17 Chronic hypertension and acute hypertensive crisis

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INTRODUCTION

Chronic hypertension occurs in up to 5% of pregnant women (1,2). Rates vary, however, according to the population studied and the criteria used for confirming the diagnosis. Terminology and criteria used to diagnose this complication can be confusing, as well as the benefit and potential harm of treatment during pregnancy. Chronic hypertension may result in maternal, fetal, or neonatal morbidity or mortality. These complications have significant economic impact, including costs of treating sick mothers and neonates and costs of intensive antenatal monitoring. The purposes of this chapter are to review the effects of chronic hypertension on pregnancy, clarify the terminology and criteria used to define and diagnose it during pregnancy, and review evidence about treatment options.

HYPERTENSION IN REPRODUCTIVE-AGE WOMEN

Young hypertensive women who are *not* pregnant are generally active individuals with increased sympathetic tone and elevated plasma renin activity. Extracellular fluid volumes are usually normal or decreased. More than 80% of hypertensive adults have primary or essential hypertension of unknown etiology, that is, without an identifiable cause (3). Most have mild hypertension, defined as a diastolic blood pressure of 90 to 104 mmHg.

Arguments have been made both for and against treating mild elevations of diastolic pressure in young adults. Antihypertensive therapy reduces morbidity and mortality from stroke, coronary artery disease, heart failure, and renal failure for all degrees of hypertension, but the benefit is modest for mild hypertension and is concentrated primarily on those with hypercholesterolemia, glucose intolerance, left ventricular hypertrophy, and cigarette smoking (4).

In the United States, nonpregnant patients with systolic pressure above 140 mmHg or diastolic pressures above 90 mmHg who have not responded to lifestyle modifications are considered to be the candidates for drug intervention. Current European recommendations for drug therapy suggest that both blood pressure and total cardiovascular risk be factored into the decision to begin pharmacotherapy (5). These specific cardiovascular risk factors include abdominal obesity, smoking, dyslipidemia, diabetes, or family history of premature cardiovascular disease.

In the past, a traditional “step-care” approach to pharmacologic treatment of hypertension involved the patient being first given a single commonly used drug such as a beta blocker, calcium channel antagonist, angiotensin-converting enzyme (ACE) inhibitor, or diuretic. The blood pressure response usually is consistent within a given class of agents; therefore, if a drug fails to control blood pressure, another agent from the same class is unlikely to be effective. At times, however, a

change within drug class may be useful in reducing adverse effects. The lowest possible effective dosage should be used to control blood pressure, adjusted every 1 to 3 months as needed. Many patients with stage 1 (mild) hypertension can attain adequate blood pressure control with single-drug therapy (3). The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial suggested that a diuretic was the best initial choice of agent for nonpregnant adults, being equally efficacious and less expensive than the alternatives (6).

When a second drug is needed, it can generally be chosen from among the other first-line agents. A diuretic should be added first, as doing so may enhance effectiveness of the first drug, yielding more than a simple additive effect (7). In considering a modification of therapy because of inadequate response to the current regimen, the physician should investigate other possible contributing factors. Poor patient compliance, use of antagonistic drugs (i.e., sympathomimetics, antidepressants, steroids, nonsteroidal anti-inflammatory drugs, caffeine, thyroid hormones, and cocaine), inappropriately high sodium intake, or increased alcohol consumption should be considered before antihypertensive drug therapy is modified (3).

Preconception Counseling and Early Prenatal Care

Generally, isolated elevated blood pressure or, less commonly, headaches are the only signs or symptoms in women with chronic hypertension. The history should seek to discover secondary causes of hypertension and note the presence of medications that can affect blood pressure (see above.)

Ideally, hypertensive women considering pregnancy should be counseled before conception. They should be informed of the potential for superimposed pre-eclampsia and worsening of renal disease or systemic illness. Valuable baseline data are provided from laboratory tests performed when hypertensive patients are first seen before conception or in early gestation. Tests to help identify target-organ damage and provide a baseline for assessing adverse effects of therapy would include the following: urinalysis, hematocrit, plasma glucose, serum potassium, serum creatinine, calcium uric acid, fasting serum cholesterol and triglyceride level, and electrocardiogram. Baseline determination of renal function (24-hour proteinuria and creatinine clearance), uric acid, transaminase levels, and platelet count are useful for comparison with values in later pregnancy to help determine if increases in blood pressure during pregnancy represent usual physiologic increases or the onset of pre-eclampsia.

Because of the risk of fetal growth restriction, an early sonogram for accurate dating is encouraged. Depending on the circumstance, other various specialized clinical tests at the initial visit may include echocardiography (for left ventricular

hypertrophy), ophthalmologic examination, and renal ultrasonography. Sleep apnea is increasingly recognized as a treatable cause of hypertension, and a screening questionnaire or sleep study may be appropriate.

Normotensive patients with intrinsic renal disease but minimal renal dysfunction usually do well in pregnancy (8). Women with significant renal disease (serum creatinine >1.4 mg/dL) may experience deterioration of renal function. Those with a serum creatinine >2.0 mg/dL and hypertension should be advised of a high incidence of superimposed pre-eclampsia, perinatal morbidity and mortality, and deteriorating renal function (8,9).

Many women with chronic hypertension are under the care of a primary care physician and already have been evaluated for causes of secondary hypertension, such as primary aldosteronism, pheochromocytoma, or Cushing's disease (3). Women with paroxysmal hypertension, frequent "hypertensive crisis," seizure disorders, or anxiety attacks should be evaluated for pheochromocytoma with measurements of 24-hour urine vanillylmandelic acid, metanephrines, or unconjugated catecholamines (10). Primary aldosteronism is rare in pregnancy, but may present with hypokalemia. Imaging studies (magnetic resonance imaging or computed tomography) may be helpful in demonstrating or localizing an adrenal tumor. Doppler flow studies or magnetic resonance angiography can reveal renal artery stenosis (3).

