Curr Atheroscler Rep (2014) 16:395
DOI 10.1007/s11883-013-0395-8

CORONARY HEART DISEASE (JA FARMER, SECTION EDITOR)

Hypertension in Pregnancy

Amanda R. Vest · Leslie S. Cho

Published online: 30 January 2014

Abstract Hypertensive disorders of pregnancy represent the second commonest cause of direct maternal death and complicate an estimated 5–10 % of pregnancies. Classification systems aim to separate hypertension similar to that seen outside pregnancy (chronic and gestational hypertension) from the potentially fatal pregnancy-specific conditions. Preeclampsia, HELLP syndrome, and eclampsia represent increasing severities of this disease spectrum. The American College of Obstetricians and Gynecologists' 2013 guidelines no longer require proteinuria as a diagnostic criterion, because of its variable appearance in the disease spectrum. The cause involves inadequate cytotrophoblastic invasion of the myometrium, resulting in placental hypoperfusion and diffuse maternal endothelial dysfunction. Changes in angiogenic and antiangiogentic peptide profiles precede the onset of clinical preeclampsia. Women with preeclampsia should be closely monitored and receive magnesium sulfate intravenously if severe features, HELLP syndrome, or eclampsia occur. Definitive therapy is delivery of the fetus. Hypertension in pregnancy increases future maternal risk of hypertension and cardiovascular disorders.

Keywords Pregnancy · Hypertension · Gestational · Preeclampsia · Eclampsia · Placenta · Angiogenic · Antiangiogenic · Antihypertensives

This article is part of the Topical Collection on *Coronary Heart Disease*

A. R. Vest
Heart Failure Fellow, Heart and Vascular Institute, Cleveland Clinic, Ohio, 9500 Euclid Avenue, Cleveland, OH 44195, USA
e-mail: vesta@ccf.org

L. S. Cho (✉)
Preventive Cardiology and Rehabilitation, Robert and Suzanne Tomsich Department of Cardiovascular Medicine, Cleveland Clinic, Ohio, 9500 Euclid Avenue, Cleveland, OH 44195, USA
e-mail: chol@ccf.org

Introduction

Hypertensive disorders of pregnancy rank as the second commonest cause of direct maternal death in the developed world [1•]. Hypertension is also the commonest medical complication encountered during pregnancy, and complicates 5–10 % of pregnancies [2, 3]. The highest rates are in black women, women over 45 years, and women with diabetes. Given the increasing prevalence of baseline hypertension, obesity, and diabetes in women of childbearing age and the trend towards advanced maternal age, the published rates may underestimate contemporary incidence. Hypertension in pregnancy is associated with increased risk of intracerebral hemorrhage, placental abruption, intrauterine growth retardation, prematurity, and intrauterine death. There are four categories of hypertensive disorders of pregnancy:

1. Preeclampsia/eclampsia
2. Chronic (preexisting) hypertension
3. Preeclampsia superimposed on chronic hypertension
4. Gestational hypertension (transient hypertension of pregnancy or chronic hypertension identified in the latter half of pregnancy)

Diagnosis

Hypertensive disorders of pregnancy are diagnosed by systolic blood pressure (BP) of 140 mmHg or greater and/or diastolic BP of 90 mmHg or greater on at least two occasions more than 4 h apart while resting. Systolic BP of 160 mmHg or greater and/or diastolic BP of 110 mmHg or greater measured on two separate occasions are generally agreed to represent severe hypertension [4–6]. However, the degree of hypertension is not associated with the risk of devastating eclamptic outcomes. Preexisting hypertension may not be

evident in the first and second trimesters owing to the physiologic reduction in BP, thus causing confusion with gestational hypertension.

The American College of Obstetricians and Gynecologists' (ACOG) Task Force on Hypertension in Pregnancy has recently revised the diagnostic criteria [7••], building on the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (NHBPEP) 2000 guidelines [8]. The major update is removal of proteinuria as a diagnostic requirement for preeclampsia/eclampsia. This reflects the recognition that as many as 14 % of women with preeclampsia do not have proteinuria [9], and such women have historically experienced delays in diagnosis and treatment as a result. As displayed in Table 1, preeclampsia can now be formally diagnosed without proteinuria when hypertension is accompanied by thrombocytopenia, transaminitis, acute kidney injury, pulmonary edema, or new-onset neurologic or visual symptoms [7••]. Proteinuria is defined by more than 300 mg protein in a 24-h urine collection or a urinary protein-to-creatinine ratio 0.3. Some guidelines permit a protein grading of 1+ or greater as measured by urinary dipstick as a diagnostic criterion, although this requires confirmation and quantification by the urinary protein-to-creatinine ratio obtained either randomly or by 24-h collection. False negatives can also occur with urine dipsticks, and hence their use is discouraged by the ACOG Task Force on Hypertension in Pregnancy [7••].

