Pathophysiology and Medical Management of Systemic Hypertension in Pregnancy

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Abstract: Hypertension in pregnancy includes a group of distinct disorders that require special consideration in both prevention and pharmacologic treatment. In recent years, there have been few advances regarding the pathophysiology and prevention of preeclampsia or in the recommendations for first-line drug therapy for its hypertensive complications. Similarly, the recommendations for pharmacologic treatment of women with chronic hypertension antedating pregnancy have changed little primarily because first-line medications have the advantage of having had more extensive research experience. Recent clinical trials have demonstrated the efficacy and safety of various second-line drugs for the hypertensive disorders of pregnancy; whether these therapies can eventually replace the standard recommended medications will require more extensive long-term investigation.

Key Words: hypertension, pregnancy, preeclampsia, drug prevention, drug therapy

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Debates related to the classification and the etiology and pathophysiology of hypertensive disorders of pregnancy are indicative of the discord that surrounds these disease processes. As a group, hypertensive disorders represent the most significant complication of pregnancy, affecting approximately 10% of all pregnancies and contributing greatly to maternal and perinatal morbidity and mortality throughout the world.[1] Fifteen percent of maternal deaths in the United States are solely the result of solely hypertensive disease, which can lead to iatrogenic preterm delivery for maternal indications as well as adverse fetal outcomes.[2] Hypertension during pregnancy carries with it the increased risk of abruptio placentae, disseminated intravascular coagulation, cerebral hemorrhage, hepatic failure, and acute renal failure.[3]

The results from recent large trials have been significant in clarifying certain issues regarding the prevention of hypertension in pregnancy. In this review, we update the latest information on pathophysiology and prevention, as well as the pharmacologic treatment of hypertensive disorders of pregnancy. Although current treatment recommendations from the American College of Obstetricians and Gynecologists (ACOG) and the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) still advise the use of traditionally proven medications, alternative agents are now being promoted in the management of hypertension during pregnancy.

CLASSIFICATION

The current National High Blood Pressure Education Program (NHBPEP) 2000 Working Group Report endorses the classification of hypertension in pregnancy originally proposed by the ACOG Committee on Terminology in 1972, which includes the following subsets[3]:

1. Preeclampsia–Eclampsia
2. Chronic Hypertension (Primary or Secondary)
3. Preeclampsia–Eclampsia Superimposed on Chronic Hypertension
4. Gestational Hypertension

Over the past several decades, the exact definition of hypertension in pregnancy has been controversial. In its most recent report, the Working Group Report defines hypertension itself as a sustained increase in blood pressure $>$140/90 mm Hg. Previous definitions, which included increases in systolic or diastolic blood pressure of 30 mm Hg and 15 mm Hg, respectively, have been determined to be no longer valid. Multiple studies have shown that up to 73% of primigravid patients have increases in diastolic blood pressure of 15 mm Hg at some point during a normotensive pregnancy without increased rates of adverse outcomes.[2] Indeed, during normal gestation, the diastolic blood pressure rises by 10 mm Hg during the third trimester, hence the definition of hypertension as an increase of 15 mm Hg in diastolic blood pressure can lead to overdiagnosis.[4] It is, however, recommended that women with a rise in blood pressure of 30 mm Hg systolic or 15 mm Hg diastolic be closely observed.

Historically, there had been considerable disagreement over which Korotkoff sound should be used to measure diastolic blood pressure. The U.S. NHBPEP has found substantial evidence to support the use of phase V in all patients.[3] To reduce the number of inaccurate blood pressure readings, the Working Group has made recommendations as to how blood pressure should be taken. First, the actual position of the patient while

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measuring blood pressure should remain consistent: in the outpatient setting, quiet sitting for 10 minutes before taking the blood pressure is reasonable, whereas lateral recumbency is the preferred position for hospitalized patients. Additionally, one should make sure that an appropriate-sized cuff is used (1.5 times the upper arm circumference or bladder covering 80% of the arm) and that no tobacco or caffeine has been used for at least 30 minutes preceding the reading.

GESTATIONAL HYPERTENSION AND PREECLAMPSIA

High blood pressure developing alone after 20 weeks' gestation in a previously normotensive woman is defined as gestational hypertension, which generally has a good prognosis. When the hypertension is accompanied by proteinuria, it is termed preeclampsia, a distinct disorder with a greater risk of complications and adverse outcomes. Previously edema was included as 1 of the diagnostic criteria; however, in accordance with several published reports, this has been eliminated.[5] Although edema is present in many women with preeclampsia, it is also found in many normal pregnancies, thus not allowing edema to be a reliable clinical marker. Preeclampsia can be further distinguished as mild or severe on the basis of the rise in blood pressure or the degree of proteinuria (Table 1). This clinical distinction can be deceiving, for as many as 20% of patients who develop eclampsia have normal diastolic blood pressure or no proteinuria[6]; similarly, some women can develop the ominous syndrome of HELLP (hemolysis, elevated serum liver enzymes, and thrombocytopenia) with or without the prior warning signs of accelerated hypertension or significant proteinuria.[7] Nevertheless, patients with preeclampsia who show signs of significant end-organ involvement or fetal growth retardation/distress are always regarded as having severe disease.[2,3] Early delivery despite fetal immaturity may be warranted, because eclampsia may be imminent.