Nonpharmacologic Therapy

Borderline or mildly elevated blood pressures can often be controlled without medication. Diastolic blood pressures from 90 to 99 mmHg are not difficult to attain, because pressures fall during the first and second trimesters in most pregnant women (1). Lifestyle modifications should be encouraged in all hypertensive patients regardless of whether they require medication. These changes may have beneficial effects on other cardiovascular risk factors. Some standard methods of treating hypertension must be changed in pregnancy. For example, weight reduction is not encouraged during gestation, although it is advisable before pregnancy for those who are obese. Saturated fats, alcohol, and smoking should be avoided. Data are insufficient to routinely recommend additional dietary calcium supplementation for the treatment of pregnant women with chronic hypertension.

The severity of hypertension correlates with the extent of plasma volume contraction and that pregnant women with chronic hypertension have lower plasma volumes than normotensive women (11). Thus, sodium is generally not restricted during pregnancy, except for the rare pregnant woman with chronic hypertension who is salt sensitive or whose creatinine clearance is reduced.

Although exercise has not been sufficiently studied in hypertensive pregnant women, theoretic concerns exist about the role of uteroplacental blood flow in the pathogenesis of pre-eclampsia. Strict bed rest is seldom necessary, but despite a lack of formal research on the subject, rest is often prescribed to lower blood pressure and promote diuresis (1). Adjustments may be necessary in child care and employment.

We encourage patients to take their blood pressures outside the physician's office and keep a record of readings (12). Self-monitoring of blood pressure is often helpful in determining

whether borderline or mildly elevated blood pressures remain elevated at home or in the work setting and whether limitation of activity is necessary to better control the blood pressures. Adjustments of drug therapy or withdrawal are more plausible with the knowledge of frequent blood pressure recordings. The patient should have formal instruction on the correct technique for applying the appropriately sized cuff, measuring the blood pressures while sitting. The patient is also to be instructed to notify the office if the blood pressure rises significantly before the next scheduled visit.

Two readings should be taken, separated by 2 minutes. Systolic blood pressure should be noted with the appearance of Korotkoff sounds (phase I) and diastolic blood pressure with the disappearance of sounds (phase V). In certain patients, the Korotkoff sounds do not disappear but are present to 0 mmHg. In this case, the initial muffling of Korotkoff sounds (phase IV) should be taken as the diastolic blood pressure. In order to reduce inaccurate readings, an appropriately sized cuff should be used (length 1.5 times upper arm circumference or a cuff with a bladder that encircles 80% or more of the arm). The appropriate position in which to measure blood pressure is sitting, with the arm at the level of the heart. Measuring BP in the "up" arm with the patient side lying gives an artifactually lower reading, which does not represent a true decrease in BP.

Mild Chronic Hypertension

The goal of treating a pregnant woman with chronic hypertension is to reduce cardiovascular risks to the mother while avoiding compromise of fetal well-being (13). Since most pregnant women with chronic hypertension have only borderline or mild elevations in blood pressure, the risk of acute cardiovascular complication is extremely low.

Pharmacotherapy of mild hypertension at diastolic levels of 90 to 99 mmHg must be undertaken cautiously because of the possibilities that medication may reduce placental blood flow or cross the placenta to directly affect the fetus (1,13). Although the literature is conflicting, many obstetricians do not prescribe drugs for chronic hypertension in pregnancy unless the mother's blood pressure remains above 150/100 mmHg or her hypertension was well controlled by medication before the pregnancy (13). Clinical trials and experience have not shown whether long-term treatment of chronic hypertension prevents pre-eclampsia.

Pharmacologic management of chronic hypertension during pregnancy is too small to either prove or disprove moderate to large benefits (>20% improvements). A paucity of scientific data exists regarding the most appropriate management of women with well-controlled or mild hypertension already taking antihypertensive medications at the time of pregnancy. Although therapy may offer long-term benefits to the mother, such therapy is of unproven short-term benefit and could interfere with uteroplacental blood flow and fetal growth. In a meta-analysis of 623 women with mild chronic hypertension from seven trials comparing antihypertensives with no therapy, drug treatment was associated with a decrease in the incidence of severe hypertension but no improvement in perinatal outcomes (14).

A systematic review of chronic hypertension management during pregnancy revealed that this condition alone doubles

the risk for placental abruption (OR, 2.1; 95% CI, 1.1, 3.9) and triples the risk for perinatal mortality (OR, 3.4; 95% CI, 3.0, 3.7) (13). Several studies in this review demonstrated an association between chronic hypertension and pre-eclampsia (variously defined) and preterm, small-for-gestational age (SGA), or low-birth weight infants when compared with normotensive women or the general obstetric population. The risk of these complications was increased even in the absence of superimposed pre-eclampsia, although the absolute increased risk from mild hypertension could not be calculated (13). In the largest clinical trial, which demonstrated a reduction in perinatal deaths, most women took methyldopa beginning before or during the second trimester. In a review of 263 women with mild hypertension randomized to methyldopa, labetalol, or no treatment at 6 to 13 weeks of gestation, treatment with antihypertensive medications did not decrease the incidence of complications such as intrauterine growth restriction, superimposed pre-eclampsia, placental abruption, or perinatal mortality (13).

