triplets, increase risk [3,6]. 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 [1,5,6]. Women over the age of 35 years and women of African American race are considered more at risk for developing preeclampsia [3,7].

While some treatments may lower blood pressure and minimize adverse effects, the only known resolution for pregnancy-induced hypertension and preeclampsia is delivery of the placenta, with signs and symptoms typically resolving shortly after delivery [3,4] . Prompt recognition of pregnancy-induced hypertension and preeclampsia is vital in preventing progression of the condition. The exact staging of hypertensive disorders during pregnancy varies slightly between several organizations. These groups maintain their own definitions of staging and diagnostic criteria for blood pressure disorders during pregnancy [1,5,7,8]. Table 1 compares several classification systems used to stage hypertensive disorders during pregnancy.

Severe symptoms include: headaches, visual disturbances, oliguria, non-reassuring fetal testing. Defines as less severe and more severe compared to mild/severe classifications.

The diagnostic criteria for gestational hypertension and

Table 1: Classifications of Hypertensive Disorders During Pregnancy [1,5,7,8,9].

	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	Royal College of Obstetricians and Gynecologists (RCOG)
Chronic Hypertension	BP ≥ 140/90 mm Hg Present before 20 weeks	BP ≥ 140/90 mm Hg Present before 20 weeks	BP ≥ 140/90 mm Hg Present before 20 weeks	***
Gestational Hypertension	BP ≥ 140/90 mm Hg Onset after 20 weeks	BP ≥ 140/90 mm Hg Present after 20 weeks	BP ≥ 140/90 mm Hg Onset after 20 weeks	***
Preeclampsia	BP ≥140/90 mm Hg Onset after 20 weeks Proteinuria*	BP ≥ 140/90 mm Hg Onset after 20 weeks Proteinuria*	BP ≥140/90 mm Hg Onset after 20 weeks Proteinuria*	Gestational hypertension Proteinuria*
Severe Preeclampsia	BP > 160/110 mm Hg Excessive proteinuria**	BP ≥ 160/110 mm Hg	DBP ≥ 110 mm Hg Severe symptoms^	BP ≥ 170/110 mm Hg (severe hypertension)
Preeclampsia Superimposed on Chronic Hypertension	BP ≥ 140/90 mm Hg Present before 20 weeks New onset proteinuria	BP ≥ 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
**Excessive proteinuria is defined as > 5 grams on 24 hour urine collection
***RCOG follows NICE guidelines

preeclampsia generally focus on measurements of blood pressure and proteinuria, with high blood pressure readings observed on at least two occasions six hours apart [7]. Several other signs and symptoms may indicate a hypertensive disorder during pregnancy and require additional evaluation. Persistent severe headaches, changes in vision, sudden swelling of face, hands or feet, vomiting, or epigastric pain may be related to increases in blood pressure [6,10]. Preeclampsia may also lead to decreased platelets, elevated serum creatinine, and an increase in liver enzymes [6,10].

The goals in treating pregnancy-induced hypertension and preeclampsia focus on both maternal and fetal well-being. The stage of pregnancy determines the course of action, along with an assessment of fetal and maternal risks and benefits. Prolonging gestation generally leads to improved outcomes for the fetus/neonate, yet may increase maternal morbidity. Full resolution of this condition is delivery of the placenta.

Objective

The objective of this literature review was to explore the pharmacologic interventions that have been utilized in treating women with pregnancy-induced hypertension and preeclampsia. The primary goal was to determine which medications were most commonly used to treat this population. Rationale for use, including the risks and benefits of individual medications, were examined. Additionally, this literature review investigated when pharmacologic intervention was initiated, as well as current data regarding when induction of labor was preferred over pharmacologic management.

Methodology

The focus of this literature review was to assess women of childbearing age who have been diagnosed with pregnancy-induced hypertension or preeclampsia. Women affected in first pregnancies or subsequent pregnancies were included, as determined by the individual study parameters. Investigation included only preeclampsia or hypertensive disorders developed after 20 weeks gestation. Research investigating chronic or preexisting hypertensive disorders and women who develoed preeclampsia superimposed on chronic hypertension were excluded from the population of interest.

