CHAPTER 50: Chronic Hypertension

A small proportion of women suffering from chronic nephritis had eclampsia. For the most part, autopsy will reveal the presence of renal changes usually of acute nephritis, though occasionally it may be engrafted upon a chronic process.

—J. Whitridge Williams (1903)

INTRODUCTION

At the time of *Williams Obstetrics*' first edition, little attention was paid to blood pressure changes, even with "toxemia." At that time, chronic hypertension was designated "senile" and thought to develop only in older individuals (Lindheimer, 2015). Indeed, chronic hypertension is not mentioned, per se, in Williams' 1903 textbook, except for some deference given to chronic anatomical renal changes occasionally associated with eclampsia.

It is now apparent that chronic hypertension is one of the most common serious complications encountered during pregnancy. This is not surprising because, according to the National Health and Nutrition Examination Survey (NHANES) from the Centers for Disease Control and Prevention (2011), the prevalence of hypertension in women aged 18 to 39 years approximates 7 percent.

The incidence of chronic hypertension complicating pregnancy varies depending on population vicissitudes. In a study of more than 56 million births from the Nationwide Patient Sample, the incidence was 1.8 percent (Bateman, 2012). And, in more than 878,000 pregnancies from the Medicaid Analytic Extract, 2.3 percent were complicated by chronic hypertension (Bateman, 2015). Despite this substantive prevalence, optimal management has not been well studied. It is known that chronic hypertension usually improves during early pregnancy. This is followed by variable behavior later in pregnancy and, importantly, by the unpredictable development of superimposed preeclampsia. The latter carries increased risks for maternal and perinatal morbidity and mortality.

GENERAL CONSIDERATIONS

To define chronic hypertension, the range of normal blood pressure must first be established. This is not a simple task because, like all polygenically determined biological variants, blood pressure norms differ between populations. And, within these norms, wide variations are found between individuals. Moreover, numerous epigenetic factors influence presentation. For example, not only do blood pressures vary between races and genders, but pressures—especially systolic—rise directly with increasing age and weight. Thus, pragmatically, normal adults have a broad range of blood pressures, but so do those with chronic hypertension. And finally, resting blood pressure measurements do not reflect daily activities.

After these variables are acknowledged, important considerations for any population are the attendant risks of chronic hypertension. It is a leading cause of death and accounts for nearly 15 percent of mortality worldwide. Approximately 65 million Americans have hypertension, and this number is growing concurrently with epidemic obesity (Kotchen, 2015). Hypertension increases substantively the risk of cardiovascular disease, coronary heart disease, congestive heart failure, stroke, renal failure, and peripheral arterial disease (Forouzanfar, 2017).

Definition and Classification

For the foregoing reasons, chronic hypertension would logically be defined as some level of sustained resting blood pressure that is associated with acute or long-term adverse effects. In this regard, most consider 140/90 mm Hg as the upper limit of normal for blood pressure values. But, in the United States, these values are based primarily on actuarial tables constructed using data derived from white adult males and compiled by life insurance companies. These "norms" disregard interrelated factors such as ethnicity, gender, and other important covariants. The importance of race, for example, was emphasized by Kotchen (2015), who cites the incidence of hypertension—defined as blood pressure >140/90 mm Hg—to be 34 percent in blacks, 29 percent in whites, and 21 percent in Mexican Americans.

For many years, the Joint National Committee has promulgated guidelines for diagnosis, classification, and management of chronic hypertension. In 2008, the National Heart, Lung, and Blood Institute discontinued these guidelines, and the Joint National Committee 8 (JNC 8) was instead asked to provide an evidence-based review (James, 2014). Findings pertinent to caring for young women with chronic hypertension are summarized in Table 50-1.

TABLE 50-1

Eighth Joint National Committee (JNC 8)—2014 Chronic Hypertension Guidelines and Recommendations

Evidence-based recommendations from randomized controlled trials

Definitions for hypertension and prehypertension not addressed

Lifestyle modifications endorsed from the Lifestyle Work Group (Eckel, 2013)

Recommend selection among four specific medication classes: angiotensin-converting enzyme inhibitors (ACE-I), angiotensin-receptor blockers (ARB), calcium-channel blockers, or diuretics:

- General population: <60 years old—initiate pharmacological therapy to lower diastolic pressure ≤90 mm Hg and systolic pressure ≤140 mm Hg
- Diabetics: lower pressure to <140/90 mm Hg
- Chronic kidney disease: lower pressure to <140/90 mm Hg. Also add ACE-I or ARB to improve outcomes
- General nonblack population: initial therapy should include thiazide-type diuretic, calcium-channel blocker, ACE-I, or ARB
- General black population: primary antihypertensive therapy should include thiazide-type diuretic or calcium-channel blocker
- Assess monthly, and after 1 month, if goals not met, then increase primary drug dose or add second drug. If no response, increase either or add third drug; then if no response, refer to hypertension specialist

Summarized from James, 2014.

Treatment and Benefits for Nonpregnant Adults

Proven benefits accrue with treatment of otherwise normal adults who have sustained hypertension. Numerous studies evaluating many combinations of antihypertensive therapy have been conducted. Importantly, these trials evaluated monotherapy versus combination therapeutic regimens and their ethnospecific benefits. Most evaluated cardiovascular outcomes, but many also confirmed risk reductions in rates of cerebrovascular accident, renal insufficiency, and mortality. Because of these incontrovertible benefits, the JNC 8 recommends the management outlined in Table 50-1.

Thus, even for mildly elevated blood pressure, interventions to reduce these sequelae are beneficial (SPRINT Research Group, 2015). Moreover, antihypertensive therapy in nonpregnant reproductive-aged women with sustained diastolic pressures ≥90 mm Hg is considered standard. Not clear from these observations, however, is what constitutes the best management for women being treated who contemplate pregnancy, for those undergoing treatment who become pregnant, or for those first identified to have chronic hypertension during pregnancy (August, 2015). In these women, the benefits and safety of instituting antihypertensive therapy are less clear, as subsequently discussed in Antihypertensive Treatment in Pregnancy.

Preconceptional Counseling

Women with chronic hypertension are ideally counseled before pregnancy. The duration of hypertension, degree of blood pressure control, and current therapy are ascertained. Those women who require multiple medications for control or those who are poorly controlled carry greater risk for adverse pregnancy outcomes. Home measurement devices are checked for accuracy. General health, daily activities, and dietary habits are also assessed (Table 50-2).

TABLE 50-2

Lifestyle Modifications for Hypertensive Patients

Weight reduction
Consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils, and nuts; limits sweets and red meats. Examples are DASH, USDA Food Pattern, or the AHA Diet
Lower sodium intake—consume no more than 2400 mg sodium/d; 1500 mg/d desirable
Engage in aerobic physical activity three to four sessions per week, lasting on average 40 minutes per session, and involving moderate-to-vigorous intensity physical activity
Moderation of alcohol consumption

AHA = American Heart Association; DASH = Dietary Approaches to Stop Hypertension; USDA = United States Department of Agriculture.

Summarized from Eckel, 2013; Kotchen, 2015.

For hypertensive women with disease lasting longer than 5 years or with comorbid diabetes, cardiovascular and renal function is assessed (August, 2015; Gainer, 2005). Women with evidence for organ dysfunction or those with prior adverse events such as a stroke, myocardial infarction (MI), arrhythmias, or ventricular failure are at markedly higher risk for a recurrence or worsening dysfunction during pregnancy. Renal function is evaluated by serum creatinine measurement. Also, if a urine spot protein/creatinine ratio is abnormally high (>0.3), proteinuria is further quantified with a 24-hour urine collection (Hladunewich, 2011; Kuper, 2016; Morgan, 2016a). The Working Group Report on High Blood Pressure in Pregnancy (2000) of the National Heart, Lung, and Blood Institute concluded that the risks of fetal loss and accelerated renal disease deterioration are increased if the serum creatinine level is above 1.4 mg/dL (Chap. 53, Chronic Kidney Disease).

Although pregnancy is considered by many to be contraindicated in women with severe, poorly controlled hypertension, there is no consensus. Certainly, women who maintain persistent diastolic pressures ≥110 mm Hg despite therapy; require multiple antihypertensives; have a serum creatinine level >2 mg/dL; or have a history of prior stroke, MI, or cardiac failure must be counseled as to the marked risks to themselves and to their pregnancy outcome.

DIAGNOSIS AND EVALUATION IN PREGNANCY

The hypertensive disorders that uniquely complicate pregnancy are discussed in Chapter 40 (Terminology and Diagnosis). Women are diagnosed with chronic hypertension if it is documented to precede pregnancy or if hypertension is identified before 20 weeks' gestation. Evidence also supports that *prehypertension* may herald adverse outcomes similar to those in women with chronic hypertension (Rosner, 2017). In some women without overt chronic hypertension, a history of repeated pregnancies complicated by gestational hypertension, with or without the preeclampsia syndrome, may be elicited. Each is a risk marker for latent chronic hypertension, and this is especially so for preeclampsia, and in particular early-onset preeclampsia. In many ways, gestational hypertension is analogous to gestational diabetes in that such women have a *chronic hypertensive diathesis*, in which heredity and environment play a major role.