Data are inconclusive about the benefits and potential adverse fetal effects from treatment of mild chronic hypertension during pregnancy. It would seem reasonable to defer antihypertensive therapy in women with mild hypertension who become pregnant unless they have other complicating factors (e.g., cardiovascular or renal disease) and to either stop or reduce medication in women who are already taking antihypertensive therapy (1). Adjusting or withdrawing any drug therapy should be undertaken cautiously. A conservative approach is necessary to avoid excessive reductions or rises in blood pressure. As suggested by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, therapy could be increased or reinstituted for women with blood pressures exceeding 150 to 160 mmHg systolic or 100 to 110 mmHg diastolic (15).

Since the evidence for the efficacy of antihypertensive treatment for mild hypertension during pregnancy is lacking, safety considerations are paramount for clinicians who elect to prescribe antihypertensive medication in this indication. The following areas have been suggested by Ferrer et al. for further research: (i) a better understanding of current practice, (ii) benefits and harms of commonly-used, unproven therapies to be tested in large collaborative multicenter and population-based studies among women with clearly established mild chronic hypertension, (iii) comparison between pharmacologic therapy begun early in the course of pregnancy with a placebo and commonly used alternative therapies, (iv) better surveillance systems that routinely monitor adverse events, and (v) large trials that compare alternative strategies and use clinically important outcomes to establish appropriate and cost-effective methods for monitoring (13).

DRUG THERAPY DURING PREGNANCY

Table 1 lists drugs commonly used to treat chronic hypertension before or during pregnancy (3). Standard oral dose regimens and adverse effects to mother and fetus are shown for each medication. The prescribing clinician should know the efficacy of at least a few of these drugs and their acute and long-range effects on fetal well-being.

Nearly all nonpregnant women can achieve adequate blood pressure control with many of these medications. Considerations

about safety during pregnancy are as important as the patient's hemodynamic status. Experience has shown that, except for the ACE inhibitors, the drugs currently prescribed do not alone pose any additional risk of perinatal morbidity or mortality. A detailed description of the different classes of antihypertensive drugs is presented elsewhere, but experience with their use during pregnancy is summarized below (3).

Centrally Acting Adrenergic Inhibitors

Methyldopa was the first antihypertensive used during pregnancy and remains the most commonly prescribed central adrenergic antagonist for pregnant women. Because of its long-term safety, methyldopa is considered by many authorities to be the initial drug of choice for pregnant women with chronic hypertension and the standard by which other drugs are measured (15). Long-term follow-up evaluations of outcomes are reassuring, and studies of children exposed in utero to methyldopa reported normal mental and physical development at 7¹/₂ years of age (16).

Beta-adrenergic Blocking Agents

Many women with chronic hypertension are treated with labetalol (an alpha and beta blocker) or a pure beta₁-adrenergic blocker (e.g., atenolol, metoprolol). Most studies of these drugs include relatively small numbers of cases with gestational ages at entry usually being at 29 to 33 weeks (17). Beta-blocking agents cross the placenta easily; they may interfere with interpretation of the fetal heart rate (FHR) pattern and, in theory, may compromise the fetus's ability to withstand hypoxic stress. A search for growth restriction is recommended after long-term exposure to beta blockers.

Labetalol causes a decrease in maternal blood pressure without diminishing blood flow through the fetal aorta, umbilical vein, or intervillous space (18,19). Based on experimental animal studies and human reports, labetalol therapy does not appear to increase the risk of congenital anomalies (20). This agent compares favorably with other antihypertensive medications for use during pregnancy.

In a meta-analysis of beta-receptor blockers prescribed for pregnancies complicated by hypertension, there was an increase in SGA infants born to those women who took oral beta blockers for mild hypertension (OR, 2.46; 95% CI, 1.02, 5.92) (21). In randomized trials comparing oral atenolol with metoprolol, no adverse fetal effects were demonstrated with either drug (22).

Calcium Channel Blockers

The most experience with calcium channel blockers has been during the second half of pregnancy as a treatment for hypertension or arrhythmias (23–26) or for tocolysis (27–29). Nifedipine, the best known calcium channel blocker, exerts a greater effect on vascular smooth muscle than on the myocardium (30,31). A review on 102 women who received oral nifedipine for tocolysis concluded that therapy appeared safe for mother and fetus (32). A human investigation that utilized Doppler ultrasound techniques to assess fetal and uteroplacental circulation did not uncover any significant effects after short-term nifedipine therapy (33). Oral nifedipine is rapid acting and has been used without complications; however, long-term trials of calcium channel blockers during

Table 1 Standard Oral Doses and Maternal and Fetal Adverse Effects of Antihypertensive Drugs

Drug	Initial oraldose (mg)(usual range)	Maternal adverse effects ^a	Fetal adverse effects
<i>Central adrenergic antagonists</i>			
Methyldopa	250 bid (250–2000)	Sedation, decreased mental acuity, fatigue, sodium retention, hepatic dysfunction, drug fever, positive antinuclear antibody Coombs test, hemolytic anemia, galactorrhea and postural hypotension	None reported
<i>Beta blocker agents</i>			
Metoprolol	50–100 (50–450)	Sodium retention, aggravation of heart failure, bradycardia, depression, aggravation of bronchoconstrictor disease, vivid dreams, interference of diabetic control, CNS disturbances (headache, tremulous)	Intrauterine growth retardation, hypoglycemia, respiratory depression, bradycardia
Atenolol	50 (25–100)		
Labetalol	100 bid (200–1200)		
<i>Vasodilators</i>			
Hydralazine	10 qid (30–300)	Tachycardia, palpitations, flushing, headache, sodium retention, aggravation of angina, lupus syndrome, neuropathy, dizziness	None reported on long-term use; fetal heart rate changes when given acutely at term
<i>Calcium channel blockers</i>			
Nifedipine	10 tid (30–120)	Palpations, flushing, headache, orthostatic hypotension	None reported but chance for reduced placental perfusion
<i>Diuretic</i>			
Hydrochlorothiazide	25 (12.5-50)	Decreased renal blood flow and cardiac output initially	
Furosemide	10–20 (20–320)	Electrolyte depletion, thrombocytopenia hyperuricemia	
^a Maternal adverse effects are usually dose dependent, and low doses are most commonly prescribed during pregnancy. <i>Abbreviation:</i> CNS, central nervous system.			

pregnancy are necessary (29). A comparison of nifedipine and atenolol reported no differences with either agent (34). Fetoplacental hemodynamics, birth weights, and Apgar scores were similar between the two groups.