Searches for relevant data were conducted utilizing multiple databases, including PubMed and Ovid. Searches included combinations of the key terms: pregnancy, hypertension, gestational hypertension, pregnancy-induced hypertension, preeclampsia, treatment, pharmacologic treatment, methyldopa, labetalol, nicardipine, nifedipine, hydralazine, and induction. Supplementary drug information references were accessed through Micromedex and LexiComp. Primary, secondary and tertiary resources were considered for inclusion in this review, including relevant background information from sources such as the American College of Obstetricians and Gynecologists and current textbooks.

In order to be considered for inclusion in this review, articles were required to discuss either pregnancy-induced hypertension or preeclampsia, or both. Articles of particular interest included pharmacologic treatment options and the outcomes for both mother and fetus, including safety and efficacy data. Both review and primary research articles were included. Literature published between 2000 and the present were preferentially included to elucidate the more recent developments in the area of interest.

Exclusion criteria included studies focusing primarily on treatment and management of chronic or preexisting hypertension during pregnancy. Articles not available in English were also excluded.

Results

Pharmacologic treatments

Pharmacologic treatment of pregnancy-induced hypertension and preeclampsia does not lead to resolution [1,3,4]. The only known resolution is delivery of the fetus and placenta [1,3,4]. The focus of pharmacologic treatment is management of the maternal signs and symptoms so gestation may be prolonged and fetal outcomes improved [8]. Treatment often requires balancing maternal safety and fetal safety. An increased gestation leads 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 [1].

Numerous medications are available to treat hypertension and caution should be used when selecting an agent for use during pregnancy. Treating pregnancy-induced hypertension and preeclampsia requires knowledge of the mechanism of action and the safety and efficacy profiles of the medications. Commonly used antihypertensive pharmacologic agents include labetalol, hydralazine, methyldopa, nicardipine, or nifedipine [1,3,5-7].

Certain classes of antihypertensive medications should not be used during pregnancy, including angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), some beta-blockers, and diuretics [5]. ACEIs and ARBs have been associated with detrimental effects on fetal growth and development, including renal failure and death of the fetus [11,12]. When studied 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 [5,11]. Oligohydramnios, cardiovascular, central nervous system malformations, hypotension, reversible or irreversible renal failure, and death have been reported in the second and third trimesters with use of ACEIs [5,11]. ARBs have limited human safety data during pregnancy, but as ARBs act on the renin-angiotensin-aldosterone system in a similar manner to ACEIs, the risks are thought to be comparable to that of ACEIs [5,12]. Additionally, some beta-blockers such as atenolol and metoprolol have been associated with an increased risk of intrauterine growth restriction and are therefore avoided [5,13]. Diuretics, although often helpful in treating hypertension, do not have much of a role in treating pregnancy-induced hypertension and preeclampsia since women with these conditions may already be in a state of decreased volume [5]. Use of diuretics may further deplete circulating volume, potentially leading to hypovolemia and decreased placental perfusion [5].

Other pharmacologic agents may be used to prevent seizures and progression to eclampsia. The medication most commonly used is magnesium sulfate, which decreases the incidence of seizures by 50 percent [5]. Magnesium sulfate has not been associated with any significant maternal or fetal morbidity [5].

This remainder of this discusses focuses on the five commonly used antihypertensive medications and their roles in the treatment of high blood pressure in pregnancy-induced hypertension and preeclampsia.

Hydralazine

Hydralazine lowers blood pressure by decreasing systemic vascular resistance through direct vasodilation of arterioles [14]. Acute maternal hypertensive emergency is the most common use of parenteral hydralazine during pregnancy [15].