Although uncommon, secondary causes of hypertension are always a possibility in affected women. Thus, consideration is given to underlying chronic renal disease, connective-tissue disease, primary aldosteronism, Cushing syndrome, pheochromocytoma, and myriad other causes. That said, most pregnant women with antecedent hypertension will have otherwise uncomplicated disease.

Associated Risk Factors

Several factors increase the likelihood that pregnant women will have chronic hypertension. Three of those most frequently cited are ethnicity, obesity, and diabetes. As previously discussed, chronic hypertension has a population incidence that is highest in black women and lowest in Mexican-American women (Kotchen, 2015). Related to this, hundreds of blood pressure-related phenotypes and genomic regions have been identified, including candidate genes for preeclampsia and chronic hypertension (Cowley, 2006; Ward, 2015).

The *metabolic syndrome* is a clinical cluster that includes hypertension, high blood sugar, excess fat at the waist, and abnormal cholesterol or

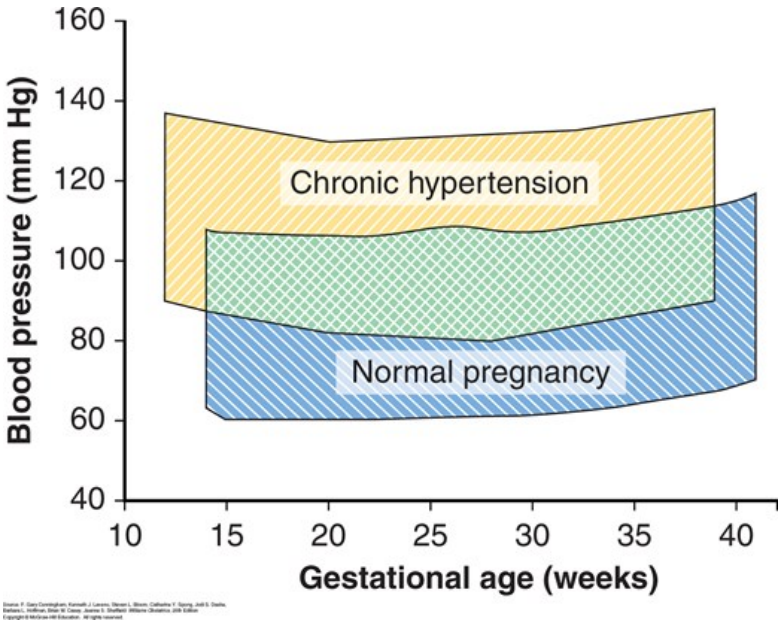
triglyceride levels. This constellation is a risk marker for superimposed preeclampsia and for persistent postpartum hypertension (Jeyabalan, 2015; Spaan, 2012). This is not surprising because obesity may increase the prevalence of chronic hypertension tenfold (Chap. 48, Pregnancy and Obesity). In addition, obese women are more likely to develop superimposed preeclampsia. Diabetes is also prevalent in chronically hypertensive women, and its interplay with obesity and preeclampsia is overwhelming (Leon, 2016). In aforementioned study from the Nationwide Patient Sample, the most frequent comorbidities associated with chronic hypertension were pregestational diabetes—6.6 percent, thyroid disorders—4.1 percent, and collagen-vascular disease—0.6 percent (Bateman, 2012). Similar comorbidities were described by Cruz and associates (2011).

Effects of Pregnancy on Chronic Hypertension

Blood pressure drops in early pregnancy in most women with chronic hypertension, and it rises again during the third trimester (Fig. 50-1). According to studies by Tihtonen and coworkers (2007), women with chronic hypertension have persistently elevated vascular resistance and possibly reduced intravascular volume expansion. Adverse outcomes in these women are dependent largely on whether superimposed preeclampsia develops. This may be related to observations reported by Hibbard and colleagues (2005, 2015) that arterial mechanical properties are most marked in women with superimposed preeclampsia.

FIGURE 50-1

Mean systolic and diastolic blood pressures across pregnancy in 107 untreated chronically hypertensive women (*yellow*) compared with blood pressures across pregnancy in 4589 healthy nulliparas (*blue*). (Data from August, 2015; Levine, 1997; Sibai, 1990a.)



ADVERSE PREGNANCY EFFECTS

Chronic hypertension is associated with several adverse maternal and perinatal outcomes listed in Table 50-3. In sum, these adversities are directly related to severity and duration of hypertension before pregnancy and whether superimposed preeclampsia develops, especially early in gestation. Importantly, in women with mild chronic hypertension, outcomes are also related to blood pressure levels during pregnancy. At this time, however, there are no proven benefits of "tight" versus "less-tight" control of chronic hypertension during pregnancy, as discussed later ("Tight Control") (Magee, 2015).

TABLE 50-3

Some Adverse Effects of Chronic Hypertension on Maternal and Perinatal Outcomes

Maternal	Perinatal
Superimposed preeclampsia	Stillbirth
HELLP syndrome	Growth restriction
Placental abruption	Preterm delivery
Stroke	Neonatal death
Acute kidney injury	Neonatal morbidity
Heart failure	
Hypertensive cardiomyopathy	
Myocardial infarction	
Maternal death	

HELLP = hemolysis, elevated liver enzyme levels, low platelet count.

Maternal Morbidity and Mortality

Most women whose chronic hypertension is well controlled with therapy before pregnancy will do well. Even these women, however, are at increased risk for adverse outcomes. Complications are more likely with severe baseline hypertension and especially with documented end-organ damage (Czeizel, 2011; Odibo, 2013). In a study of pregnancy outcomes in nearly 30,000 chronically hypertensive women, Gilbert and associates (2007) reported markedly increased rates of maternal morbidity that included stroke, pulmonary edema, and renal failure. These observations were verified in the report from the Nationwide Patient Sample by Bateman and colleagues (2012). In this latter study, hypertension complications included stroke—2.7 per 1000, acute renal failure—5.9 per 1000, pulmonary edema—1.5 per 1000, mechanical ventilation—3.8 per 1000, and in-house maternal mortality—0.4 per 1000. The contribution of hypertension to pregnancy-related strokes is discussed in Chapter 60 (Cerebrovascular Diseases) and to hypertensive and idiopathic peripartum cardiomyopathy in Chapter 49 (Dilated Cardiomyopathy).

Pregnancy-aggravated hypertension may be due to gestational hypertension or to superimposed preeclampsia. In either instance, blood pressures can be dangerously elevated. As emphasized by Clark and Hankins (2012), systolic pressure ≥160 mm Hg or diastolic pressure ≥110 mm Hg will rapidly cause renal or cardiopulmonary dysfunction or cerebral hemorrhage. With superimposed severe preeclampsia or eclampsia, the maternal prognosis is poor unless the pregnancy is ended. Placental abruption is a common and serious complication (Chap. 41, Placental Abruption). In addition to hypertensive heart failure mentioned above, aortic dissection was described by Weissman-Brenner and coworkers (2004) and is discussed in Chapter 49 (Diseases of the Aorta).

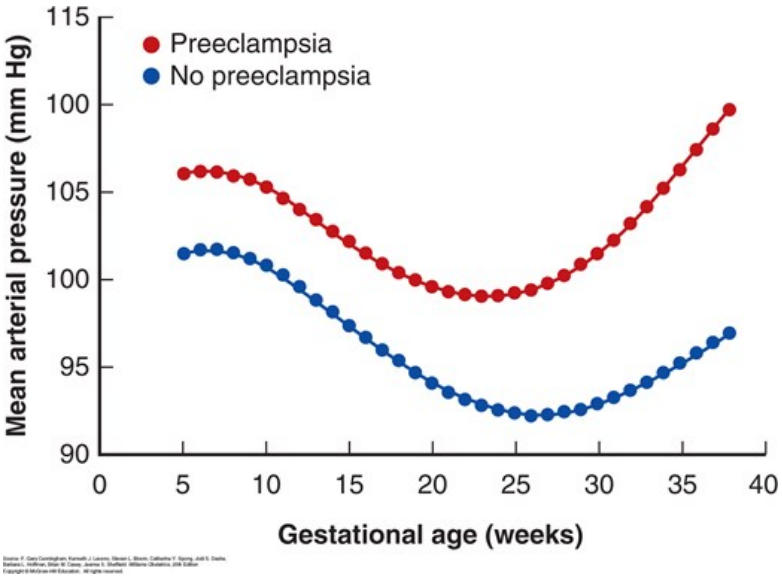
In aggregate, chronic hypertension is associated with a fivefold risk for maternal death (Gilbert, 2007). This is emphasized by the report by Creanga and colleagues (2015) describing 3358 pregnancy-related deaths in the United States from 2006 through 2010. Hypertensive disorders, including chronic hypertension and preeclampsia syndrome, accounted for 9.4 percent of these deaths. Undoubtedly related were other causes of death such as cardiovascular conditions—14.6 percent, cerebrovascular conditions—6.2 percent, and cardiomyopathy—11.8 percent. Moodley (2007) reported similar findings with 3406 maternal deaths from South Africa.