ACE Inhibitors and Angiotension II Receptor Blockers

Angiotensin-converting enzyme (ACE) inhibitors, such as captopril and enalapril, are commonly prescribed to reproductive-age women. Side effects are minimal, and the drugs have considerable appeal for patients with renal disease. First-trimester effects were suggested by one study but have not been established (35). Women who inadvertently become pregnant on these medications can be switched to an alternative antihypertensive agent.

The U.S. Food and Drug Administration has issued a Public Health Advisory about ACE inhibitors in pregnancy. Use in the second and third trimesters is discouraged because of multiple risks to the fetus, including oligohydramnios, hypoplasia of the calvarium, possible death, and patent ductus arteriosus or anuria in the neonate. Hypoplasia of the fetal calvarium may result from uterine pressure, oligohydramnios, or decreased perfusion to the developing head (36). The teratogenic risk appears to be similar for the entire drug class (37).

Angiotensin receptor blockers are not used in pregnancy by extrapolation from the effects of ACE inhibitors.

Vasodilators

Hydralazine, a peripheral vasodilator, is ineffective when used orally as a sole agent (3). In pregnant women with chronic hypertension, it should be limited to use as a second- or third-line drug. Hydralazine is most often prescribed with methyldopa in treating preexisting hypertension in pregnancy. When hydralazine is combined with a beta-adrenergic blocking agent, reflex tachycardia is lessened and blood pressures are reduced.

It is considered safe for both mother and fetus, although one survey in Scandinavia reported fetal thrombocytopenia (38). Use of the parenteral form is discussed in the section on hypertensive crisis.

Diuretics

Diuretics reduce intravascular volume, and women who use diuretics from early in pregnancy do not develop the expanded blood volume normal in pregnancy (39). Based on experimental animal studies and human experience, hydrochlorothiazide use during pregnancy is not expected to

increase the risk of congenital malformations (37). Theoretically, use during pregnancy might produce fetal biochemical abnormalities and decreased uteroplacental perfusion, but these problems are not believed to occur in women treated chronically with thiazide diuretics beginning prior to conception.

A meta-analysis of nine randomized trials involving more than 7000 patients revealed a tendency toward less edema or hypertension with no increase in adverse fetal effects (40). The National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy concluded, "If diuretics are indicated, they are safe and efficacious agents that can markedly potentiate the response to other antihypertensive agents and are not contraindicated in pregnancy except in settings in which uteroplacental perfusion is already reduced" (15).

Aspirin

Small doses of aspirin (60–100 mg) by women at high risk of pre-eclampsia may reduce the incidence of pregnancy-induced hypertension (41). Conclusions from a multinational study of more than 90,000 women indicated that low-dose aspirin begun before 20 weeks reduced fetal morbidity in a select population (42). These women had preexisting disorders, such as chronic hypertension or renal disease, or had developed pre-eclampsia before 32 weeks of gestation in a previous pregnancy.

No fetal complications attributable to the aspirin have been identified. Low-dose aspirin therapy during pregnancy does not alter fetal cardiovascular wave forms, decrease fetal urine excretion, or increase neonatal bleeding complications (43–45).

WORSENING HYPERTENSION

Risks to women with diastolic blood pressures of 100 mmHg or greater are sufficient to warrant drug therapy. Hospitalization is sometimes necessary. Methyldopa and labetalol are commonly the initial drugs of choice (46). If neither is successful or the patient does not tolerate it, reasonable alternatives are dual therapy, diuretics, or calcium channel blockers.

No evidence exists to show that antihypertensive therapy improves fetal well-being or reduces risks of placental abruption, disseminated intravascular coagulation, seizures, or other maternal complications: (15) with or without drug therapy, both fetus and mother should receive frequent assessments, with special alertness for signs of renal disease or superimposed pre-eclampsia.

It is often difficult, if not impossible, to distinguish worsening chronic hypertension from superimposed pre-eclampsia. The prevalence of superimposed pre-eclampsia averages 15% to 25% among women with chronic hypertension (1). Some studies have shown that infants of chronically hypertensive women who do not develop superimposed pre-eclampsia do as well as those born to normotensive women (1). *However, other studies reported higher perinatal loss rates in otherwise uncomplicated hypertensive pregnancies than those without hypertension.* Coexisting conditions such as renal disease, diabetes, and obesity also affect the risk of perinatal loss.

Signs of superimposed pre-eclampsia may mimic worsening primary renal disease. Conversely, pre-eclampsia may be disguised by pre-existing proteinuria or antihypertensive medications. Some investigators suggest that the diagnosis can be improved by monitoring for decreasing platelet counts and increasing serum uric acid levels. A sudden rise in blood pressure complicated by proteinuria or symptoms of central nervous system irritability should strongly raise the suspicion of superimposed pre-eclampsia. With either superimposed pre-eclampsia or eclampsia, the outlook for both infant and mother can be grave, unless the pregnancy is terminated.