A 2003 meta-analysis by Magee et al evaluated the use of hydralazine during pregnancy [16]. When compared to nifedipine, hydralazine was found to be less efficacious in lowering maternal blood pressure [16]. Labetalol and hydralazine did not differ significantly in effectiveness [16]. Increased incidence of certain adverse maternal and fetal outcomes was observed with hydralazine compared to other antihypertensive medications in the Magee et al study, including more maternal hypotension, increased number of cesarean sections, and lower Apgar scores at one minute [16]. (denotes neonate's breathing effort, heart rate, muscle tone, grimace response/reflex irritability, and skin color at deliver; normal score is 7-9). Women taking hydralazine also had more headaches and tachycardia than with other antihypertensive agents [16]. The study team concluded that hydralazine should not be used as a first line agent because of an increase in adverse effects without any increased benefit [16].

A 2002 randomized trial compared the efficacy of nifedipine to hydralazine in severe preeclampsia [17]. This study included 126 women with a baseline blood pressure above 160/110 mm Hg who were randomized to either sublingual nifedipine or intravenous hydralazine [17]. Goal diastolic blood pressure was 90-100 mm Hg [17]. Both treatment groups achieved effective blood pressure control, but hydralazine exhibited a significantly shorter time to next hypertensive crisis, 2.1 hours compared to 3.1 hours with nifedipine [17]. Rates of adverse effects were similar for both groups [17]. Tachycardia and headache were most commonly reported, with more tachycardia observed in women taking hydralazine [17]. Apgar scores were similar between the two groups [17].

Common side effects of hydralazine may present as nausea, vomiting, and headache in up to 50 percent of patients with preeclampsia [18]. Hydralazine may cause maternal hypotension, reflex tachycardia, and flushing [1]. Maternal use of hydralazine has also been associated with thrombocytopenia in neonates [5].

Labetalol

Labetalol is a non-selective antagonist at $alpha_1$, $beta_1$, and $beta_2$ adrenergic receptors, and is FDA approved for the treatment of hypertension and hypertensive emergencies [19,13]. Pregnancy-induced hypertension and preeclampsia are off-label uses [19]. Labetalol may be preferred over other beta blockers as it dilates arterioles and decreases vascular resistance without significantly lowering cardiac output [20]. Labetalol may be administered as an oral or intravenous product [19]. Comparisons of the onset, duration, and peak levels of labetalol and other anti-hypertensive therapies are found in Table 2.

Hypotension, bradycardia, and hypoglycemia are common adverse effects of beta blockers, and a retrospective chart review published in 2011 in Early Human Development focused on the prevalence of these effects in neonates who were exposed to labetalol in utero [26]. The study included the records of women who had severe preeclampsia per the International Society for the Study of Hypertension in Pregnancy (ISSHP) criteria, and records were compared between those whose blood pressure was managed using labetalol versus those whose blood pressure was controlled without antihypertensive medications [26]. The records of the infants exposed to labetalol were compared to those of the control group for gestational age at birth, birth weight, hypotension, hypoglycemia, bradycardia, and mortality [26]. Hypotension was found to be significantly increased in the labetalol group (29.1% versus 7.4%) within the first 48 hours of life [26]. Mortality was also significantly increased in the labetalol group, with 4.6% mortality rate in labetalol exposed infants compared to no deaths in the control group [26]. The deaths were due to ongoing sepsis, progressive respiratory

Table 2: Pharmacokinetics of Antihypertensive Agents [14,19,21-25,27,30,31].

	Route	Onset	Time to Peak	Duration	Half Life
hydralazine	IV	5-15 min	10-80 min	1-4 h	3-7 h
labetalol	IV	2-5 min	< 5 min	16-17 h *	5.5 h
	PO	2-4 h	1-4 h	8-12 h	6-8 h
methyldopa	IV/PO	3-6 h	3-6 h	12-24 h	75-80 min
nicardipine	IV	10 min	-	< 8 h	2-4 h
	PO	0.5-1 h	-	IR <8h, SR 8-12 h	2-4 h
Nifedipine	PO	20 min	-	4-8 h	2-4 h
	SL	1-5 min	20-30 min	4-5 h	-

*Duration is dose dependent
- None listed

insufficiency, or gastrointestinal perforation, and were thought to be related to the severity of maternal disease and not necessarily related to labetalol use [26]. No significant differences were found in occurrence of bradycardia and hypoglycemia between treatment and control groups [26]. No significant differences in rates of bradycardia, hypotension and hypoglycemia were found when intravenous and oral labetalol were compared [26]. The authors hypothesized that hypoglycemia may be more due to prematurity than to drug therapy, as hypoglycemia affected over 40% of infants in both the labetalol and control groups [26]. Additionally, the authors observed the adverse effects of maternal labetalol on neonates may be less severe than previously thought, and this topic warrants further study [26].