Superimposed Preeclampsia

Because superimposed preeclampsia is not precisely defined in women with chronic hypertension, the reported incidence varies from 13 to 40 percent (American College of Obstetricians and Gynecologists, 2013; Bramham, 2016; Kim, 2016b; Moussa, 2017). August and colleagues (2015) posit that this predilection may stem from similar genetic, biochemical, and metabolic abnormalities. For example, the risk for superimposed preeclampsia is directly related to the severity of baseline hypertension (Ankumah, 2014; Morgan, 2016b). In a Maternal-Fetal Medicine Units (MFMU) Network trial, Caritis and coworkers (1998) identified superimposed preeclampsia in 25 percent of hypertensive gravidas. The rate was 29 percent in a California database study (Yanit, 2012). And, women whose hypertension becomes severe enough to warrant chronic antihypertensive therapy during pregnancy are at inordinately high risk for superimposed preeclampsia (Morgan, 2016a). And, this risk is even higher if there is baseline proteinuria. Finally, and shown in Figure 50-2, chronically hypertensive women destined to develop severe superimposed preeclampsia have higher initial blood pressures that nadir earlier than those of women who do not develop severe disease.

FIGURE 50-2

Blood pressure trends in treated, chronically hypertensive women with and without superimposed preeclampsia. Mean maternal pressures (MAPs) at entry ($p = 0.002$) and throughout gestation ($p < 0.001$) are significantly different for each group. MAP nadir at 23.3 weeks (95% CI, 22.5–24.1) for superimposed preeclampsia versus 26.4 weeks (95% CI, 22.5–27.6) for those without preeclampsia is significant (3.1 weeks, 95% CI, 2.3–4.3). (Data from Morgan, 2016a.)



Thus far, clinical prognostic and predictive tests for superimposed preeclampsia have been disappointing (Conde-Agudelo, 2015). Di Lorenzo and colleagues (2012) studied serum markers for Down syndrome to predict preeclampsia and calculated a sensitivity of 60 percent, with a 20-percent false-positive rate. Similar results were found using antiangiogenic factors to discriminate among chronic hypertension, gestational hypertension, and preeclampsia (Costa, 2016; Sibai, 2008). According to Anton and coworkers (2013), microRNA assays may prove valuable as predictors of pregnancy-associated hypertension.

Prevention

Trials of various medications to prevent preeclampsia in women with chronic hypertension have generally been disappointing and show little or no benefit. Low-dose aspirin has been evaluated most frequently (Mol, 2016; Staff, 2015). In the MFMU Network study by Caritis (1998) cited above, the incidence of superimposed preeclampsia, fetal-growth restriction, or both is similar in women given low-dose aspirin or placebo. Using the same database, Moore and associates (2015) found that early administration of low-dose aspirin (<17 weeks' gestation) resulted in a significant 41-percent lower frequency of superimposed preeclampsia in chronically hypertensive women—18 versus 31 percent. Duley (2007) and Meads (2008) and their colleagues performed systematic reviews and noted that low-dose aspirin was beneficial in some high-risk women. Moderate benefits were also found from a metaanalysis by Askie and coworkers (2007). In a secondary analysis, Poon and associates (2017) noted that aspirin was ineffective to reduce

the incidence of preterm preeclampsia.

The U.S. Preventive Services Task Force recommends treatment with low-dose aspirin for chronically hypertensive women at high risk for preeclampsia (Henderson, 2014). The recommendation to initiate 81 mg between 12 and 28 weeks' gestation and continue therapy until delivery was adopted by the American College of Obstetricians and Gynecologists (2016b). In addition to chronic hypertension, indications for aspirin prophylaxis for those at high-risk of preeclampsia include a history of preeclampsia, multifetal gestation, diabetes, renal disease, and autoimmune disease.

Antioxidants to prevent preeclampsia have been studied. Spinnato and coworkers (2007) randomly assigned 311 women with chronic hypertension to treatment with vitamins C and E or with a placebo. A similar number in both groups developed preeclampsia—17 versus 20 percent, respectively.

Placental Abruption

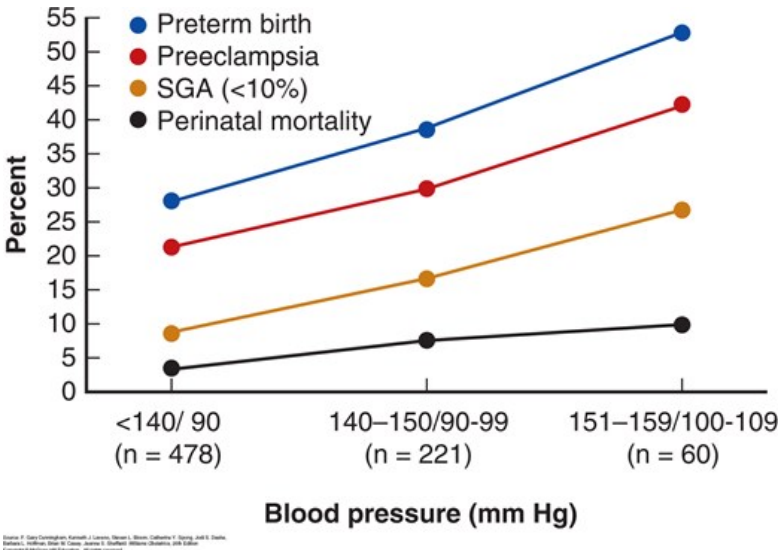
Chronic hypertension augments the risk two- to threefold for premature placental separation. The general obstetrical population risk is 1 in 200 to 300 pregnancies, and this rises to 1 in 60 to 120 pregnancies in women with chronic hypertension (Ankumah, 2014; Cruz, 2011; Magee, 2015). The abruption risk is elevated further if the woman smokes. Most abruptions are in women with worsening gestational hypertension or superimposed preeclampsia. The abruption risk is highest with severe hypertension, and Vigil-De Gracia and colleagues (2004) reported it to be 8.4 percent. From medical record data from the Norwegian Birth Registry, folic acid and/or multivitamin supplements slightly lowered the abruption incidence in women with chronic hypertension (Nilsen, 2008).

Perinatal Morbidity and Mortality

Rates of almost all adverse perinatal outcomes are greater in women with chronic hypertension than in nonaffected controls. As expected, for the entire group of hypertensive women, those who developed preeclampsia have substantially higher adverse outcome rates compared with those without preeclampsia. As shown in Figure 50-3, adverse outcome rates rise incrementally with rising blood pressures. Evidence also supports that chronic hypertension—treated or untreated—is associated with congenital anomalies. Bateman and coworkers (2015) from the Medicaid Analytic Extract cited earlier found an elevated risk for severe congenital malformations—especially cardiac defects. Moreover, severe hypertension and fetal esophageal atresia or stenosis have been associated (Bánhidy, 2011; Van Gelder, 2015).

FIGURE 50-3

Frequency of selected adverse maternal and perinatal outcomes by blood pressure stratification in women with mild chronic hypertension. SGA = small for gestational age. (Data from Ankumah, 2014.)



The stillbirth frequency with chronic hypertension is substantively greater in most reports (Chap. 35, Risk Factors). In the Nationwide Patient Sample study, the stillbirth rate was 15.1 per 1000 births (Bateman, 2012). This is similar to that of 18 per 1000 from a Norwegian study by Ahmad and coworkers (2012) and of 24 per 1000 births from a Network study reported by Ankumah and colleagues (2014) and described in "Tight Control". Low-

birthweight neonates are also common. They are due to fetal-growth restriction, preterm delivery that is largely clinically indicated, or both (see Fig. 50-3). In the California database study noted earlier, a fourth of fetuses were delivered preterm (Yanit, 2012).

These and other studies attest to the elevated risk for fetal-growth restriction, and the incidence averages 20 percent. Zetterström and coworkers (2006) reported a 2.4-fold risk for fetal-growth restriction in 2754 chronically hypertensive Swedish women compared with the risk in normotensive women. Broekhuijsen and associates (2012) found a 1.3-fold increased risk for 1609 Dutch nulliparas with chronic hypertension compared with that in normotensive controls. As with other complications, fetal-growth dysfunction is more likely in chronically hypertensive women who develop superimposed preeclampsia. In one study, the incidence of growth-restricted fetuses born to women with superimposed preeclampsia was almost 50 percent compared with only 21 percent in chronically hypertensive women without preeclampsia (Chappell, 2008). Finally, women with chronic hypertension severe enough to warrant treatment had an 11-percent incidence of fetal-growth restriction to a degree yielding birthweights ≤3rd percentile (Morgan, 2016a). For all of these reasons, neonates born to these women have a correspondingly high rate of intensive-care nursery admission.

All of these adverse perinatal effects of chronic hypertension contribute to the greater perinatal mortality rate, which is three- to fourfold higher than the rate in nonaffected gravidas (American College of Obstetricians and Gynecologists, 2013). In the Network study by Ankumah (2014) referenced in Figure 50-3, the perinatal death rate was 31 per 1000 births with mild hypertension, 72 per 1000 births with moderate disease, and 100 per 1000 births in women with severe chronic hypertension. And, in the study from Parkland Hospital by Morgan (2016a), the perinatal mortality rate was 32 per 1000 births in women who were treated for their chronic hypertension. Again, as expected, the highest rates are in women who develop superimposed preeclampsia, for whom the risk doubled from 4 to 8 percent. Finally, if diabetes coexists with chronic hypertension, then preterm delivery, fetal-growth restriction, and perinatal mortality rates are increased even more (Gonzalez-Gonzalez, 2008; Yanit, 2012).