INDICATIONS FOR DELIVERY

Delivery is recommended, even preterm, if superimposed pre-eclampsia develops, renal function deteriorates, severe fetal growth restriction is confirmed, or fetal compromise is suspected on biophysical assessment. The most common techniques of antepartum fetal surveillance are fetal movement counting, nonstress testing, and biophysical profiles. Daily fetal movement charting can begin early in the third trimester. Weekly FHR testing is typically recommended, beginning by the 32nd gestational week. Earlier or more intensive surveillance is probably appropriate if hypertension is more difficult to control or if placental insufficiency is suspected (47).

Serial ultrasound examinations to assess fetal growth are commonly recommended every 3 to 4 weeks during the second half of pregnancy. As long as the fetus continues to grow appropriately and the quantity of amniotic fluid is adequate, it can be inferred that placental function and uterine blood flow are adequate at that time. Oligohydramnios may signify less effective placental perfusion and is associated with umbilical cord compression before and during labor. Doppler assessment of the fetal arterial or venous system is often used as an adjunct.

Hospitalization is indicated when systolic and diastolic values are persistently above 170 and 110 mmHg respectively (despite medication adjustment), the clinician suspects superimposed pre-eclampsia or fetal growth restriction, or antenatal fetal surveillance warrants. Hospitalization allows for intensified maternal and fetal surveillance, for ancillary therapies such as antenatal steroids, and for additional consultation if needed. If maternal condition deteriorates rapidly or fetal compromise persists in the hospital, delivery is indicated. The predictive value of fetal surveillance testing may be invalidated by rapid changes in the maternal health. Evidence of reduced perfusion should be sought periodically in the brain, kidneys, liver, and placenta.

Fetal considerations often dictate the timing of delivery. The physician should reconsider delivery as soon as fetal lungs are documented mature, if control of blood pressure remains problematic, if fetal growth is suboptimal, or if maternal or fetal complications could be ameliorated by delivery. When delivery is anticipated before 34 weeks, corticosteroids are to be given to enhance fetal lung maturity if the mother's condition is stable, and delivery can be delayed at least 24 hours (48). Amniocentesis may be done if determination of pulmonary maturity would influence decision-making.

Whether these plans of action improve perinatal outcome is unclear. Despite good intentions, the approach toward

delivering a very premature but surviving perinate who requires intensive care and faces the attendant risk of long-range developmental disability is open to debate. Such an approach is probably best attempted at tertiary care centers staffed by specialized personnel.

INTRAPARTUM CARE

Vaginal delivery is preferable to cesarean delivery, regardless of gestational age. If the condition permits, an induction of labor should be attempted regardless of cervical condition. A clear endpoint is encouraged from the onset, with delivery usually being expedited within 24 to 48 hours after the decision to induce labor (49). If vaginal delivery cannot be effected within a reasonable time, a cesarean may be preferable. Regional anesthesia is preferred to general anesthesia because of the risk of provoking uncontrolled hypertension when the airway is instrumented.

Although intrapartum analgesia with narcotics may be used, attempting to manage or prevent eclampsia with profound maternal sedation is dangerous and ineffective. Epidural anesthesia is permissible when an experienced anesthesiologist is available and no coagulopathies are present. Hazards include the possibility of extensive sympathectomy with resultant decreased cardiac output, maternal hypotension, and impairment of an already compromised uteroplacental perfusion (1). The advantage, of course, is that epidural anesthesia blunts the sympathetic response to pain, which may be exaggerated in women with preexisting hypertension. Women with chronic hypertension complicated by significant cardiovascular or renal disease require special attention to intake and urine output, because they may be susceptible to fluid overload with resultant pulmonary edema.

POSTPARTUM CONSIDERATIONS

Acute hypertensive changes usually dissipate within the first few days after delivery. The likelihood of underlying chronic hypertension is greatly increased if hypertension persists more than 3 days after delivery. In such cases, oral antihypertensive therapy is often begun before discharge and the women are reevaluated in the next week. Hypertension that persists longer than the postpartum period (12 weeks post delivery) is classified as chronic (1).

Reinstituting the prepregnancy regimen treatment is often appropriate for women who were previously well controlled. As an alternative, either oral nifedipine or labetalol is commonly prescribed, using the lower doses shown in Table 1. Self-blood pressure monitoring at home or work is helpful in determining the need to continue any antihypertensive agent. If prepregnancy blood pressures were normal or unknown, it is reasonable to stop medications after 3 to 4 weeks and observe.

Many chronically hypertensive women wish to breastfeed. When hypertension is mild, medication may be withheld and the blood pressure should be observed closely. For a breastfeeding mother with more elevated recordings, the clinician should continue drug therapy at the lowest effective dose. All agents have low but measurable amounts in the milk, and no clinical trials have studied the cardiovascular effects of an antihypertensive agent on the breast-fed infant (50). Most antihypertensive drugs, including ACE inhibitors, are

considered "compatible with breastfeeding" by the American Academy of Pediatrics.

Postpartum contraception is advisable to reduce the risk of an unplanned pregnancy. Oral contraceptives, depot medroxyprogesterone acetate (Depo Provera), and other hormonal contraception are not contraindicated in chronically hypertensive patients who are under 35 and do not smoke, as long as the blood pressure is controlled and monitored (51).

HYPERTENSIVE CRISIS

Hypertensive emergencies still occur, albeit less frequently: in the years before the availability of antihypertensive drugs, 7% of individuals with hypertension could expect to develop a hypertensive emergency (with an associated 1-year mortality risk nearly 80%); the figure is now 1% to 2% (52,53). Most patients who develop a hypertensive crisis have a history of hypertension, often inadequately treated. This may not be the case in pregnancy, however, where hypertensive crisis may manifest against a background of either chronic hypertension or pre-eclampsia.