Furthermore, a retrospective chart review compared labetalol or nifedipine in women with a diagnosis of gestational hypertension, mild preeclampsia, severe preeclampsia, and HELLP syndrome. They were grouped according to diagnosis and the safety and efficacy of the two agents were compared [13]. In the severe preeclampsia and HELLP syndrome group, there were no significant differences found in rates of maternal blood pressure control, rates of cesarean section, intrauterine growth restriction, gestational age at delivery, birth weight, and Neonatal Intensive Care Unit (NICU) admissions [13]. However, significant differences were found within the gestational hypertension/preeclampsia group [13]. The labetalol group showed a 38.8% incidence of intrauterine growth restriction compared to 15.5% in the nifedipine group, and the labetalol group also demonstrated higher rates of fetal worsening as demonstrated by fetal heart monitoring (33.3% versus 14.2%) [13]. The study found no significant differences in rates of adverse effects, with headache and nausea being the most frequently observed adverse effects of both medications [13].

Labetalol was compared to methyldopa for use in pregnancy-induced hypertension in a prospective randomized trial completed by Molvi, et al [20]. One hundred fifty women were randomized to receive labetalol plus standard care, methyldopa plus standard care, or the control group of standard care alone [20]. The primary outcome was any maternal or fetal adverse events, including maternal death, preeclampsia, eclampsia, cesarean section, fetal death, neonatal death within first week, preterm birth, low Apgar score of less than 5 at five minutes, and neonatal intensive care unit admissions [20]. Occurrence of severe hypertension and proteinuria were significantly reduced in both treatment groups compared to the control group [20]. Severe hypertension occurred in 16.3% of the women treated with methyldopa, while only 4% of the labetalol treatment progressed to severe hypertension [20]. There were also significantly fewer preterm births and small for gestational age babies in the treatment groups, and the authors concluded that antihypertensive therapy was beneficial in preventing morbidity associated with pregnancy-induced hypertension [20].

Methyldopa

Methyldopa, or α-methyldopa, is an alpha$_2$ adrenergic agonist which causes a reduction in blood pressure by decreasing the effects of the sympathetic nervous system [27]. Methyldopa is frequently used to treat hypertension during pregnancy [5]. This medication may be administered by either intravenous or oral routes [27].

Methyldopa has the most long-term safety data to support its use during pregnancy [28]. No adverse effects on growth and development were seen in a 7.5 year follow-up in children exposed to methyldopa in utero [28]. The effects of methyldopa on placental perfusion were studied using the results of uterine artery Doppler scans at baseline, after 24 hours, and after 48 hours of initiation of medication therapy [29]. Methyldopa significantly reduced blood pressure when compared to a control group, and did not exert any significant changes on uterine artery Doppler measurements from baseline to 24 hours and 48 hours after medication initiation [29].

When compared to patients treated with labetalol, women given methyldopa had a higher incidence of severe hypertension and higher rates of antenatal hospitalizations [20]. The infants of women treated with methyldopa were admitted to the neonatal intensive care unit more often than those exposed to labetalol (22.4% versus 8%) [20].