MANAGEMENT DURING PREGNANCY

The diagnosis of chronic hypertension in pregnancy should be confirmed. The American College of Obstetricians and Gynecologists (2013) recommends use of ambulatory monitoring to exclude suspected white-coat hypertension before initiating antihypertensive therapy. Goals for chronic hypertension management include rate reductions of adverse maternal or perinatal outcomes just discussed. Treatment is targeted to prevent moderate or severe hypertension and to delay or dampen the severity of pregnancy-aggravated hypertension. To some extent, these goals can be achieved pharmacologically. Blood pressure self-monitoring is encouraged, but for accuracy, automated devices must be properly calibrated (Brown, 2004; Staessen, 2004). Personal health modification includes dietary counseling and reduction of behaviors such as tobacco, alcohol, cocaine, or other substance use (see Table 50-2). A low-sodium diet is not required (American College of Obstetricians and Gynecologists, 2013).

Some women—especially those with long-term or untreated hypertension—have complications that increase the risk of adverse pregnancy events. For example, in one study, a fourth of gravidas with chronic hypertension also had concentric ventricular hypertrophy (Ambia, 2017; Kim, 2016a). Thus, if not already accomplished, assessment during pregnancy is done for the cardiovascular and renal systems (Morgan, 2016a,b).

Antihypertensive Drugs

As concluded by the American College of Obstetricians and Gynecologists (2013, 2016a), treatment of hypertension during pregnancy has included every drug class, but information is still limited regarding safety and efficacy (Czeizel, 2011; Podymow, 2011). Although many studies indicate greater perinatal adverse effects in gravidas requiring treatment, it is still not known whether this is due to cause or effect (Orbach, 2013). The following summary of antihypertensive drugs is abstracted from several sources, including the *2016 Physicians' Desk Reference*. Many of these drugs are also discussed throughout Chapter 12 (Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blocking Drugs) and have been reviewed by Umans and associates (2015).

Adrenergic-Receptor Blocking Agents

Peripherally acting β-adrenergic-receptor blockers cause a generalized decline in sympathetic tone and decreased cardiac output. Examples are propranolol, metoprolol, and atenolol. Labetalol is a popular and commonly used α/β-adrenergic blocker that is considered safe.

Some adrenergic-blocking drugs act *centrally* by reducing sympathetic outflow to effect a generalized decreased vascular tone. These include clonidine and α-methyldopa. Drugs in this class most frequently used in pregnancy to treat hypertension are methyldopa or an α- or β-receptor

blocking agent such as labetalol.

Calcium-Channel Blocking Agents

These drugs are divided into three subclasses based on their modification of calcium entry into cells and interference with binding sites on voltage-dependent calcium channels. Common agents include nifedipine—a dihydropyridine, and verapamil—a phenylalkyl amine derivative. These agents have negative inotropic effects and thus can worsen ventricular dysfunction and congestive heart failure. Theoretically, they may potentiate the vasoactive actions of magnesium sulfate that is given for eclampsia neuroprophylaxis. Although data are limited regarding their use during pregnancy, they appear to be safe therapy for chronic hypertension (Briggs, 2015; Umans, 2015).

Diuretics

Thiazide diuretics are sulfonamides, and these were the first drug group used to successfully treat chronic hypertension (Beyer, 1982). These agents and loop-acting diuretics such as furosemide are commonly used in nonpregnant hypertensive patients. In the short term, they provide sodium and water diuresis with volume depletion. But with time, there is *sodium escape,* and volume depletion is partially corrected. Some aspect of lowered peripheral vascular resistance likely contributes to their effectiveness in reducing long-term morbidity (Umans, 2015).

Thiazide drugs may be mildly diabetogenic, and expected volume expansion may be curtailed in pregnant women. Sibai and colleagues (1984) showed that plasma volume expanded only about 20 percent over time in hypertensive pregnant women who continued diuretic therapy compared with a 50-percent expansion in women who discontinued treatment. Although perinatal outcomes were similar in these women, such concerns have led to practices of withholding diuretics as first-line therapy for chronic hypertension, particularly after 20 weeks' gestation (Working Group Report, 2000). Even so, in a Cochrane review, Churchill and associates (2007) reported no differences in perinatal outcomes in 1836 nonhypertensive women randomly assigned to a thiazide diuretic or placebo for primary preeclampsia prevention. Overall, thiazide diuretics are considered safe in pregnancy (Briggs, 2015). But for preeclampsia treatment, they are considered to be ineffective (Umans, 2015).

Vasodilators

Hydralazine relaxes arterial smooth muscle and has been used parenterally for decades to safely treat severe peripartum hypertension (Chap. 40, Hydralazine). Oral hydralazine monotherapy for chronic hypertension is not generally used because of its weak antihypertensive effects and resultant tachycardia. It may be an effective adjunct for long-term use with other antihypertensives, especially if there is chronic renal insufficiency. In one study, vasodilator treatment of chronically hypertensive women was associated with a twofold rise in rates of low-birthweight and growth-restricted neonates (Su, 2013).

Angiotensin-Converting Enzyme Inhibitors

These drugs inhibit the conversion of angiotensin-I to the potent vasoconstrictor angiotensin-II. They can cause severe fetal malformations when given in the second and third trimesters. These include oligohydramnios, hypocalvaria, and renal dysfunction (Chap. 12, Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blocking Drugs). Some preliminary studies also suggest teratogenic effects, and because of this, they are not recommended at any time during pregnancy (Briggs, 2015; Podymow, 2011).

Angiotensin-receptor blockers act in a similar manner. But, instead of blocking the production of angiotensin-II, they inhibit binding to its receptor. They are presumed to have the same fetal effects as angiotensin-converting enzyme inhibitors and thus are also contraindicated.

Antihypertensive Treatment in Pregnancy

Severe Chronic Hypertension

The prognosis for pregnancy outcome with chronic hypertension is somewhat dependent on the severity of disease antedating pregnancy. This may be related to findings that many women with severe hypertension have renal disease—as either cause or effect (Cunningham, 1990; Morgan, 2016a). It follows that women whose hypertension is severe enough to require antihypertensive therapy are at inordinately high risk for superimposed preeclampsia.

Sibai and coworkers (1986) described outcomes from 44 pregnancies in women whose blood pressure at 6 to 11 weeks' gestation was ≥170/110 mm Hg. All were given oral treatment with α-methyldopa and hydralazine to maintain pressures <160/110 mm Hg. Of the 44 pregnancies, superimposed preeclampsia developed in half, and all adverse perinatal outcomes were in this group. Moreover, all neonates of women in the superimposed group were delivered preterm, nearly 80 percent were also growth restricted, and 48 percent suffered perinatal death. Conversely, those women with severe chronic hypertension who did not develop superimposed preeclampsia had reasonably good outcomes. There were no perinatal deaths, and only 5 percent of fetuses were growth restricted. Webster and colleagues (2017) found labetalol and nifedipine to be equally effective for chronic hypertension in pregnant women.

Morgan and coworkers (2016a) reported 447 women whose chronic hypertension required treatment beginning prior to 20 weeks. More than half of these women developed superimposed severe preeclampsia. The rate of preeclampsia was 53 percent for those whose 24-hour protein excretion was <300 mg. But for those with antecedent baseline proteinuria >300 mg/day, 79 percent developed severe preeclampsia.

Mild or Moderate Hypertension

Continuing prepregnancy antihypertensive treatment during pregnancy is debatable for those with mild or moderate hypertension. Although blood pressure reduction certainly benefits the mother long term, it at least theoretically can reduce uteroplacental perfusion. In older observational reports, most pregnancy outcomes in women with mild to moderate hypertension generally were good without treatment and unless superimposed preeclampsia developed (Chesley, 1978; Umans, 2015).

Newer data are accruing that address potential salutary effects on pregnancy outcomes by simply lowering blood pressure. Earlier studies were relatively small and had widely varying inclusion and outcome criteria. In a Cochrane review of 49 of these studies that included a total of 4723 women with mild to moderate hypertension, Abalos and coworkers (2014) confirmed that the risk for subsequent severe hypertension was lowered with therapy. Compared with untreated women, the frequencies of superimposed preeclampsia, eclampsia, abruption, preterm birth, fetal-growth restriction, and perinatal or maternal mortality did not differ. This latter Cochrane review raised concerns for fetal-growth restriction with β-blocking drugs, notably atenolol. It is not resolved, however, because diminished placental perfusion secondary to lowered maternal blood pressure is confounded by the fact that worsening blood pressure itself is associated with abnormal fetal growth. Some also posit that the drugs have a direct fetal action (Umans, 2015). In two of the larger randomized trials, however, the incidence of growth restriction was not altered in women randomly assigned to treatment (Gruppo di Studio Ipertensione in Gravidanza, 1998; Sibai, 1990a).