TABLE 1. Clinical Signs and Symptoms of Severe Disease in Patients With Preeclampsia

Blood pressure >160 mm Hg systolic or >110 mm Hg diastolic
Proteinuria >5 g/24 h
Elevated serum creatinine (>1.2 mg/dL)
Grand mal seizures (eclampsia)
Pulmonary edema
Oliguria <500 mL/24 h
Microangiopathic hemolysis
Thrombocytopenia (platelet count <100,000)
Elevated hepatic enzymes (ALT or AST)
IUGR or oligohydramnios
Symptoms suggesting end-organ involvement: headache, visual disturbances, epigastric
Or right upper quadrant pain

Reproduced from Awad K, Ali P, Frishman WH, et al. Pharmacologic approaches for the management of systemic hypertension in pregnancy. *Heart Dis.* 2000;2:125.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; IUGR, intrauterine growth retardation.

PREECLAMPSIA

Etiology

Preeclampsia is exclusively a disease of pregnancy, with resolution of the disease occurring only on delivery. Long before the clinical appearance of preeclampsia, immunologically mediated abnormal trophoblastic invasion leads to formation of a placenta in which the uterine spiral arteries fail to undergo the normal thinning out of muscular walls that permit enhanced perfusion of the placenta.[8] Vascular transformation is normally complete by 20 to 22 weeks' gestation; hence, pathologic changes must have occurred by this time, before clinical disease becomes evident. Intrauterine growth retardation (IUGR) as a result of placental ischemia precedes the manifestation of preeclampsia, further strengthening the observation that the vascular pathology of preeclampsia predates the manifestation of clinical disease and that patients are earmarked early in pregnancy for the development of preeclampsia.

There is evidence suggesting a familial tendency for preeclampsia, because it may be inheritable by either a recessive gene or a dominant maternal gene with 50% penetrance.[9] Others have suggested an association between preeclampsia and the presence of the angiotensinogen T235 gene variant, as well as a role for factor V Leiden mutation in the pathophysiology of preeclampsia.[10] Not all cases have a genetic component; other predisposing factors for developing preeclampsia include those disorders characterized by microvascular disease such as preexisting hypertension, collagen vascular disease, raised plasma concentrations of asymmetric dimethylarginine,[11] the antiphospholipid syndrome, and diabetes, as well as conditions associated with a large placenta—multiple pregnancy, hydatidiform mole, and hydropic placenta. Additionally, it has been found that in many preeclamptic women, sympathetic activity is reversibly increased causing added vasoconstriction.[10] What unifies all of these proposed mechanisms is they result in poor placental perfusion, and it is generally agreed that reduced blood flow to the placenta results in production of specific circulating factors, which play an important role in the pathogenesis of preeclampsia.

Local and Systemic Involvement

Reduced placental perfusion triggers the multiorgan systemic disease seen in preeclampsia. The poorly perfused fetoplacental unit releases bloodborne products that target vascular endothelium, causing endothelial dysfunction either through activation or injury. High circulating concentrations of von Willebrand factor, endothelin, cellular fibronectin, and an increased thromboxane:prostacyclin ratio in the sera of preeclamptic women are evidence of the activated coagulation cascade and increased sensitivity to pressors seen in the setting of endothelial cell dysfunction.[8] Consequently, the normal cardiovascular adaptations of pregnancy, namely increased plasma volume, decreased systemic vascular resistance, and increased cardiac output, do not occur.

In addition, it is now established that an alteration in placental angiogenesis is an important feature in the development of preeclampsia.[12] A recent study has demonstrated

the presence of increased levels of soluble fms-like tyrosine kinase-1 (sflt-1) and reduced levels of placental growth factor (PIGF) in pregnant women prone to developing preeclampsia.[13,14] It is proposed that high levels of sflt-1 can cause placental vascular insufficiency and systemic manifestations of preeclampsia by antagonizing the angiogenic and vasodilatory effects of vascular endothelial growth factor and PIGF.[14,15] It has also been shown that altered angiogenesis and insulin resistance are additive insults in causing preeclampsia.[12]

The Renin–Angiotensin–Aldosterone Axis

In normal pregnancy, increased activity of the renin–angiotensin–aldosterone (RAA) system is coupled with a lower density of angiotensin II receptors, which leads to increased resistance to the pressor effects of angiotensin II. The opposite phenomenon occurs in women with preeclampsia, in whom there is decreased RAA activity; however, angiotensin II refractoriness is lost, resulting in an abnormally increased sensitivity to the vasopressor effects of angiotensin II.[1] Whether this is linked to increased expression of angiotensin receptors or to an autoantibody that binds to the AT1 receptor in preeclamptic patients is yet to be determined.[16]