Nicardipine/nifedipine

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, leading to decreased systemic vascular resistance [18]. Both nicardipine and nifedipine have been studied for use during pregnancy [1,5]. Nicardipine has been found to be highly selective for vascular smooth muscle compared to cardiac muscle [18]. Nicardipine has also been found to have more selective effects than nifedipine, resulting in less reflex tachycardia and less pronounced negative inotropic effects [18]. Nicardipine is available in both oral and intravenous dosage forms, while nifedipine is only available in oral forms [30,31]. Both nicardipine and nifedipine have been shown to be effective at lowering blood pressure in pregnant women [17,18,32]. 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 nicardipine [32]. Maternal blood pressure at baseline ranged from 168-205 mm Hg systolic and 105-135 mm Hg diastolic [32]. Although the decrease in mean arterial pressure was significant, a significant increase in maternal heart rate was also noted [32]. Two patients were noted to have severe increases in heart rate of more than 50% from baseline that required dose reduction and concurrent beta blocker therapy for management [32]. Other side effects such as headache, flushing, dizziness, and nausea were observed in some patients, but these effects were considered to be well-tolerated by the patients [32]. Nine out of thirteen patients who presented with headaches and blurred vision upon admission also experienced resolution of these symptoms while on nicardipine therapy [32]. Fetal outcomes were measured through fetal heart rate monitoring, gestational age at birth, Apgar scores, and birth weight [32]. During fetal heart rate monitoring, decreases in accelerations were noted along with an increased incidence of decelerations, but these changes were not severe enough to require immediate delivery of the fetus [32]. Infants were between 29-34 weeks at delivery with birth weights ranging from 770-2720 grams and Apgar scores between 6 to 10 at 1 minute and 8 to 10 at 5 minutes [32]. Four infants were delivered within one hour of therapy, and gestation was increased by 2 to 12 days in the other sixteen pregnancies [32].

An open, prospective study published in the Journal of Hypertension in 2005 investigated the use of nicardipine as a second line agent in preeclampsia [33]. Twenty-seven patients ranging from 21 weeks, 1 day to 32 weeks, 4 days gestation who had failed treatment on intravenous ketanserin, hydralazine, or labetalol were enrolled (average gestation of 27 weeks, 1 day) [33]. Ketanserin is a 5-HT$_{2A}$

antagonist used to treat high blood pressure in several countries, but may not elicit a meaningful response in many patients [33]. It is not available in the United States. The goal diastolic blood pressure in this study was less than 100 mm Hg or less than 90 mm Hg if the patient developed HELLP syndrome [33]. All 27 patients reached the blood pressure goals in less than one hour on doses ranging from 3 to 9 mg/h [33]. Hypotension (diastolic blood pressure < 70 mm Hg) was noted in 30% of the patients, which required dose reduction or temporary cessation of therapy [33]. Most patients in this study were also taking oral methyldopa, which may make the results more difficult to interpret and compare with other studies and therapies [33]. Tachycardia severe enough to warrant dose adjustment was not noted in any patients, although 18% of patients did have a heart rate greater than 120 bpm for a short period of time [33]. It is difficult to assess this side effect in this study as the heart rate lowering effects of methyldopa may have decreased the occurrence of tachycardia in some women [33]. Common maternal side effects observed included fatigue, decreased appetite, and constipation [33]. Postpartum hemorrhage occurred in six of the patients, five of whom required blood transfusions [33]. Although nicardipine has not been associated with adverse maternal-fetal blood flow during gestation, it may decrease uterine tone and is a potent vasodilator [18,24]. Average gestational age at birth was 28 weeks 2 days and all neonates were admitted for either intensive or medium levels of care [33]. Three pregnancies out of 27 ended in fetal loss, and eight of the 24 premature infants experienced hypotension which required treatment with volume expansion and/or medications [33].

In 2010, the Obstetrical and Gynecological Survey published a review that analyzed data compiled from five studies of nicardipine use in preeclampsia [18]. Significant reduction in blood pressure was observed in these studies, with 91% of patients achieving blood pressure goals in less than 130 minutes (n=147) [18]. The most frequent maternal side effects found were transient hypotension, nausea, headache, and flushing [18]. 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 pregnancy [18]. Three babies were noted to have Apgar scores of less than 7 after 5 minutes [18].

A randomized trial published in 2002 compared hydralazine and nifedipine efficacy and adverse effects [17]. Nifedipine led to quicker control of diastolic blood pressure compared to hydralazine, but this was not statistically significant (9.6 minutes versus 10.4 minutes) [17]. However, nifedipine did show a significantly prolonged average time to new hypertensive crisis of 3.1 hours compared to 2.1 hours with IV

hydralazine [17]. Tachycardia was observed more in the hydralazine group, while headache was more common in the nifedipine group [17]. It is interesting to note that the nifedipine group had an increased urine output compared to hydralazine, leading the authors to believe nifedipine may have some positive renal effects [17]. No significant differences were noted in gestational age or Apgar scores [17].