The observations of Morgan and colleagues (2016a) support the findings of the Cochrane review by Abalos. Specifically, they reported that despite therapy for chronic hypertension, there was frequent superimposed preeclampsia, fetal-growth restriction, preterm delivery, and perinatal mortality. Moreover, and as shown in Table 50-4, women with baseline proteinuria >300 mg/d had even worse obstetrical outcomes.

TABLE 50-4

Selected Pregnancy Outcomes in Women with Chronic Hypertension Treated During Pregnancy with and without Baseline Proteinuria[a]

Outcome	Baseline Proteinuria[a]	No Proteinuria	*P*-value
Superimposed preeclampsia	79%	49%	<0.001
Abruption	0	1%	0.45
EGA at delivery (mean)[b]	35.1 ± 4.3 wks	37.2 ± 3.3 wks	<0.001
≤30 weeks	18%	6%	0.001
≤34 weeks	34%	17%	0.005
≤37 weeks	48%	26%	0.002
Birthweight (mean)[b]	2379 ± 1028 g	2814 ± 807 g	<0.001
≤3rd percentile	20%	9%	0.01
≤10th percentile	41%	22%	<0.001
Perinatal mortality	36/1000	31/1000	0.47

[a]Defined as ≥300 mg/d protein excretion before 20 weeks' gestation.

[b]Mean ± standard deviations.

EGA = estimated gestational age.

Data from Morgan, 2016b.

"Tight Control"

During the past decade, the concept of *tight control* of blood pressure has been espoused as a means of optimizing maternal and perinatal outcomes. Such control is analogous to that of glycemic control for management of the pregnant diabetic patient. The observational study by Ankumah (2014) noted earlier lends credence to tighter control of blood pressure. These investigators showed that the risk of adverse pregnancy outcomes in 759 women with chronic hypertension was lower when blood pressures before 20 weeks were <140 mm Hg compared with higher pressure categories and increasing blood pressures. Unfortunately, this did not hold up when less-tight was compared with tight control. Specifically, Magee and coworkers (2015) randomized 987 women with chronic hypertension or gestational hypertension to either one of these two management schemes. Except for a lower rate of severe hypertension in the tightly controlled group, they found no significant differences between these two groups' other adverse pregnancy outcomes (Table 50-5). Tight control was also not more costly (Ahmed, 2016). These and similar findings prompted an ongoing randomized controlled trial—Project CHAP (ClinicalTrials.gov, 2016)—to answer this question.

TABLE 50-5

Selected Maternal and Perinatal Outcomes in Pregnant Women with Chronic Hypertension According to Less-Tight versus Tight Control

Outcome	Less-Tight Control (n = 493)	Tight Control (n = 488)
Maternal		
Placental abruption	2.2%	2.3%
Severe hypertension[a]Preeclampsia	41%	28%
Preeclampsia	49%	46%
HELLP syndrome	1.8%	0.4%
Perinatal		
Deaths	28/1000	23/1000
<10th percentile	16%	20%
<3rd percentile	4.7%	5.3%
Respiratory problem	17%	14%

[a] $p < 0.001$, all other comparisons $p > 0.05$.

HELLP = hemolysis, elevated liver enzyme levels, low platelet count.

Data from Magee, 2015.

Recommendations for Therapy

Until there are data to confirm any salutary effects of treatment of uncomplicated mild to moderate chronic hypertension in pregnancy, it seems reasonable to follow the guidelines of the American College of Obstetricians and Gynecologists (2013) and the Society for Maternal-Fetal Medicine (2015). Pregnant women with *severe hypertension* must be treated for maternal neuro-, cardio-, and renoprotection. Treatment is also mandatory for women with prior adverse outcomes such as strokes, MIs, and evidence for cardiac or renal dysfunction. With end-organ dysfunction, treatment to diastolic pressure level ≤90 mm Hg is reasonable to mitigate further organ damage.

For most women with mild to moderate hypertension, the College recommends that treatment be withheld as long as systolic blood pressure is <160 mm Hg and diastolic blood pressure is <105 mm Hg. Some find it reasonable to begin antihypertensive treatment in otherwise healthy pregnant women with persistent systolic pressures >150 mm Hg or diastolic pressures of 95 to 100 mm Hg or greater (August, 2015; Working Group Report, 2000). At Parkland Hospital we initiate treatment with antihypertensive agents for blood pressures of 150/100 mm Hg or higher. Our preferred regimens include monotherapy with a β-blocking drug such as labetalol or a calcium-channel blocking agent such as amlodipine. For women in the first half of pregnancy, therapy with a thiazide diuretic seems reasonable. This is especially true in black women, in whom there is a high prevalence of salt-sensitive chronic hypertension.

It is controversial whether or not women who present early in pregnancy and who are already taking antihypertensive drugs should continue to take these (Rezk, 2016). According to the American College of Obstetricians and Gynecologists (2013) and the Society for Maternal-Fetal Medicine (2015), for women with mild to moderate hypertension, it is *reasonable* to discontinue medications during the first trimester and to restart them if blood

pressures approach the severe range. Our practice at Parkland Hospital is to continue treatment if the woman is already taking drugs when she presents for prenatal care. Exceptions are discontinuation of angiotensin-converting enzyme inhibitors and receptor blockers.

Some women will have persistently worrisome hypertension despite usual therapy (Samuel, 2011; Sibai, 1990a). In these women, primary attention is given to the likelihood of pregnancy-aggravated hypertension, with or without superimposed preeclampsia. Other possibilities include inaccurate blood-pressure measurements, suboptimal treatment, and antagonizing substances such as chronic ingestion of nonsteroidal antiinflammatory drugs (NSAIDs) (Moser, 2006; Sowers, 2005).

Pregnancy-Aggravated Hypertension or Superimposed Preeclampsia

As discussed, the frequency of superimposed preeclampsia for women with chronic hypertension varies depending on the study population and hypertension severity (Ankumah, 2014). Importantly, in 40 to 50 percent of chronically hypertensive women, superimposed preeclampsia develops before 37 weeks (Chappell, 2008; Harper, 2016). This proportion is even higher in women who required hypertension treatment during pregnancy (Morgan, 2016a).

The diagnosis may be difficult to make, especially in women with hypertension who have underlying renal disease with chronic proteinuria (Cunningham, 1990; Morgan, 2016b). As discussed in Chapter 40 (Preeclampsia Superimposed on Chronic Hypertension), conditions that support the diagnosis of superimposed preeclampsia include worsening hypertension, new-onset proteinuria, neurological symptoms such as severe headaches and visual disturbances, generalized edema, oliguria, and certainly, convulsions or pulmonary edema. Making the diagnosis based on worsening proteinuria in women with baseline proteinuria is problematic. Supporting laboratory abnormalities are rising serum creatinine or hepatic transaminase levels, thrombocytopenia, or any of the facets of HELLP (hemolysis, elevated liver enzyme levels, low platelet count) syndrome. For women with chronic hypertension and superimposed preeclampsia with severe features, magnesium sulfate for maternal neuroprophylaxis is recommended (American College of Obstetricians and Gynecologists, 2013). Severe hypertension is treated as described in Chapter 40 (Management Considerations).

Some pregnant women with chronic hypertension have worsening hypertension with no other findings of superimposed preeclampsia. This is most commonly encountered near the end of the second trimester. In the absence of other supporting criteria for superimposed preeclampsia, this likely represents the higher end of the normal blood-pressure curve shown in Figure 50-1. In such women, if preeclampsia can be confidently excluded, it is reasonable to begin or to increase the dose of antihypertensive therapy.

Fetal Assessment

Women with well-controlled chronic hypertension who have no complicating factors can generally be expected to have a good pregnancy outcome. Because even those with mild hypertension have a greater risk of superimposed preeclampsia and fetal-growth restriction, serial antepartum assessment of fetal well-being is recommended by many. That said, according to the American College of Obstetricians and Gynecologists (2013), with the exception of sonographic fetal-growth monitoring, described in Chapter 44 (Fetal-Growth Restriction Recognition), no conclusive data address either benefit or harm associated with various antepartum surveillance strategies.

Expectant Management of Early-Onset Preeclampsia

Given that many women with chronic hypertension develop superimposed preeclampsia before term, considerations for expectant management may be reasonable in some cases. In a study from Magee-Women's Hospital, 41 carefully selected women with a median gestational age of 31.6 weeks were expectantly managed (Samuel, 2011). Despite liberal criteria to mandate delivery, 17 percent developed either placental abruption or pulmonary edema. The latency period was extended by a mean of 9.7 days. There were no perinatal deaths, however, salutary outcomes were similar. These investigators recommend randomized trials to study expectant management before this becomes usual care.

Delivery

For chronically hypertensive women who have complications such as fetal-growth restriction or superimposed preeclampsia, the decision to deliver is made by clinical judgment. The route of delivery is dictated by obstetrical factors. Certainly, most women with superimposed severe preeclampsia are better delivered even when the fetus is markedly preterm. Increased risk for placental abruption, cerebral hemorrhage, and peripartum heart failure attend delivery delays (Cunningham, 1986, 2005; Martin, 2005).