Prostaglandins

Prostaglandins play an important role in normal pregnancy and preeclampsia. The increased ratio of endothelial cell-produced prostacyclin to platelet-derived thromboxane in normal pregnancy not only favors a vasodilatory state, but it also enhances pressor resistance. In preeclampsia, the ratio is reversed, with the increased thromboxane promoting a vasoconstricted and proaggregatory state.[1] In a recent study in which the urinary metabolites of prostacyclin (PGI2) and thromboxane (TxA2) were measured, it was demonstrated that the reduced production of PGI2 and not the increased production of TxA2 occurs months before the clinical onset of preeclampsia.[17]

Multiorgan System Involvement in Preeclampsia

Cardiovascular

Cardiac output and plasma volume are reduced in preeclampsia. The hypertension is caused primarily by a marked increase in systemic vascular resistance resulting from increased sensitivity to pressors, an increased thromboxane:prostacyclin ratio, and impaired endothelial-dependent relaxation.[18,19] These changes are in marked contradistinction to the normal cardiovascular adaptations of pregnancy, in which increased plasma volume and cardiac output and decreased systemic vascular resistance contribute to optimize uteroplacental perfusion.

Renal

As a result of reduced renal perfusion, the glomerular filtration rate is decreased, more than renal blood flow, resulting in a lowered filtration fraction. Decreased clearance of uric acid is an important marker in preeclampsia, because it is often detected before overt disease is manifested.[20] Glomerular damage and subsequent proteinuria ranging from mild to severe is another important feature of preeclampsia. The abnormality usually remits rapidly after delivery, but may persist until the third or fourth month postpartum. Sodium retention is nearly universal in preeclampsia, and renal excretion of calcium is also altered in preeclampsia, a phenomenon that has been the basis of recent trials attempting to prevent the onset of preeclampsia with calcium supplementation. Normal pregnancy is characterized by a hypercalciuric state, whereas preeclamptic pregnancies are characterized by reductions in the fractional excretion of calcium and pronounced hypocalciuria. Both reduced plasma levels of dihydroxyvitamin D[1,21,22] and increased parathyroid hormone levels[23] have been demonstrated in preeclampsia, suggesting an increased distal tubular reabsorption of calcium.

Hepatic

The combination of vasospasm and precipitation of fibrin may lead to injury of the liver. Hepatic dysfunction in preeclampsia ranges from the presence of mild hepatic enzyme elevations in the serum to the more extreme HELLP syndrome, subcapsular bleeding, or even hepatic rupture.

Central Nervous System

Cerebral hemorrhage is the most serious central nervous system (CNS) complication of preeclampsia. Other CNS manifestations of preeclampsia include headache, blurred vision, scotoma, and cortical blindness. All are transient, resolving with control of hypertension or on delivery. When complicated by grand mal seizures, preeclampsia enters the eclamptic stage, which portends greater maternal morbidity and mortality. The precise etiology of the seizures is not clear and is not always correlated with the elevation in blood pressure; however, gross inspection of the brain invariably shows hemorrhages and petechiae.[24] Whether the hemorrhage is the result of vasospasm and ischemia, the severity of hypertension, vascular infiltration with fibrinoid leading to edema, thrombus, and rupture, or other causes, remains debatable.[1]

Early Recognition of Preeclampsia

It is clear that a wide spectrum of physiological derangements occur early in pregnancies destined to be complicated by preeclampsia, thereby prompting investigators to try to identify a test or combination of tests that could accurately identify patients at high risk for developing preeclampsia. These women could then be considered for therapy aimed at minimizing or preventing maternal and perinatal morbidity and mortality. Despite numerous studies aimed at countless serum markers, there remains no uniformly reliable clinical test that identifies patients destined to develop preeclampsia.[3,25] Furthermore, there is no gold standard used in clinical practice to define preeclampsia. In 1 retrospective study of laboratory parameters associated with poor outcomes in patients with pregnancy-induced hypertension, the factors found to be significant in heralding poor outcomes were severe hypertension requiring medical treatment (ie, diastolic blood pressure >110 mm Hg), the early onset of severe hypertension, oliguria, proteinuria of 5 g/d, platelets $<100{,}000$, elevated liver enzymes, hemolysis, serum uric acid levels >6 units, and CNS manifestations.[26] Other studies

have shown limited use with the measurement of urinary calcium to creatinine ratios[27] and serum uric acid levels[28] in early pregnancy.

In summary, there are no current data to support the routine use of any 1 test or set of tests beyond the standard history and physical examination and the presence of urinary protein to detect preeclampsia before its overt clinical manifestations.[29] A study demonstrated that a history of preeclampsia in a previous pregnancy, chronic hypertension lasting at least 4 years, and diastolic blood pressure >100 mm Hg early in pregnancy were significantly associated with a higher rate of preeclampsia. As well, the presence of proteinuria early in pregnancy was associated with adverse neonatal outcomes independent from the development of preeclampsia.[30]

Prevention

Strategies to prevent preeclampsia continue to be investigated; however, little progress has been made as the exact etiology of preeclampsia has yet to be identified. Currently, there is little evidence that the pathophysiology of preeclampsia can be reversed by any therapy. All pharmacologic therapies that are in use today are only able to slow the progression of this disorder, permitting continuation of the pregnancy until delivery is imminent.[3]

Diuretics

Because preeclampsia is often characterized by edema and increased blood pressure, investigators believed early on that sodium retention was etiologically related to the disorder, and therefore attempts were made to prophylactically administer diuretics. It is now known that in many women with preeclampsia, the plasma volume is lower than expected in the normal pregnant state, and there is a tendency toward hemoconcentration.[20] Diuretics can thus exacerbate the hypovolemia, which in turn will stimulate the renin–angiotensin system and aggravate hypertension. This, in combination with rare reports of adverse drug effects in the mother and/or fetus from the drugs,[4] have led clinicians to abandon recommending the prophylactic use of diuretics during pregnancy.