Medication therapy versus induction of labor

Currently, there is no clear consensus on when to treat hypertensive disorders in pregnancy. Several organizations recommend treatment thresholds varying from 140/90 mm Hg to

170/110 mm Hg based on differing criteria [5]. The American College of Obstetricians and Gynecologists recommends treating pregnancy-induced hypertension when blood pressure increases to 150-160 mm Hg systolic or 100-110 mm Hg diastolic [5]. Table 3 lists the treatment thresholds of several organizations and guidelines. A lack of consensus exists on target blood pressure during treatment as well [5].

In pregnancies complicated by pregnancy-induced hypertension and preeclampsia between 20 weeks gestation and the age of viability, the maternal risk seems to be substantially increased with low survival rates for the fetus [8]. This is further complicated by the fact that various institutions define the age of viability differently, ranging between 23 weeks, 0 days to 24 weeks, 6 days depending on local definitions [8].

There is insufficient data for clear guidelines in pregnancies before 34 weeks gestation. In two randomized, controlled trials in women with severe preeclampsia between 28-34 weeks or 28-32 weeks gestation, aggressive or expectant management was compared and found that duration of gestation had been increased by 7.1 and 15 days, respectively [36,37]. A prospective observational trial published in the American Journal of Obstetrics and Gynecology in 2004 studied maternal and fetal outcomes with expectant management between 24 to 33 weeks [35]. The primary target of this study was the number of days of gestation by which the pregnancy was prolonged after admission [35]. Other maternal outcomes included death, eclampsia, DIC, HELLP syndrome, pulmonary edema, placental abruption, and acute renal failure [35]. Fetal outcomes included death, respiratory distress syndrome, necrotizing enterocolitis, NICU admissions, and days spent in NICU [35]. Nicardipine and labetalol were used intravenously to maintain maternal blood pressure less than 150/110 mm Hg. Ultrasound, fetal heart rate monitoring, and twice daily evaluation of fetal movements were used to assess fetal well-being [35]. The study found that expectant management increased gestation

Table 3: Treatment Thresholds for Hypertension in Pregnancy [5,7].

	Treatment Threshold (mm Hg)
National High Blood Pressure Education Program (US) Working Group Report 2000	150-160 systolic 100-110 diastolic
American College of Obstetricians and Gynecologists Practice Bulletin 2002	>105-110 diastolic
European Society of Cardiology 2011	150/95 or 140/90 if high risk
Society of Obstetricians and Gynaecologists of Canada 2008	160/110
Society of Obstetric Medicine of Australia and New Zealand 2008	170/110 or 160/100 if chronic hypertension 140-160/90-100 treatment is reasonable
National Institute for Health and Care Excellence (UK) 2010	150-159/100-109 140/90 if end-organ damage in chronic hypertension

by an average of six days for women less than 29 weeks gestation, and four days for both the 29 to 32 week group, as well as the 32 to 33 week group [35]. During the study, there were no maternal deaths, and 12 out of 13 perinatal deaths occurred in infants delivered before 29 weeks gestation [35]. The study found no significant differences in maternal outcomes based on weeks gestation. Furthermore, expectant management incurred minimal risks for the mother, but pregnancy prolongation provides benefits for the fetus/neonate [35].