Incidence and Definition

Hypertensive crisis can occur at any time before or after delivery. There are no reliable data on the incidence of hypertensive crisis complicating pregnancy. A query of the National Hospital Discharge Survey for severe maternal morbidity included 50 million deliveries and reported 36,000 cases of eclampsia and 6000 cerebrovascular accidents in the United States across the time period from 1991 to 2003 (54). This excludes those pregnant women whose hypertensive crisis did not result in one of those diagnoses, but it would appear that in the United States at least 3500 women per year develop a hypertensive crisis during pregnancy, which is roughly 1 per 1000 live births. Figures from Canada appear to be about half of that (55).

The clinical entity of hypertensive crisis is poorly defined, but this term has replaced earlier terms such as "malignant hypertension" and "accelerated hypertension." While it seems intuitively obvious that it refers to a state of severe hypertension, there is no consensus as to the degree of hypertension involved. The Joint National Committee (JNC) on Detection, Evaluation, and Treatment of High Blood Pressure (JNC) reports of 1993 and 1997 divided acute severe hypertension into categories of "hypertensive emergency" and "hypertensive urgency" (56,57). The distinction between the two related not to blood pressure measurement but to the presence of end-organ damage. The most recent iteration, JNC 7, does not address hypertensive emergency specifically but refers to stage 1 (systolic BP 140–159 mmHg or diastolic 90–99 mmHg) and stage 2 (systolic ≥ 160 mmHg or diastolic ≥ 100 mmHg) hypertension, largely for the purposes of initiating outpatient drug therapy (7). JNC 8 is scheduled for release in 2010 and may redress this flaw (58).

Pathophysiology

The pathophysiology of hypertensive crisis is still inadequately understood. Because blood pressure is determined by cardiac output and peripheral vascular resistance, and cardiac output itself is a product of heart rate and stroke volume, there are several possible triggers, but it appears that an abrupt increase

in systemic vascular resistance is most commonly involved (53). Mechanical stress causes vascular endothelial damage, which in turn provokes increased permeability, activation of the coagulation cascade, and fibrin deposition. Fibrinoid necrosis of the arterioles can further decrease vascular perfusion and thus activate the mediators commonly associated with ischemia, further worsening injury. In many (but not all) hypertensive crises, the renin–angiotensin system is activated, forcing further vasoconstriction and production of inflammatory cytokines (59). Because of pressure natriuresis, effective circulating volume is decreased: this stimulates the kidney to produce vasoconstrictive mediators. A feed-forward loop or vicious circle becomes difficult to break.

Hypertensive Crisis: Emergency Vs. Urgency

Individuals with systolic blood pressure ≥ 180 mmHg, or diastolic ≥ 110 mmHg, are commonly considered to be in a state of hypertensive crisis (53). If evidence exists for acute target-organ involvement (Table 2), then pressures must emergently be reduced, within the next 1 to 2 hours, to limit damage or prevent further organ failure: this qualifies as a hypertensive *emergency*. In the absence of end-organ findings, while it is certainly prudent to begin measures to lower blood pressures, the process can be allowed to take 24 hours or longer, and the situation is hypertensive *urgency*.

This cutoff point, admittedly arbitrary, is even less well defended in the case of hypertension in pregnancy. Current guidelines from the American College of Obstetricians and Gynecologists allow a diagnosis of severe pre-eclampsia if a systolic pressure of ≥ 160 mmHg is achieved or any of the criteria in Table 3 is met (60). Comparing these with the standard list of clinical syndromes, which defines hypertensive emergency, CNS findings, pulmonary edema, and thrombocytopenia or microangiopathic hemolytic anemia are common to both. Martin et al. have suggested that systolic blood pressure in pre-eclampsia is far more important than diastolic and reported that in 96% cases of stroke related to pre-eclampsia, systolic pressure was greater than 160 mmHg immediately preceding the event (61).

While nonpregnant patients with hypertensive crisis most commonly present to emergency care with symptoms related to target-organ involvement, this may not be true for pregnant patients, who have many interactions with the health-care system during pregnancy. The pregnant patient with hypertensive crisis (e.g., hypertensive urgency rather than emergency) may be asymptomatic and be admitted for evaluation after hypertension is noted in the office. As a rule, the patient with abnormally high blood pressure but no signs or symptoms of target-organ damage is considered to have a hypertensive *urgency* rather than *emergency*. Unlike true hypertensive emergency, hypertensive urgency allows 24 to 48 hours to normalize blood pressure: oral agents are acceptable. It is prudent to lower mean arterial pressure gradually so that the limits of autoregulation are not exceeded.

Initial Evaluation and Management

If a hypertensive crisis is suspected, then diagnosis, assessment, and therapy should proceed at equal pace. In the setting of hypertensive emergency, speed of intervention is important in limiting complications. A history should be obtained, focusing

Table 2 Hypertensive Emergency: Organ System and Clinical Manifestation

Cerebral	Hypertensive encephalopathy Stroke
Cardiovascular	Acute aortic dissection Acute myocardial infarction Acute left ventricular failure
Renal	Acute renal failure
Hematologic	Microangiopathic hemolytic anemia
Placental	Severe pre-eclampsia (?) Eclampsia HELLP syndrome

Abbreviation: HELLP, hemolysis, elevated liver enzymes, and low platelet count.