Antihypertensive Medications

Drug therapy to lower blood pressure in patients presenting with mild gestational hypertension or preeclampsia remote from term has not been shown to either prevent the onset of preeclampsia or to improve fetal outcome.[31] This is not surprising considering that multisystemic involvement in preeclampsia is not the direct result of an elevated blood pressure. Additionally, the incidence of adverse side effects from blood pressure-lowering medications can pose problems, ie, total placental hypoperfusion. There does appear to be a role, however, for the pharmacologic treatment of severe hypertension.[21]

Calcium Supplementation

Based on the theory that insufficient dietary intake of calcium leads to a compensatory rise in parathyroid hormone, increased smooth muscle contraction,[32] and consequent hypertension, investigators have proposed that calcium supplementation can reduce the incidence of preeclampsia. Early reports of hypocalciuria, increased sensitivity to angiotensin II, and reduced levels of dihydroxyvitamin D[1,21] in women with preeclampsia prompted several trials using calcium supplementation, yielding disparate results, mostly as a result of wide variations in the study methodologies used and the populations studied.[4,33–35] The most convincing study to date, a large, multicenter, randomized, prospective trial of 2 g of elemental calcium versus placebo in healthy nulliparous women started during the second trimester, showed no significant differences in the incidence or severity of preeclampsia, the prevalence of any hypertensive disorders, or the occurrence of adverse outcomes.[36] However, the case is not closed on calcium. Recent trials have showed significant results when calcium supplementation is used in women at high risk.[31] Larger studies need to be conducted before physicians should recommend its use to patients at high risk of developing preeclampsia.

Aspirin

Evidence that early-onset, widespread endothelial dysfunction and platelet disturbances are at least partly responsible for the preeclamptic syndrome has prompted many investigators to explore the possibility of administering prophylactic low-dose aspirin in the prevention of preeclampsia. Low-dose aspirin could be effective in preeclampsia because it inhibits thromboxane synthesis and thus platelet aggregation; other beneficial effects of aspirin include inhibition of lipid peroxide formation and restoration of vascular refractoriness in angiotensin II-sensitive pregnant women.[37–39]

In the 1980s, some trials with aspirin showed significant reductions in the incidence of gestational hypertension and preeclampsia.[40] The limited size of these trials, however, precluded definitive conclusions from being drawn regarding the benefits of taking aspirin. Subsequently, large trials failed to demonstrate either significant reduction in the incidence of preeclampsia or improved outcomes. One of the most pivotal of these studies was the 1994 CLASP study (Collaborative Low Dose Aspirin Study in Pregnancy), a randomized, placebo-controlled multicenter prospective study of 9364 pregnant women.[41] Data obtained from this study did not support the routine prophylactic or therapeutic administration of low-dose aspirin to all women at increased risk of preeclampsia or fetal growth retardation. However, the CLASP group suggested that low-dose aspirin might be beneficial in a subgroup of women at risk for early-onset, severe preeclampsia. This prompted a multicenter study conducted by the ECPPA (Estudo Colaborativo para Provencao da Pre-eclampsia com Aspirina) in 1996[42] in which the effects of aspirin were examined in specifically high-risk pregnancies. The study included all patients with high blood pressure at the initial visit, angiotensin II sensitivity, a history of chronic hypertension, or primigravidas. The ECPPA study as well as a study by Sibai et al. in 1998[30] failed to demonstrate any decreases in the incidence of preeclampsia or any improvement in outcomes in high-risk pregnancies. These results confirmed the finding from other studies regarding the use of low-dose

aspirin therapy in pregnant women at high risk for developing preeclampsia.[43,44]

The final word on aspirin, however, is not in. In a review of the various trials investigating aspirin use in pregnancy, Dekker emphasizes the problems with compliance in the larger studies and the consequent effects on the results.[37] The 1 trial he considered the most methodologically correct, of 600 healthy nulliparous women, demonstrated a significant decrease in the occurrence of preeclampsia as well as a reduction in pregnancy losses.[45] A 2003 review found that earlier studies in women with historical risk factors failed to show significant benefits as a result of a lack of power.[46] Through metaanalysis of previous randomized trials, they found the use of low-dose aspirin to significantly reduce the risk of developing preeclampsia and the morbidities associated with this condition.