The recommendations for pregnancies between 34 and 36 weeks gestation are also unclear. The Hypertension and Preeclampsia Intervention Trial at Term (HYPITAT) study group completed a multicenter, randomized, controlled trial of 756 women to compare the outcomes of induction of labor versus expectant management in pregnancy-induced hypertension and mild preeclampsia [40]. Women enrolled were between 36 and 41 weeks gestation and were included if blood pressure was below 170/110 mm Hg [40]. Women in the expectant management group had a higher percentage use of antihypertensive medications and had a significantly higher composite adverse maternal outcome, including significantly increased incidence of severe hypertension [40]. In a subgroup analysis, women at 36 to 37 weeks gestation may show benefit from expectant monitoring [40]. Overall neonatal outcomes were not significantly different between groups [40]. Average birth weight was significantly lower in the induction groups, which would be expected, as the average gestational age at delivery was lower in this group [40]. The HYPITAT group concluded that induction of labor after 37 weeks gestation was associated with better maternal outcomes, decreased rates of cesarean section and should be recommended in gestational hypertension and mild preeclampsia [40]. Additionally, the Working Group on High Blood Pressure in Pregnancy recommends induction of labor for women with mild preeclampsia at 38 weeks gestation if favorable cervix, and induction at 40 weeks for all women [41]. The HYPITAT study group is currently conducting a multicenter, randomized, controlled trial of induction of labor versus expectant management, known as the HYPITAT-II study [38]. HYPITAT-II aimed to study the primary outcomes of composite maternal morbidity, progression to severe disease, maternal complications, and neonatal respiratory distress syndrome, with additional outcomes measuring rates of cesarean sections and several measures of neonatal morbidity and mortality [38]. While data collection was completed as of February 2013, the results are still being analyzed. An article by Baha M. Sibai reiterates the need for further study in this area, recommending delivery of the fetus during the late preterm period if severe hypertension, preterm labor, vaginal bleeding, or abnormal

fetal testing occur [39]. The authors of a 2010 Lancet article state that in late preterm pregnancies, the benefits of expectant management should be considered, but the severity of the disease may favor delivery [8].

Discussion

Pregnancy-induced hypertension and preeclampsia present a unique challenge for the practitioners who care for these patients. Numerous studies have validated the efficacy of hydralazine, labetalol, methyldopa, nicardipine, and nifedipine in managing the blood pressure of women with hypertensive disorders during pregnancy, but none are without risk. Additionally, the risks and benefits for both the mother and fetus need to be considered. Currently, there is no standardized method for accurately screening women during early pregnancy, although this is an area of much needed study. Research has centered around early screening utilizing various markers to attempt to predict preeclampsia, such as placental growth factor (PlGF), free β human Chorionic Gonadotropin (β-hCG), Pregnancy-Associated Plasma Protein-A (PAPP-A), A Disintegrin And Metalloprotease 12 (ADAM12), Inhibin A, Activin A, uterine artery Doppler, mean arterial pressure, and maternal factors [42-44]. These studies may lead to development of better screening methods and potentially better outcomes for a woman and fetus.

It may be difficult to interpret and compare much of literature due to varying definitions and diagnostic criteria for pregnancy-induced hypertension and preeclampsia [1,5,7-9]. The treatment thresholds and goals for blood pressure during pregnancy also vary greatly [5]. Many of the trials are observational studies or retrospective chart reviews; thus, it is hard to determine if other factors obscure the results. Smaller study populations in some clinical trials may make it more difficult to apply results to a larger population.

While hydralazine, labetalol, methyldopa, nicardipine and nifedipine may all have a role in treating hypertensive disorders during pregnancy, it may be difficult for practitioners to determine which agent should be first line. Unfortunately, there are not guidelines for first-line treatments, and practice varies with region, severity of disease, fetal and maternal status, and stage of gestation [1,5]. The side effect profiles, available dosage forms, pharmacokinetics, and contraindications for use also determine which pharmacologic agents may be appropriate for each patient, as outlined in table 4.

Practitioners should evaluate each clinical situation balancing the positive and negative aspects of each medication with gestational age to determine which agent may be most suitable. A meta-analysis

Table 4: Maternal and Fetal Adverse Effects and Contraindications for Use of Antihypertensive Medications [1,5,14,19,27,30,31].