For women with chronic hypertension without preeclampsia, expectant management at later gestational ages was reported recently by Harper and colleagues (2016). They concluded that expectant management beyond 39 weeks' gestation was associated with an increasing incidence of severe preeclampsia and that planned delivery before 37 weeks was associated with a rise in rates of adverse neonatal outcomes.

For women with mild to moderate chronic hypertension who continue to have an uncomplicated pregnancy, the American College of Obstetricians and Gynecologists (2013) recommends delivery not be pursued until $38^{0/7}$ weeks. The consensus committee findings by Spong and associates (2011) recommend consideration for delivery at 38 to 39 weeks, that is, ≥37 completed weeks. A trial of labor induction is preferable, and many of these women respond favorably and will be delivered vaginally (Alexander, 1999; Atkinson, 1995).

Intrapartum Considerations

For women with severe preeclampsia, peripartum management is the same as described in Chapter 40 (Consideration for Delivery). Epidural analgesia for labor and delivery is optimal with the caveat that it is not given to treat hypertension (Lucas, 2001). That said, women with severe superimposed preeclampsia are more sensitive to the acute hypotensive effects of epidural analgesia (Vricella, 2012). Also in this group, magnesium sulfate neuroprophylaxis is initiated for prevention of eclampsia. Severe hypertension—diastolic blood pressure ≥110 mm Hg or systolic pressure ≥160 mm Hg—is treated with either intravenous hydralazine or labetalol. Some prefer to treat women when the diastolic pressure reaches 100 to 105 mm Hg. Vigil-De Gracia and colleagues (2006) randomly assigned 200 women to intravenous hydralazine or labetalol to acutely lower severe high blood pressure in pregnancy. Outcomes were similar except for significantly more maternal palpitations and tachycardia with hydralazine and significantly more neonatal hypotension and bradycardia with labetalol.

Postpartum Care

In most respects, postpartum observation, prevention, and management of adverse complications are similar in women with severe chronic hypertension and in those with severe preeclampsia–eclampsia. For persistent severe hypertension, consideration is given for a cause such as pheochromocytoma or Cushing disease (Sibai, 2012). And, in women with chronic end-organ damage, certain complications are more common. These include cerebral or pulmonary edema, heart failure, renal dysfunction, or cerebral hemorrhage, especially within the first 48 hours after delivery (Martin, 2005; Sibai, 1990b, 2012). These frequently are preceded by sudden elevations—"spikes"—of mean arterial blood pressure and of the systolic component (Cunningham, 2000, 2005).

Following delivery, as maternal peripheral resistance rises, left ventricular workload also grows. This elevation is further aggravated by appreciable and pathological amounts of interstitial fluid that are mobilized to be excreted as endothelial disruption from preeclampsia resolves. In these women, sudden hypertension—either moderate or severe—may exacerbate diastolic dysfunction, cause systolic dysfunction, and lead to pulmonary edema (Cunningham, 1986; Gandhi, 2001). Prompt hypertension control, along with furosemide-evoked diuresis, usually quickly resolves pulmonary edema.

The antihypertensive regimen given antepartum can be restarted in the puerperium. It is also possible in many women to forestall postpartum hypertension by administering intravenous or oral furosemide to augment the normal postpartum diuresis. In one study, 20-mg oral furosemide given daily for 5 days to postpartum women with severe preeclampsia aided blood pressure control (Ascarelli, 2005). Daily weights are helpful in this regard. On average, a woman should weigh 15 pounds less immediately after delivery. Excessive extracellular fluid can then be estimated. Other studies are in progress to determine aspects of postpartum blood pressure management (Cursino, 2015).

Some evidence supports that *chronic* ingestion of NSAIDs in the puerperium elevates blood pressure in women with severe preeclampsia (Vigil-De Gracia, 2017). This may not be problematic if these drugs are given only as needed (Wasden, 2014).

Women with chronic hypertension have special considerations for contraceptive and sterilization choices. These are discussed in detail throughout Chapters 38 and 39.

Long-Term Prognosis

Ultimately, women with chronic hypertension are at high risk for lifetime cardiovascular complications, especially when accompanied by diabetes, obesity, and the metabolic syndrome. Recent evidence also suggests that these women are at greater risk to develop cardiomyopathy remote from pregnancy (Behrens, 2016).

REFERENCES

Abalos E, Duley L, Steyn DW, et al: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev 2:CD002252, 2014

Ahmad AS, Samuelsen SO: Hypertensive disorders in pregnancy and fetal death at different gestational lengths: a population study of 2 121 371 pregnancies. BJOG 119(12):1521, 2012 [PubMed: 22925135]

Ahmed RJ, Gafni A, Hutton EK, et al: The cost implications of less tight versus tight control of hypertension in pregnancy (CHIPS Trial). Hypertension 68(4):1049, 2016 [PubMed: 27550914]

Alexander JM, Bloom SL, McIntire DD, et al: Severe preeclampsia and the very low birth weight infant: is induction of labor harmful? Obstet Gynecol 93:485, 1999 [PubMed: 10214819]

Ambia AM, Morgan JL, Wilson KL, et al: Frequency and consequences of ventricular hypertrophy in pregnant women with treated chronic hypertension. Am J Obstet Gynecol 217:467.e1, 2017

American College of Obstetricians and Gynecologists: Chronic hypertension in pregnancy and superimposed preeclampsia. In: Hypertension in Pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. 2013

American College of Obstetricians and Gynecologists: Hypertension. In Clinical Updates in Women's Health Care, Volume XV, No. I, January 2016a

American College of Obstetricians and Gynecologists: Practice advisory on low-dose aspirin and prevention of preeclampsia: updated recommendations. 2016b. Available at: http://www.acog.org/About-ACOG/News-Room/Practice-Advisories/Practice-Advisory-Low-Dose-Aspirin-and-Prevention-of-Preeclampsia-Updated-Recommendations. Accessed January 5, 2017

Ankumah NA, Cantu J, Jauk V, et al: Risk of adverse pregnancy outcomes in women with mild chronic hypertension before 20 weeks of gestation. Obstet Gynecol 123(5):966, 2014 [PubMed: 24785847]

Anton L, Olarerin-George AO, Schwartz N, et al: miR-210 inhibits trophoblast invasion and is a serum biomarker for preeclampsia. Am J Pathol 183(5):1437, 2013 [PubMed: 24035613]

Ascarelli MH, Johnson V, McCreary H, et al: Postpartum preeclampsia management with furosemide: a randomized clinical trial. Obstet Gynecol 105(1):29, 2005 [PubMed: 15625138]

Askie LM, Duley L, Henderson-Smart DJ, et al: Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. Lancet 369(9575):1791, 2007 [PubMed: 17512048]

Atkinson MW, Guinn D, Owen J, et al: Does magnesium sulfate affect the length of labor induction in women with pregnancy-associated hypertension? Am J Obstet Gynecol 173(4):1219, 1995 [PubMed: 7485324]

August P, Jeyabalan A, Roberts JM: Chronic hypertension and pregnancy. In: Taylor RN, Roberts JM, Cunningham FG, et al (eds): Chesley's Hypertensive Disorders in Pregnancy. Amsterdam, Academic Press, 2015

Bánhidy F, Ács N, Puhó EH, et al: Chronic hypertension with related drug treatment of pregnant women and congenital abnormalities in their offspring: a population-based study. Hypertens Res 34(2):257, 2011 [PubMed: 21107325]

Bateman BT, Bansil P, Hernandez-Diaz S, et al: Prevalence, trends, and outcomes of chronic hypertension: a nationwide sample of delivery admissions. Am J Obstet Gynecol 206(2):134.e1, 2012

Bateman BT, Huybrechts KF, Fischer MA, et al: Chronic hypertension in pregnancy and the risk of congenital malformations: a cohort study. Am J Obstet Gynecol 212:337.e1, 2015

Behrens I, Basit S, Lykke JA, et al: Association between hypertensive disorders of pregnancy and later risk of cardiomyopathy. JAMA 315(10):1026, 2016 [PubMed: 26954411]

Beyer KH: Chlorothiazide. J Clin Pharmacol 13:15, 1982

Bramham K, Hladunewich MA, Jim B, et al: Pregnancy and kidney disease. NephSAP Nephrology Assessment Program 15(1):1, 2016

Briggs GG, Freeman RK: Drugs in Pregnancy and Lactation, 10th ed. Philadelphia, Lippincott Williams & Wilkins, 2015

Broekhuijsen K, Langeveld J, van den Berg P, et al: Maternal and neonatal outcomes in pregnancy in women with chronic hypertension. Am J Obstet Gynecol 206:S344, 2012

Brown M, McHugh L, Mangos G, et al: Automated self-initiated blood pressure or 24-hour ambulatory blood pressure monitoring in pregnancy? BJOG 111:38, 2004 [PubMed: 14687050]

Caritis S, Sibai B, Hauth J, et al: Low-dose aspirin to prevent preeclampsia in women at high risk. N Engl J Med 338(11):701, 1998 [PubMed: 9494145]

Centers for Disease Control and Prevention: Vital signs: prevalence, treatment, and control of hypertension—United States, 1999–2002 and 2005–2008. MMWR 60(4):1, 2011