The 1 common thread in all of these trials is the consensus that low-dose aspirin (<81 mg/d) is safe in pregnancy. The disparate results concerning the benefits of taking aspirin only further reflect the multifactorial and still-elusive etiology of the disease.[47] Perhaps therapies aimed at targeting other major factors in preeclampsia such as nitric oxide and serotonin, or alternative attempts at correcting the prostaglandin imbalance such as thromboxane A2 inhibitors, will prove to be effective in protecting against preeclampsia.[48–50]

Vitamins C and E

Oxidative stress from the release of placental factors triggered by poor placental perfusion has been proposed as 1 cause of maternal endothelial cell dysfunction.[51,52] Initial studies focusing on the use of antioxidants to treat women who had already developed preeclampsia had little success in improving their condition.[53] More recently, researchers have investigated the use of vitamins C and E to prevent preeclampsia in women at high risk.[54,55] It was seen that the rate of developing preeclampsia was significantly lower in high-risk women begun on antioxidant therapy at 16 to 20 weeks' gestation as compared with placebo. There, however, continues to be a need for larger studies, including those that examine factors such as safety to the fetus and optimum dosing before recommendations of antioxidant use can be made.

Management of Preeclampsia

Indications for Delivery

The only cure for preeclampsia is delivery, which is the treatment of choice for any woman with preeclampsia (mild or severe) and a favorable cervix for induction at term. Delivery is also warranted for women who develop severe preeclampsia after 34 weeks of gestation. For women between 32 and 34 weeks of gestation with severe preeclampsia, prompt delivery should be considered, especially if prior attempts at conservative management have failed. Women at <28 weeks of gestation who develop severe preeclampsia can be managed conservatively if the mother and fetus are closely monitored in a tertiary perinatal center.[20]

Pharmacology of Mild Preeclampsia

Women who develop mild preeclampsia should be closely observed for signs of rapid deterioration. If such signs are present (ie, headache, epigastric pain, visual changes, or abnormal laboratory results), the patient should be admitted to the hospital. When the blood pressure elevation is mild, the laboratory results are normal, and the fetal evaluation is favorable, management is conservative. Whether the patient is managed conservatively as an inpatient or as an outpatient is dependent on patient compliance. Patients who will maintain bedrest and return biweekly for fetal nonstress testing, and for fetal growth assessment every 2 weeks, can be managed as outpatients. Otherwise, patients can be conservatively managed as inpatients.

There is currently little evidence to support pharmacologic management of mild gestational hypertension or preeclampsia. The primary goal of hypertension treatment in patients remote from term is to prolong pregnancy; however, there have been no compelling studies that have shown prolonged gestational length or improved clinical outcome for patients who are managed with antihypertensive drugs. In fact, studies that have used labetalol to treat women with mild gestational hypertension or preeclampsia have shown no improvement in perinatal outcome, with an increased incidence of infants who were small for gestational age.[56–58] Nonetheless, the risk:benefit ratio for drug treatment in women with mild preeclampsia is unclear,[20] and there is no current uniform recommendation or compelling indication to administer antihypertensive medications to this subgroup.

Pharmacology of Severe Preeclampsia

Before delivery, the treatment goal for women with severe hypertension is to lower the blood pressure to prevent cerebral hemorrhage, the leading cause of maternal death from preeclampsia–eclampsia. Most authors in the current literature agree that treatment should be initiated when systolic levels reach 160 mm Hg and/or diastolic levels reach 110 mm Hg. The U.S. NHBPEP Working Group suggests a threshold of 105 mm Hg with a goal of maintaining the systolic and diastolic pressure between 140–155 mm Hg and 90–100 mm Hg, respectively.[3,31]

Despite considerable investigation of alternative agents with improved side effect profiles (Table 2), intravenous hydralazine, a direct vasodilator, remains the drug of choice for treating severe hypertensive emergencies in pregnancy.[3,21,59] Hydralazine acts directly on the uteroplacental vasculature to reverse vasospasm, and has a long history of success in gestation with acceptable immediate maternal side effects (tachycardia, headache, ventricular arrhythmias) and a low incidence of short- or long-term fetal effects (rarely, thrombocytopenia). There have been no studies showing that hydralazine causes congenital defects.[60]

Parenteral labetalol, an alpha–beta-adrenergic blocker, is rapidly replacing hydralazine as the most commonly used antihypertensive in the treatment of severe preeclampsia. It permits a more rapid and reliable reduction of blood pressure with less acute side effects than hydralazine, most notably, fewer ventricular arrhythmias.[61,62] Risk to the fetus appears

TABLE 2. Drug Therapy for Acute and Severe Hypertension in Pregnancy*

Drug	Dose and Route	Onset of Action	Adverse Effects†	Comments
Hydralazine (C)	5 mg IV or IM, then 5–10 mg every 20–40 min up to 30 mg; constant infusion of 0.5–10 mg/h	IV: 10 min; IM: 10–30 min	Headache, flushing, tachycardia, and possibly arrhythmias, nausea, vomiting	Drug of choice according to NHBPEP Working Group, broad experience of safety and efficacy
Labetalol (C)	20 mg IV, then 40 mg 10–15 min later, then 80 mg every 10–15 min, up to 220 mg; constant infusion of 1–2 mg/min to desired effect, then stop or reduce to 0.5 mg/min	5–10 min	Flushing, nausea, vomiting, tingling of scalp, older literature noted retroplacental bleeding	Experience in pregnancy considerably less than that of hydralazine
Nifedipine (C)	5–10 mg po; repeat in 30 min if necessary, then 10–20 mg po every 3–6 h	10–15 min	Flushing, headache, tachycardia, nausea, inhibition of labor	May have synergistic interaction with magnesium sulfate; experience in pregnancy limited
Diazoxide (C)	30–50 mg IV every 5–15 min	2–5 min	Inhibition of labor; hyperglycemia, fluid retention with repeated doses; rarely used in 1990s	Doses of 150–300 mg may cause severe hypotension; may displace phenytoin from serum protein-binding sites
Sodium nitroprusside‡(C)	0.5–10 μg/kg/min by constant IV infusion	Instant	Cyanide toxicity, nausea, vomiting	Use only in critical care unit at low doses for briefest time feasible; may cause fetal cyanide toxicity