Medication	Maternal Adverse Effects	Fetal and Neonatal Adverse Effects	Contraindications of Use
hydralazine	Nausea, vomiting, hypotension, tachycardia, headaches, palpitations, flushing, fluid retention	Neonatal thrombocytopenia	Aortic aneurysm, hypersensitivity to hydralazine
labetalol	Hypotension, headache, bradycardia	Intrauterine growth restriction, neonatal bradycardia, neonatal hypotension	Congestive heart failure, myocardial disease; caution in asthma
methyldopa	Drowsiness, dizziness, dry mouth, nausea	*	Concurrent MAOI therapy, liver disease; avoid in women with depression, congestive heart failure
nicardipine	Headache (most common), tachycardia, nausea, flushing, dizziness	Neonatal hypotension	Aortic stenosis, caution in heart failure; hypersensitivity to nicardipine
nifedipine	Rebound tachycardia, nausea, flushing, dizziness	Neonatal hypotension	Hypersensitivity to nifedipine, concomitant use of strong CYP3A4 inducers, caution in hepatic failure or heart failure

*No risks found in long-term follow-up study [28].

concluded that hydralazine may have an increased incidence of maternal hypotension, headaches, and tachycardia [16]. Labetalol was found to have an increased risk of neonatal hypotension and may lead to increased incidence of intrauterine growth restriction [13,26]. Methyldopa has long been used to treat blood pressure conditions during pregnancy and is often considered to be the most commonly used antihypertensive agent during pregnancy [5]. It has been found to have minimal effects on the fetus/neonate in a long term follow-up study [28]. Nicardipine and nifedipine may cause reflex tachycardia, decreased uterine tone, and vasodilation [32]. Although adverse neonatal effects have been noted in some studies, it may be difficult to discern if these were due to the medication itself, maternal disease, or effects of prematurity.

Currently, many practitioners would opt for induction of labor when the pregnancy achieves 37 weeks gestation, although this is a subject of debate [8,40,45]. The results of the HYPITAT trial suggest that induction of labor is beneficial after this stage; however, some are critical of the HYPITAT results and question its applicability to the general population of women with pregnancy-induced hypertension and preeclampsia [8,40,45]. The severity of disease and maternal/fetal condition may still be the deciding factor for practitioners at this stage. Studies have shown that expectant management with antihypertensive medications before 37 weeks gestation may increase the risks to the mother, but preterm management imparts benefit to the fetus by increasing the length of gestation [5,8,39]. Induction of labor is required when maternal disease progresses to eclampsia, HELLP syndrome, DIC, pulmonary edema, or significant renal dysfunction [34]. Advances in NICU services have improved survival for many of these preterm neonates. Although preterm birth places an infant at significant risk for several morbidities, their survival is much increased from previous generations. The results of more clinical trials, such as the HYPITAT-II study, will likely bring increased knowledge to assist practitioners in determining when to treat with medications or initiation of labor induction [38]. Other areas of potential study include complications of postpartum preeclampsia and investigation of immunology based research that are beyond the scope of this discussion.

Conclusion

Pregnancy- induced hypertension and preeclampsia are complications that present a unique treatment challenge for health care providers. Hypertensive disorders during pregnancy are a major cause of morbidity and mortality worldwide, warranting further research to improve maternal and fetal outcomes. Antihypertensive medications play an important role in managing maternal blood pressure. Hydralazine, labetalol, methyldopa, nicardipine, and nifedipine have all demonstrated efficacy in trials, but may cause adverse effects. Studies show that although not without risks, these medications can reduce progression of disease for the mother and improve fetal and neonatal outcomes. Practitioners must rely on knowledge of the severity of maternal disease, the stage of pregnancy, and characteristics of the individual medications when deciding on a treatment plan. Continued research beyond traditional approaches may elucidate future management of pregnancy-induced hypertension and preeclampsia.

In conclusion, treatment thresholds recommend initiation of pharmacologic therapy at similar elevated blood pressure values. Various antihypertensive medications exist; however, the severity of blood pressure elevation dictates the choice of agent. First line approach for severe maternal preeclampsia hypertensive emergency would be hydralazine. In treating hypertension in pregnancy, methyldopa is the preferred drug. In no instance, should ACE Inhibitors, ARBs, or diuretics be used in pregnancy due to their teratogenic or volume depleting properties.

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