Table 3 Criteria for Diagnosis of Severe Pre-eclampsia (One or More of the Following)

BP ≥ 160 mmHg systolic <i>or</i> ≥ 110 diastolic (two occasions, at least 6 hr apart)
Proteinuria ≥ 5 g in 24 hr
Oliguria (<500 ml in 24 hr)
Cerebral or visual disturbances
Pulmonary edema or cyanosis
Epigastric or right upper quadrant pain
Impaired liver function
Thrombocytopenia
Fetal growth restriction

on any known history of hypertension, medications (prescribed, over-the-counter, and illicit), obstetric history, and symptoms. Blood pressure should be measured in each arm, with the patient sitting, using the correctly sized cuff. The remainder of the physical examination should incorporate assessment for pulmonary edema, peripheral pulses, and neurologic evaluation. In the nonpregnant patient with hypertensive crisis, fundoscopic examination of the retinas and auscultation of the flanks for bruits in the renal arteries are recommended as well (53), but in the hands of an obstetrician–gynecologist inexperienced in these examinations, they are likely to be of low yield.

Blood should be sent for electrolytes, blood urea nitrogen, serum creatinine, hepatic function, complete blood count, and coagulation profile. If a specific concern exists (illicit drug use, pheochromocytoma), additional laboratory testing should be ordered as relevant. Fetal assessment is important. Fetal cardiac activity should be confirmed or excluded immediately upon admission. Ultrasound assessment for fetal growth, amniotic fluid, Doppler, and the like should be deferred until after the maternal condition is stabilized. The utility of electronic fetal monitoring is discussed below.

Once diagnosed with a hypertensive *emergency* (abnormally high BP plus evidence of target-organ damage), the patient must be treated immediately with the goal of reducing BP within 1 to 2 hours. This will require parenteral medication and high-acuity nursing care. It will often require minute-to-minute evaluation, so the threshold for intra-arterial monitoring should be low. There are no good clinical trials that could

Table 4 Drug Therapy for Acute Hypertensive Crisis

Drug	Drug classification	FDA pregnancy category	Dose (initial)	Dose adjustment	Onset	Duration	Side effect profile	Notes
Clevidipine	Calcium channel blocker (dihydropyridine)	C	1–2 mg/hr iv infusion	Initially, double dose q 90 sec; as target BP approached, lengthen interval to 5–10 min, decrease to less than doubling, based on patient response; max 16 mg/hr	2–4 min	5–15 min after stopping infusion	Atrial fibrillation, nausea, headache, tachycardia	Lipid emulsion; cannot use if allergic to soy or eggs; adverse effects on lipid profile
Enalaprilat	Angiotensin-converting enzyme inhibitor	C (first trimester)	1.25 mg iv	Repeat q 6 hr, max 5 mg			Nausea, vomiting, headache	
Esmolol	Beta ₁ blocker	C	500 mcg/kg/min load over 1 minute, followed by 50 mcg/kg/min × 4 min	May repeat loading dose (500 mcg/kg/min), then increase infusion rate by 50 mcg/kg/min, q 5 min; as target approached, lengthen interval or decrease increment	Immediate	<10 min	Bradycardia, injection site pain, nausea	Metabolized by red blood cell esterases; independent of hepatic or renal function
Fenoldopam	Dopamine (D1) receptor agonist	B	No bolus dose; begin infusion at 0.03–0.1 mcg/kg/min	Increase q 15 min by 0.05–0.1 mcg/kg/min, max dose 1.6 mcg/kg/min		5 min	Flushing, nausea, headache, tachyarrhythmia	
Hydralazine	Peripheral vasodilator (arteriolar)	C	5 mg IV bolus	10 mg, 20 mg	15–20 min	3–6 hr	Tachyarrhythmia, headache, nausea, dyspnea	Rarely: hepatotoxicity, lupus. Promotes salt/water retention. Tachyphylaxis common
Ketanserin	Serotonin receptor blocker	n/a	5–10 mg IV bolus followed by 4 mg/hr	Repeat bolus, increase infusion rate by 2 mg/hr; dose may be adjusted at 20-min intervals, max infusion rate 14 mg/hr	10–20 min	13–16 hr	May inhibit uterine contractions. Failure rate appears to be high. Q–T prolongation	Not FDA approved; used in Europe, South Africa

Labetalol	Mixed alpha and beta blocker (beta predominates, 7:1)	C	10–20 mg IV bolus	Repeat q 5–10 min, doubling the dose to max bolus 80 mg. Continuous infusion 1–2 mg/min is an alternate to bolus dosing	2–5 min	3–6 hr	Bradycardia, dizziness, GI effects, abnormal liver function, hypoglycemia	
Nicardipine	Calcium channel blocker (dihydropyridine)	C	Initial rate 5 mg/hr	Increase rate by 2.5 mg/hr q 5–15 min; max 15 mg/hr	5–10 min	1–4 hr	Tachycardia, dizziness, headache, edema	
Nitroglycerin	Nitrate, vasodilator (venous and arteriolar)	C	Initial rate 5 mcg/min	Increase rate by 5 mcg/min q 3–5 min, max 100 mcg/min	2–5 min	3–5 min	Tachyarrhythmia, headache, nausea, dizziness, visual disturbance; rare hematologic	
Sodium nitroprusside	Vasodilator (venous and arteriolar)	C	No bolus; begin at 0.2–0.3 mcg/kg/min	Increase by 0.2–0.5 mcg/kg/min (q 5 min) to usual max 2 mcg/kg/min; rarely as high as 5 mcg/kg/min. Use lowest dose possible, shortest time possible	Instant	~1 min	Bradyarrhythmia, tachyarrhythmia, rash, sweating, dizziness, headache, altered mental status, restlessness, azotemia	Metabolic acidosis, cyanide toxicity, thiocyanate toxicity. Therapeutic and toxic ranges may overlap. No quick lab test for cyanide level exists
Phentolamine	Alpha blocker	C	1–5 mg iv bolus		1–2 min	5–15 min	Dysrhythmia, nasal congestion	
Trimethaphan	Ganglionic blocker	D	Initial rate 0.5–1 mg/min	Increase by 0.5–1 mg/min, max 15 mg/min	1–5 min	10 min	Tachyarrhythmia, hyperglycemia, hypokalemia, GI symptoms, diplopia, pupillary dilation, paralytic ileus, urinary retention	