*Indicated for acute elevation of Korotkoff phase V blood pressure >105 mm Hg; goal is gradual reduction to 90–100 mm Hg.
†All agents may cause marked hypotension, especially in severe preeclampsia.
‡Relatively contraindicated. (C) Pregnancy risk per U.S. Food and Drug Administration, adverse effects in animals, no controlled trials in humans, use if risk appears justified.
Adapted from Barron WM: Hypertension. In: Barron WM, Lindheimer MD, eds. *Medical Disorders During Pregnancy,* 2nd ed. St. Louis: Mosby Year Book; 1995.
IV, intravenous; IM, intramuscular; NHBPEP, National High Blood Pressure Education Program; po, orally.

to be lower because fetal heart rate and uteroplacental blood flow do not change significantly with labetalol.[63] Although both drugs appear to be similarly efficacious and well-tolerated,[64] the effects of intravenous labetalol on the fetus and neonate have not been studied as extensively. Some investigators have observed fetal distress and neonatal bradycardia with use of the drug, which may be longlasting.[65] Another roadblock to using labetalol is that the dosing requirements are unpredictable.[63] In various trials, women have required between 20 mg and 300 mg of the drug intravenously to achieve adequate blood pressure control.

Sublingual nifedipine, a calcium channel blocker, has been used for severe hypertension and appears to be at least as effective as hydralazine and labetalol in lowering blood pressure. In fact, 1 recent study found nifedipine to be superior to hydralazine in controlling blood pressure in severe preeclampsia.[66] It was able to achieve blood pressure control more rapidly and to maintain control for a longer period of time. Calcium channel blockers have the capability of lowering maternal blood pressure without compromising placental function. One study showed a significant increase in uteroplacental blood flow that was not observed with other drugs.[67] They also cause a relaxant effect on the cerebral vasculature, and they may help reduce platelet aggregation.[65] Nifedipine use has not been associated with adverse effects on uteroplacental hemodynamics or fetal well-being; however, clinical experience is relatively limited.[68] The 1 main concern with calcium channel blockers is their possible synergy with magnesium sulfate (used for seizure prophylaxis), producing excessive calcium channel blockade and potentiating hypotension and neuromuscular blockade in cases of coadministration.[4] Data regarding this adverse effect are inconclusive, because the effects of synergy have not been demonstrated in any observational or randomized trial.[68] However, several case reports have been published showing the combination of nifedipine and magnesium sulfate to cause these phenomena mentioned here.[69–71] Currently, nifedipine is being used as a second-line drug in those patients who have failed treatment with hydralazine and labetalol.[31]

CHRONIC HYPERTENSION

Classification and Risks

It has been proposed that the trend of women waiting to have children until later in life has caused the incidence of chronic hypertension in pregnancy to rise.[72] Hypertension before pregnancy or a blood pressure of >140/90 mm Hg before the 20th gestational week occurs in up to 5% of pregnant women, who are then considered to have chronic hypertension.[3,72] Most patients with chronic hypertension have essential hypertension, which tends to occur more often in older, obese, black women.[73] The diagnosis can be problematic in women whose blood pressure before pregnancy is unknown, because hypertension before the 20th gestational week could be an early

manifestation of preeclampsia. Moreover, the normal fall in blood pressure in the second trimester may obscure chronic hypertension in a patient who is being evaluated for the first time. The distinction between a patient whose hypertension antedates pregnancy and one who develops a mild rise in blood pressure before 20 weeks' gestation is prognostically significant, because the latter group has excellent clinical outcomes compared with the former group.[74]

Chronic hypertension in pregnancy is further classified as either mild or severe; there is no consensus on the parameters of mild chronic hypertension; however, a diastolic blood pressure >110 mm Hg is classified as severe.[73] The risks associated with pregnancies complicated by chronic hypertension such as fetal growth retardation, premature birth, superimposed preeclampsia, abruptio placentae, perinatal morbidity and mortality, and maternal morbidity correlate more with the onset of proteinuria and elevated uric acid levels than with actual blood pressure levels.[75,76] The exception to this is when the diastolic blood pressure rises to >110 mm Hg during the first trimester, in which case fetal and maternal morbidity and mortality are dramatically increased.[21] Antihypertensive therapy decreases the incidence of stroke and cardiovascular complications in women with diastolic blood pressures >110 mm Hg, as demonstrated by randomized trials in nonpregnant women[77] and retrospective studies in gravidas.[78] Other indicators of poor prognosis include a failure of blood pressure to normalize in midgestation, the presence of secondary hypertension, preexisting cardiovascular, or renal disease, and a history of longstanding severe hypertension.[4,21]