Chappell LC, Enye S, Seed P, et al: Adverse perinatal outcomes and risk factors for preeclampsia in women with chronic hypertension: a prospective study. Hypertension 51(4):1002, 2008 [PubMed: 18259010]

Chesley LC: Superimposed preeclampsia or eclampsia. In Chesley LC (ed): Hypertensive Disorders in Pregnancy. New York, Appleton-Century-Crofts, 1978

Churchill D, Beevers GD, Meher S, et al: Diuretics for preventing pre-eclampsia. Cochrane Database Syst Rev 1:CD004451, 2007

Clark SL, Hankins GD: Preventing maternal death. 10 clinical diamonds. Obstet Gynecol 119(2):360, 2012 [PubMed: 22270288]

ClinicalTrials.gov: Chronic Hypertension and Pregnancy (CHAP) Project. 2016. Available at: https://clinicaltrials.gov/ct2/show/NCT02299414. Accessed January 5, 2017

Conde-Agudelo A, Romero R, Roberts JM: Tests to predict preeclampsia. In Taylor RN, Roberts JM, Cunningham FG, et al (eds): Chesley's Hypertensive Disorders in Pregnancy, 4th ed. Amsterdam, Academic Press, 2015

Costa RA, Hoshida MS, Alves EA, et al: Preeclampsia and superimposed preeclampsia: the same disease? The role of angiogenic biomarkers. Hypertens Pregnancy 35(2): 139, 2016 [PubMed: 26930132]

Cowley AW Jr: The genetic dissection of essential hypertension. Nat Rev Genet 7:829, 2006 [PubMed: 17033627]

Creanga AA, Berg CJ, Syverson C, et al: Pregnancy-related mortality in the United States, 2006–2010. Obstet Gynecol 125(1):5, 2015 [PubMed: 25560097]

Cruz MO, Gao W, Hibbard JU: Obstetrical and perinatal outcomes among women with gestational hypertension, mild preeclampsia, and mild chronic hypertension. Am J Obstet Gynecol 205:260.e1, 2011

Cunningham FG: Severe preeclampsia and eclampsia: systolic hypertension is also important. Obstet Gynecol 105:237, 2005 [PubMed: 15684145]

Cunningham FG, Cox SM, Harstad TW, et al: Chronic renal disease and pregnancy outcome. Am J Obstet Gynecol 163:453, 1990 [PubMed: 2386131]

Cunningham FG, Pritchard JA, Hankins GD, et al: Idiopathic cardiomyopathy or compounding cardiovascular events? Obstet Gynecol 67:157, 1986 [PubMed: 2935758]

Cunningham FG, Twickler D: Cerebral edema complicating eclampsia. Am J Obstet Gynecol 182(1):94, 2000 [PubMed: 10649162]

Cursino T, Katz L, Coutinho I, et al: Diuretics vs. placebo for postpartum blood pressure control in preeclampsia (DIUPRE): a randomized clinical trial. Reprod Health 12:66, 2015 [PubMed: 26242730]

Czeizel AE, Bánhidy F: Chronic hypertension in pregnancy. Curr Opin Obstet Gynecol 23(2):76, 2011 [PubMed: 21178774]

Di Lorenzo G, Ceccarello M, Cecotti V, et al: First trimester maternal serum PIGF, free b-hCG, PAPP-A, PP-13, uterine artery Doppler and maternal history for the prediction of preeclampsia. Placenta 33(6):495, 2012 [PubMed: 22459245]

Duley L, Henderson-Smart DJ, Meher S, et al: Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev 2:CD004659, 2007

Eckel RH, Jakicic JM, Ard JD, et al: 2013 AHA/ACC guidelines on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 129(25 Suppl 2):S76, 2013 [PubMed: 24222015]

Forouzanfar MH, Liu P, Roth GA, et al: Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990–2015. JAMA 317:165, 2017 [PubMed: 28097354]

Gainer J, Alexander J, McIntire D, et al: Maternal echocardiogram findings in pregnant patients with chronic hypertension. Presented at the 25th Annual Meeting of the Society for Maternal-Fetal Medicine, Reno, February 7–12, 2005

Gandhi SK, Powers JC, Nomeir A, et al: The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med 344(1):17, 2001 [PubMed: 11136955]

Gilbert WM, Young AL, Danielsen B: Pregnancy-outcomes in women with chronic hypertension: a population-based study. J Reprod Med 52(11):1046, 2007 [PubMed: 18161404]

Gonzalez-Gonzalez NL, Ramirez O, Mozas J, et al: Factors influencing pregnancy outcomes in women with type 2 versus type 1 diabetes mellitus. Acta Obstet Gynecol Scand 87(1):43, 2008 [PubMed: 18158626]

Gruppo di Studio Ipertensione in Gravidanza: Nifedipine versus expectant management in mild to moderate hypertension in pregnancy. BJOG 105(7): 718, 1998

Harper LM, Biggio JR, Anderson S, et al: Gestational age of delivery in pregnancies complicated by chronic hypertension. Obstet Gynecol 127(6):1101, 2016 [PubMed: 27159754]

Henderson JT, Whitlock EP, O'Connor E, et al: Low-dose aspirin for prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med 160(10): 695, 2014 [PubMed: 24711050]

Hibbard JU, Korcarz CE, Nendaz GG, et al: The arterial system in pre-eclampsia and chronic hypertension with superimposed pre-eclampsia. BJOG 112(7):897, 2005 [PubMed: 15957989]

Hibbard JU, Shroff SG, Cunningham FG: Cardiovascular alterations in pregnancy and preeclamptic pregnancy. In Taylor RN, Roberts JM, Cunningham FG, et al (eds): Chesley's Hypertensive Disorders in Pregnancy. Amsterdam, Academic Press, 2015

Hladunewich MA, Schaefer F: Proteinuria in special populations: pregnant women and children. Adv Chronic Kidney Dis 18(4):267, 2011 [PubMed: 21782133]

James PA, Oparil S, Carter BL, et al: 2014 evidence-based guidelines for the management of high blood pressure in adults. Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 311(5):507, 2014 [PubMed: 24352797]

Jeyabalan A, Hubel CA, Roberts JM: Metabolic syndrome and preeclampsia. In Taylor RN, Roberts JM, Cunningham FG, et al (eds): Chesley's Hypertensive Disorders in Pregnancy, 4th ed. Amsterdam, Academic Press, 2015

Kim MJ, Seo J, Cho KI, et al: Echocardiographic assessment of structural and hemodynamic changes in hypertension-related pregnancy. J Cardiovasc Ultrasound 24:28, 2016a

Kim SA, Park JB: OS 23–03 Midtrimester risk prediction of superimposed pre-eclampsia in pregnant women with chronic hypertension. J Hypertens 34 Suppl 1:e241, 2016b

Kotchen TA: Hypertensive vascular disease: In Kasper DL, Fauci AS, Hauser SL, et al (eds): Harrison's Principles of Internal Medicine, 19th ed. New York, McGraw-Hill Education, 2015

Kuper SG, Tita AT, Youngstrom ML, et al: Baseline renal function tests and adverse outcomes in pregnant patients with chronic hypertension. Obstet Gynecol 128:93, 2016 [PubMed: 27275794]

Leon MG, Moussa HN, Longo M, et al: Rate of gestational diabetes mellitus and pregnancy outcomes in patients with chronic hypertension. Am J Perinatol 33(8):745, 2016 [PubMed: 26890438]

Levine RJ, Hauth JC, Curet LB, et al: Trial of calcium to prevent preeclampsia. N Engl J Med 337(2):69, 1997 [PubMed: 9211675]

Lindheimer MD, Taylor RN, Roberts JM et al: Introduction, history, controversies, and definitions. In Taylor RN, Roberts JM, Cunningham FG, et al (eds): Chesley's Hypertensive Disorders in Pregnancy, 4th ed. Amsterdam, Academic Press, 2015

Lucas MJ, Sharma SK, McIntire DD, et al: A randomized trial of labor analgesia in women with pregnancy-induced hypertension. Am J Obstet Gynecol 185(4):970, 2001 [PubMed: 11641687]

Magee LA, von Dadelszen P, Rey E, et al: Less-tight versus tight control of hypertension in pregnancy. N Engl J Med 372(5):407, 2015 [PubMed: 25629739]

Martin JN Jr, Thigpen BD, Moore RC, et al: Stroke and severe preeclampsia and eclampsia: a paradigm shift focusing on systolic blood pressure. Obstet Gynecol 105(2):246, 2005 [PubMed: 15684147]

Meads CA, Cnossen JS, Meher S, et al: Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling. Health Technol Assess 12(6):1, 2008

Mol BW, Roberts CT, Thangaratinam S, et al: Pre-eclampsia. Lancet 387(10022):999, 2016 [PubMed: 26342729]

Moodley J: Maternal deaths due to hypertensive disorders in pregnancy: Saving Mothers report 2002–2004. Cardiovasc J Afr 18:358, 2007 [PubMed: 18092109]