form the basis for the management of hypertensive emergencies, let alone hypertensive emergencies in the setting of pregnancy. Management as currently recommended is driven largely by expert and consensus opinion. Given these caveats, the recommendation is to aim for a reduction in mean arterial pressure of 15% to 25% over 1 to 2 hours (53,62,63). While the presence of symptoms is a clear indicator that blood pressure is dangerously high, a too-rapid or too-acute lowering risks worsening the ischemia, which already accompanies hypertensive crisis and may exceed the threshold of autoregulation, particularly in the cerebral circulation. At this time, it seems appropriate to remark upon the sensitivity of the uteroplacental circulation to perfusion pressure and to note that an exaggerated drop in blood pressure is frequently reflected in decelerations in the FHR tracing.

Drug Therapy

The ideal agent for use would be easily administered, have a rapid time to both onset and offset, be easily titratable, free of side effects, and well tested in pregnancy. Unfortunately, none of the agents currently available meet these criteria. Hydralazine and labetalol are the drugs most commonly used in obstetrics for hypertensive crises. Hydralazine, contrary to popularly held opinion, has a number of factors that render it unsuitable in the setting of hypertensive crisis (53). Its onset of action can be delayed by as long as 20 minutes after bolus injection, its effect is unpredictable (especially in the common scenario of volume depletion), and its duration is unacceptably long (up to 6 hours). It has been shown in a meta-analysis to produce far higher rates of maternal hypotension than other antihypertensives, more adverse effects on the FHR, and more maternal side effects: these side effects are commonly headache and nausea, which are easily confused with deterioration of the clinical condition (64). While labetalol shares with hydralazine a long duration of effect, the response to labetalol is typically seen within 5 minutes, so the risk of overshoot is lower.

Other drugs that have been used to treat hypertensive crisis include sodium nitroprusside, nitroglycerin, nicardipine, esmolol, clevidipine, fenoldopam, phentolamine, trimethaphan, enalaprilat, ketanserin, and diazoxide (Table 4). Because of their immediate effects, they are best given when the patient has an arterial line in place. Most of these are given by continuous infusion and must be titrated to effect. Depending on local protocol, the use of vasoactive infusions may require the patient be admitted to an intensive care unit. The intravenous form of diazoxide is no longer manufactured, and so it is of historical interest only. Enalaprilat has occasionally been used for hypertensive crisis in nonpregnant patients, but like all ACE inhibitors, it should not be used in pregnancy.

Data in pregnancy are limited for most of these drugs: nicardipine, nitroglycerin, sodium nitroprusside, and esmolol have been reported. Nicardipine is developing a track record in pregnancy. It has been used successfully as a second-line treatment for pre-eclampsia after failure of ketanserin, labetalol, or hydralazine (65). In a small randomized trial, intravenous nicardipine was just as efficacious as labetalol for controlling blood pressure in hypertensive emergency during pregnancy (66). It has definite advantages over hydralazine, being a more predictable and titratable drug, with a much shorter time to onset and quicker disappearance once discontinued.

Trimethaphan and phentolamine have largely been replaced by other drugs of better efficacy and greater predictability, and ketanserin is not available in the United States. There are, as yet, no data on fenoldopam or clevidipine in pregnancy.

Whichever drug is chosen, the goal is to reduce mean arterial pressure by 15% to 25% within 1 to 2 hours and then gradually lower BP into the range of 160/100 over the next 2 to 6 hours (67). During this period of time, judicious volume repletion should also occur, since the majority of patients in hypertensive crisis will be significantly volume depleted because of pressure natriuresis. Precipitating factors should be corrected if identified (i.e., conditions of catecholamine excess, drugs that may contribute to hypertension, etc.). The FHR should be monitored both as a sign of uteroplacental perfusion and as a sign of fetal status: placental abruption is an ongoing concern in severe hypertension, and fetal growth restriction, a common complication of pre-eclampsia, signifies a tenuous fetal status that may require intervention. It is inappropriate, however, to rush to delivery before maternal status is stabilized. In cases in which fetal compromise is thought to exist, if delivery is contemplated, it will usually be by cesarean, and both anesthesia and surgery entail risks in the unstable patient. Stroke is an especially feared complication when a patient with inadequately controlled hypertension requires laryngoscopy and intubation for a general anesthetic.

Once blood pressure control has been achieved with parenteral agents, oral medications can generally be started while the parenteral drug is being tapered (68). However, in case of pregnancy, hypertensive crisis often means a commitment to delivery. Absorption of oral medications may be unpredictable in labor, and is not feasible during abdominal surgery, and therefore the plan is often to defer oral agents until after delivery, whether vaginal or cesarean. Oral agents should be started at a low dose and increased as necessary to the desired effect. Agents that have been used in pregnancy include nifedipine, clonidine, and labetalol; postpartum, the ACE inhibitors can also be used. There is no good role for methyldopa or oral hydralazine as a follow-up agent after hypertensive crisis in pregnancy, because adequate blood pressure control is crucial in preventing another episode.

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