Superimposed Preeclampsia

Superimposed preeclampsia is classically defined as an exacerbation of preexisting hypertension by 30 mm Hg systolic or 15 mm Hg diastolic along with the development of proteinuria. The most reliable indicators of superimposed preeclampsia, however, are not the level of blood pressure or edema, but the onset of significant proteinuria (at least 300 mg/d) or an elevated uric acid level (at least 6 mg/dL) during the second half of pregnancy.[73] The incidence of superimposed preeclampsia varies according to the diagnostic criteria and the severity of the chronic hypertension: 28% to 52% of patients with severe hypertension in the first trimester will develop superimposed preeclampsia unaffected by antihypertensive medications. As few as 4.7% of patients with mild hypertension will go on to develop superimposed preeclampsia.[73] The highest rates of developing superimposed preeclampsia are seen in those women who have renal insufficiency, hypertension for ≥4 years, or hypertension in a previous pregnancy.[30] Women with superimposed preeclampsia need to followed especially closely because the incidence of abruptio placentae is markedly increased.[30]

Indications for Treatment

The issue of whether to initiate drug therapy in a pregnant woman with chronic hypertension remains controversial. Most experts advise against starting treatment in patients with chronic hypertension and diastolic pressures <100 mm Hg because although a reduction in blood pressure may be beneficial for the mother, it has not been shown to improve fetal outcome and may even jeopardize fetal development.[3,4,79] Additional factors to consider in evaluating a patient for drug therapy are the risk of target organ damage and the presence or absence of preexisting cardiovascular disease.[73]

Drug Therapy for Chronic Hypertension in Pregnancy

Women who take antihypertensive medications should be counseled before conception to discontinue those drugs harmful to the developing fetus (angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor blockers, and atenolol) and to replace them with medications proven to be safe and effective in pregnancy (methyldopa, labetalol) (Table 3). The NHBPEP recommends that women with longstanding hypertension, those with target organ damage, and those on multiple antihypertensive medications can be safely

TABLE 3. Antihypertensive Drugs Used in Pregnancy

Drug	Comments
First-line	
Centrally acting α-agonists	Methyldopa (C) is the drug of choice, recommended by the National High Blood Pressure Education Program Working Group; limited data with clonidine (C)
Second-line	
α-blockers	Little data with prazosin, doxazosin, and terazosin (C) except in pheochromocytoma in pregnancy where phenoxybenzamine and prazosin have been used
β-blockers	Atenolol (C) and metoprolol (C) appear to be safe and effective in late pregnancy; labetalol (C), an α-β blocker, is rapidly becoming a first-line drug
Calcium antagonists	Potential synergism with magnesium sulfate may lead to precipitous hypotension (C)
Diuretics	Diuretics (C) are recommended for chronic hypertension if prescribed before gestation or if patients appear to be salt-sensitive; they are not recommended in preeclampsia
Direct vasodilators	Hydralazine (C) is the parenteral drug of choice, based on its long history of safety and efficacy; in combination with methyldopa or β-blockers in those who have failed monotherapy
Contraindicated	
ACE inhibitors, angiotensin II receptor blockers	Fetal abnormalities, including death, can be caused; these drugs should not be used in pregnancy (D)

Adapted from Awad K, Ali P, Frishman WH, et al. Pharmacologic approaches for the management of systemic hypertension in pregnancy. *Heart Dis.* 2000;2:130.

tapered off of their drug therapies. If indicated, they may continue antihypertensive use during pregnancy, with the exception of using ACE inhibitors, angiotensin II receptor blockers, and beta blockers (early on in gestation).[3,80] An alternative strategy for patients with mild essential hypertension is to stop all medications early on in anticipation of a physiological decrement in blood pressure. If the patient then experiences moderate to severe hypertension or develops proteinuria, she can be placed on methyldopa regardless of her previous regimen.[4]

First-Line Therapy

Methyldopa

Any antihypertensive medication has potential adverse maternal and fetal/neonatal side effects that may not manifest until childhood. In addition to their blood pressure-lowering effects, antihypertensive medications can compromise uteroplacental blood flow and affect umbilical or fetal cardiovascular circulation. Methyldopa, a centrally acting agent, remains the first-line blood pressure medicine, because it is the most extensively studied drug in pregnancy with a safety and efficacy profile documented in several prospective randomized trials and in a 7 1/2-year follow-up study of children born to treated mothers.[3,4,80–84] Despite earlier concern, methyldopa has been shown to maintain stable uteroplacental blood flow and fetal hemodynamics.[85] There are very little clinical data with other centrally acting antihypertensive drugs such as clonidine during pregnancy.