Moore GS, Allshouse AA, Post AL. et al: Early initiation of low-dose aspirin for reduction in preeclampsia risk in high-risk women: a secondary analysis of the MFMU high-risk aspirin study. J Perinatol 35(5):328, 2015 [PubMed: 25474553]

Morgan JL, Nelson DB, Roberts SW, et al: Blood pressure profiles across pregnancy in women with chronic hypertension. Am J Perinatol 33(12):1128, 2016a

Morgan JL, Nelson DB, Roberts SW, et al: The association of baseline proteinuria and adverse pregnancy outcomes in pregnant women with treated chronic hypertension. Obstet Gynecol 128:270, 2016b

Moser M, Setaro JF: Resistant or difficult-to-control hypertension. N Engl J Med 355:385, 2006 [PubMed: 16870917]

Moussa HN, Leon MG, Marti A, et al: Pregnancy outcomes in women with preeclampsia superimposed on chronic hypertension with and without severe features. Am J Perinatol 34(4):403, 2017 [PubMed: 27606778]

Nilsen RM, Vollset SE, Rasmussen SA, et al: Folic acid and multivitamin supplement use and risk of placental abruption: a population-based registry study. Am J Epidemiol 167(7):867, 2008 [PubMed: 18187445]

Odibo I, Zilberman D, Apuzzio J, et al: Utility of posterior and septal wall thickness in predicting adverse pregnancy outcomes in patients with chronic hypertension. Abstract No. 624, Am J Obstet Gynecol 208:S265, 2013

Orbach H, Matok I, Gorodischer R, et al: Hypertension and antihypertensive drugs in pregnancy and perinatal outcomes. Am J Obstet Gynecol 208(4):301.e1, 2013

Physicians' Desk Reference, 70th ed. Chestertown, PDR Network, 2016

Podymow T, August P: Antihypertensive drugs in pregnancy. Semin Nephrol 31(1):70, 2011 [PubMed: 21266266]

Poon LC, Wright D, Rolnik DL, et al: Aspirin for evidence-based preeclampsia prevention trial: effect of aspirin in prevention of preterm preeclampsia in subgroups of women according to their characteristics and medical and obstetrical history. Am J Obstet Gynecol August 4, 2017 [Epub ahead of print]

Rezk M, Eliakwa H, Gamal A, Emara M: Maternal and fetal morbidity following discontinuation of antihypertensive drugs in mild to moderate chronic hypertension: a 4-year observational study. Pregnancy Hypertens 6:291, 2016 [PubMed: 27939471]

Rosner JY, Gutierrez M, Dziadosz M, et al: Prehypertension in early pregnancy: what is the significance? Am J Perinatol 34(2):117, 2017 [PubMed: 27322669]

Samuel A, Lin C, Parviainen K, et al: Expectant management of preeclampsia superimposed on chronic hypertension. J Matern Fetal Neonatal Med 24(7):907, 2011 [PubMed: 21142774]

Sibai BM: Etiology and management of postpartum hypertension-preeclampsia. Am J Obstet Gynecol 206(6):470, 2012 [PubMed: 21963308]

Sibai BM, Anderson GD: Pregnancy outcome of intensive therapy in severe hypertension in first trimester. Obstet Gynecol 67(4):517, 1986 [PubMed: 3960423]

Sibai BM, Grossman RA, Grossman HG: Effects of diuretics on plasma volume in pregnancies with long-term hypertension. Am J Obstet Gynecol 150(7):831, 1984 [PubMed: 6507509]

Sibai BM, Koch MA, Freire S, et al: Serum inhibin A and angiogenic factor levels in pregnancies with previous preeclampsia and/or chronic hypertension: are they useful markers for prediction of subsequent preeclampsia? Am J Obstet Gynecol 199(3):268.e1, 2008

Sibai BM, Mabie WC, Shamsa F, et al: A comparison of no medication versus methyldopa or labetalol in chronic hypertension during pregnancy. Am J Obstet Gynecol 162(4):960, 1990a

Sibai BM, Villar MA, Mabie BC: Acute renal failure in hypertensive disorders of pregnancy. Pregnancy outcome and remote prognosis in thirty-one consecutive cases. Am J Obstet Gynecol 162(3):777, 1990b

Society for Maternal-Fetal Medicine: SMFM statement: benefit of antihypertensive therapy for mild-to-moderate chronic hypertension during pregnancy remains uncertain. Am J Obstet Gynecol 213(1):3, 2015 [PubMed: 26004324]

Sowers JR, White WB, Pitt B, et al: The effects of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory therapy on 24-hour blood pressure in patients with hypertension, osteoarthritis, and type 2 diabetes mellitus. Arch Intern Med 165(2):161, 2005

Spaan JJ, Sep SJ, van Balen VL, et al: Metabolic syndrome as a risk factor for hypertension after preeclampsia. Obstet Gynecol 120(2 Pt 1):311, 2012 [PubMed: 22825090]

Spinnato JA 2nd, Freire S, Pinto E, Silva JL, et al: Antioxidant therapy to prevent preeclampsia: a randomized controlled trial. Obstet Gynecol 110(6):1311, 2007 [PubMed: 18055726]

Spong CY, Mercer BM, D'Alton M, et al: Timing of indicated late-preterm and early-term birth. Obstet Gynecol 118(2 Pt 1):323, 2011 [PubMed: 21775849]

SPRINT Research Group, Wright JT Jr, Williamson JD, et al: A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 373(22):2103, 2015 [PubMed: 26551272]

Staessen JA, Den Hond E, Celis H, et al: Antihypertensive treatment based on blood pressure measurement at home or in the physician's office: a randomized controlled trial. JAMA 291(8):955, 2004 [PubMed: 14982911]

Staff CA, Sibai BM, Cunningham FG: Prevention of preeclampsia and eclampsia. In Taylor RN, Roberts JM, Cunningham FG, et al (eds): Chesley's Hypertensive Disorders in Pregnancy, 4th ed. Amsterdam, Academic Press, 2015

Su CY, Lin HC, Cheng HC, et al: Pregnancy outcomes of anti-hypertensives for women with chronic hypertension: a population-based study. PLoS One 8(2):e53844, 2013 [PubMed: 23405075]

Tihtonen K, Kööbi T, Huhtala H, et al: Hemodynamic adaptation during pregnancy in chronic hypertension. Hypertens Pregnancy 26(3):315, 2007 [PubMed: 17710580]

Umans JG, Abalos E, Cunningham FG: Antihypertensive treatment. In Taylor RN, Roberts JM, Cunningham FG, et al (eds): Chesley's Hypertensive Disorders in Pregnancy, 4th ed. Amsterdam, Academic Press, 2015

Van Gelder MM, Van Bennekom CM, Louik C, et al: Maternal hypertensive disorders, antihypertensive medication use, and the risk of birth defects: a case control-study. BJOG 122(7):1002, 2015 [PubMed: 25395267]

Vigil-De Gracia P, Lasso M, Montufar-Rueda C: Perinatal outcome in women with severe chronic hypertension during the second half of pregnancy. Int J Gynaecol Obstet 85(2):139, 2004 [PubMed: 15099775]

Vigil-De Gracia P, Lasso M, Ruiz E, et al: Severe hypertension in pregnancy: hydralazine or labetalol a randomized clinical trial. Eur J Obstet Gynecol Reprod Biol 128(1–2):157, 2006 [PubMed: 16621226]

Vigil-De Gracia P, Solis V, Ortega N: Ibuprofen versus acetaminophen as a post-partum analgesic for women with severe pre-eclampsia: randomized clinical study. J Matern Fetal Neonatal Med 30(11):1279, 2017 [PubMed: 27384376]

Vricella LK, Louis JM, Mercer BM, et al: Epidural-associated hypotension is more common among severely preeclamptic patients in labor. Am J Obstet Gynecol 207(4):335.e1, 2012

Ward K, Taylor RN: Genetic factors in the etiology of preeclampsia/eclampsia. In Taylor RN, Roberts JM, Cunningham FG, et al (eds): Chesley's Hypertensive Disorders in Pregnancy, 4th ed. Amsterdam, Academic Press, 2015

Wasden SW, Ragsdale ES, Chasen ST, et al: Impact of non-steroidal anti-inflammatory drugs on hypertensive disorders of pregnancy. Pregnancy Hypertens 4:259, 2014 [PubMed: 26104814]

Webster LM, Myers JE, Nelson-Piercy C, et al: Labetalol versus nifedipine as antihypertensive treatment for chronic hypertension in pregnancy: a randomized controlled trial. Hypertension 70:915, 2017

Weissman-Brenner A, Schoen R, Divon MY: Aortic dissection in pregnancy. Obstet Gynecol 103:1110, 2004 [PubMed: 15121626]

Working Group Report on High Blood Pressure in Pregnancy: Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 183:S1, 2000

Yanit KE, Snowden JM, Cheng YW, et al: The impact of chronic hypertension and pregestational diabetes on pregnancy outcomes. Am J Obstet Gynecol 207(4):333.e1, 2012

Zetterström K, Lindeberg SN, Haglund B, et al: Chronic hypertension as a risk factor for offspring to be born small for gestational age. Acta Obstet Gynecol Scand 85(9):1046, 2006 [PubMed: 16929408]