Second-Line Therapy

Beta-Adrenergic Blockers

Second-line therapies fall into 1 of 2 general categories: those that are promising but not yet adequately investigated and those causing known adverse side effects that make them less preferable to methyldopa. The use of beta blockers has been widely documented in pregnancy; however, their safety remains unstudied in large trials. These agents cross the placenta and have been associated with various adverse effects, including IUGR, neonatal respiratory depression, bradycardia, and hypoglycemia. Most of these side effects are the consequence of therapies initiated earlier in pregnancy (12–24 weeks).[86] A recent study found atenolol use in pregnancy to be associated with a decreased birth weight in infants compared with no therapy. This effect was seen more often in women given the drug earlier in pregnancy and when it was continued for longer periods of time.[87] Atenolol has also been shown to have adverse effects on uteroplacental and fetal hemodynamics.[88] It is important to note that recent trials demonstrating no significant adverse effects associated with beta blocker use in pregnancy also began treatment later in pregnancy, generally at 29 to 33 weeks' gestation.[4] Beta blockers, therefore, should generally be avoided before the third trimester unless blood pressure cannot be sufficiently controlled by other antihypertensive agents such as methyldopa or hydralazine.

Labetalol

Labetalol, a beta blocker with some alpha-adrenoceptor-blocking activity, has been the subject of much attention because it is a potentially superior antihypertensive agent when compared with those traditionally used in pregnancy. Randomized trials have shown it to be as effective as methyldopa in lowering maternal blood pressure with no significant adverse fetal effects.[81,89,90] However, labetalol has not convincingly been shown to be superior to methyldopa, and there are little or no follow-up data in children born to mothers treated with labetalol during pregnancy. Therefore, based on the available data, this medication is currently recommended as a second-line antihypertensive agent for chronic hypertension in pregnancy.[3]

Hydralazine

As the first-line parenteral drug used in hypertensive emergencies,[91] hydralazine can also be administered orally to control chronic hypertension. Because of its known side effects such as palpitations, headache, and dizziness when the drug is used alone, it is usually administered in combination with methyldopa or a beta blocker. When added as a second-line agent in combination with methyldopa or a beta blocker in patients who have failed monotherapy, the drug appears to be both safe and efficacious.[4] Although hydralazine has not been reported to have any significant adverse effects on the fetus with chronic treatment, long-term follow-up studies are lacking. This drug is currently being recommended for use as a second-line agent.

Calcium Channel Blockers

As discussed previously, dihydropyridine calcium channel blockers are potent vasodilators that have been used successfully in pregnant patients with acute hypertension refractory to hydralazine and labetalol.[31,73] With short-term use, nifedipine, in particular, has been shown to be effective without significant adverse maternal, fetal, or neonatal effects. However, initial reports with nifedipine use in chronic hypertension are limited. When administered alone, ie, not in conjunction with magnesium sulfate, nifedipine (and other dihydropyridine calcium channel blockers) appears to be safe and free of adverse side effects.[92,93] However, data regarding its efficacy in treating chronic hypertension in pregnancy are conflicting. A recent randomized, placebo-controlled trial testing isradipine in women with gestational hypertension or preeclampsia showed a therapeutic blood pressure-lowering effect only for those women with gestational hypertension and not in those women with preeclampsia. Moreover, drug therapy did not halt the progression to proteinuria.[94] In other trials, chronic nifedipine therapy has been shown to successfully lower maternal blood pressure without adverse side effects; however, no significant difference was noted in maternal or fetal outcomes.[95–98] A longitudinal study that investigated the effects of long-term nifedipine therapy for gestational hypertension and preeclampsia demonstrated that drug treatment was not effective in reducing blood pressure.[99] Like with other second-line agents, multiple long-term studies with these drugs are lacking. Nevertheless, nifedipine appears to be safe and, in most cases, efficacious, and can be considered for long-term blood pressure control in pregnancy.[66]

Diuretics

The use of diuretics in pregnancy remains controversial. The current NHBPEP and JNC reports do not discourage continuation of diuretic therapy in patients who were on therapy before pregnancy[3,80]; however, diuretics should always be discontinued if the patient develops superimposed preeclampsia to prevent further volume contraction.[21,73] The Working Group proposes that if diuretics were indicated before pregnancy, they can be continued alone or used to potentate response to other antihypertensives.[3]

Contraindicated

ACE inhibitors and angiotensin II receptor blockers are uniformly contraindicated in pregnancy and should be discontinued before conception because they are known teratogens, causing fetal wastage, renal failure, IUGR, and calvarial hypoplasia.[4]

CONCLUSION

The etiology and pathogenesis of preeclampsia remain unclear, accounting for much of the confusion and discord regarding recommendations for pharmacologic treatment. At present, it is most reasonable to conclude that the disease has a multifactorial etiology, hence the prevention of the disease will most likely entail a combination of therapies. As a result of a lack of long-term follow-up data with the use of newer antihypertensive therapies in pregnancy related to the difficulty (as well as ethical issues) in performing such studies, most investigators and agencies still recommend hydralazine for treatment of acute hypertension and methyldopa for treatment of chronic hypertension in pregnancy.[80] Current second-line drugs that have been used for both acute and long-term control warrant further study because they may offer improved side effect profiles and more stable control of hypertension. Currently, labetalol and nifedipine appear to be the most promising of these drugs.[84,100,101]

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