The identification of superimposed preeclampsia in the patient with chronic hypertension requires particular vigilance [10]. Diagnostic triggers include new or suddenly worsening proteinuria, hypertension, and proteinuria onset before 20 weeks' gestation, loss of established BP control, symptoms/signs such as headache, blurred vision, right upper quadrant or epigastric pain, hyperreflexia, or new thrombocytopenia or transaminitis. HELLP syndrome (hemolysis, elevated levels of liver enzymes, and low platelet count syndrome) is a laboratory diagnosis that represents a sector of the preeclampsia spectrum with poorer outcomes. "Severe preeclampsia" is a term used to distinguish multiorgan involvement and has therapeutic implications. Any of BP of 160/110 mmHg or greater, HELLP syndrome, acute kidney injury, pulmonary edema, or neurologic involvement such as cerebral edema (a variation on the posterior reversible encephalopathy syndrome) denotes severe preeclampsia. The degree of proteinuria is poorly correlated to preeclamptic outcomes and so using 5 g or more in 24 h to imply greater disease severity is now discouraged [7••].

Eclampsia, the life-threatening development of grand mal seizures in a woman with preeclampsia, is the severest manifestation of the spectrum. It is rare, with an incidence of 2.7 cases per 10,000 births in the UK [11]. Eclampsia may be preceded by a history of preeclampsia or may arise unexpectedly in a woman with minimally elevated BP and no proteinuria. There is significant risk of cardiorespiratory arrest during

Table 1 Classification and diagnosis of hypertensive disorders in pregnancy

Disorder	Features	Percentage of pregnancies
Chronic hypertension	Blood pressure of 140/90 mmHg or greater present prior to pregnancy, before the 20th week of gestation, or persisting beyond the 42nd postpartum day	1-5 %
Gestational hypertension	Hypertension that (a) develops beyond 20 weeks' gestation, (b) can be with or without proteinuria, but is not associated with other features of preeclampsia, and (c) usually resolves within 42 days postpartum	6-7 %
Preeclampsia	Hypertension presenting beyond 20 weeks' gestation with 300 mg protein per 24-h urine collection, or a urinary protein-to-creatinine ratio greater than 0.3, or a urine dipstick protein grade of 1+ or greater if other methods are unavailable. In the absence of proteinuria, new-onset hypertension with one of the following: platelet count below 100,000/μL; serum creatinine concentration of 1.1 mg/dL, or doubling of the serum creatinine concentration in the absence of other renal disease; levels of liver transaminases elevated to twice the normal concentration; pulmonary edema; cerebral or visual symptoms	2-5 %
Eclampsia	The occurrence of seizures in a pregnant woman with preeclampsia	Approximately 0.0003 % [11]
Preeclampsia/eclampsia superimposed on chronic hypertension	The onset of features diagnostic of preeclampsia/eclampsia in a woman with chronic hypertension beyond 20 weeks' gestation	20-25 % of chronic hypertension pregnancies

Adapted from the 2013 recommendations of the Task Force on Hypertension in Pregnancy of the American College of Obstetricians and Gynecologists [7••]

or after the seizure. Thirty-five percent of eclamptic seizures occur in the antepartum period, 9 % occur intrapartum, and 28 % occur postpartum. Late postpartum seizures (more than 48 h after delivery) are increasingly recognized [12].

Etiology and Risk Factors

Chronic hypertension occurs in around 20 % of women of childbearing age, with the exact prevalence dependent on age, ethnicity, and comorbidities such as diabetes and obesity. The pathophysiologic mechanisms of gestational hypertension are unknown, but are probably the same as those of essential hypertension in the nonpregnant individual, because gestational hypertension increases future postpregnancy hypertension risk. Gestational hypertension and preeclampsia are separate disease processes with different mechanisms. Evidence supporting this theory includes the differential risk factors, specific histologic changes in the placenta and kidneys associated with preeclampsia only, antiangiogenic peptides of placental origin, the levels of which are elevated in preeclampsia but not in gestational hypertension, and a far lower circulating volume in women with preeclampsia compared with women with gestational hypertension.

Table 2 summarizes the features currently considered to be preeclampsia risk factors. Extremes of maternal age (younger than 18 years or older than 35 years) were previously considered risk factors, but recent analysis concluded that young maternal age is not an independent predictor of preeclampsia [13]. Of additional relevance to the cardiologist is the elevated preeclampsia risk with aortic coarctation, pulmonary stenosis, pulmonary atresia with ventricular septal defect, and transposition of the great vessels. Older age, black race, Latina ethnicity, obesity, and gestational diabetes are all risk factors for new-onset late postpartum preeclampsia [14].

The pathophysiologic mechanisms of preeclampsia remain elusive, but it is widely accepted that the placenta is the inciting organ, provoking a syndrome of endothelial dysfunction and vasospasm. During early pregnancy, fetal chorionic villi that contact the uterine wall generate columns of cytotrophoblasts. Cytotrophoblastic invasion into the uterine wall occurs in two stages: invasion of the decidual segments of the spiral arteries at 10–12 weeks' gestation, followed by deeper invasion of the myometrium at 15–16 weeks. In preeclampsia, invasion of the myometrial arteries is aberrant and the spiral arteries remain narrowed and resistive. Placental hypoperfusion results, which may prompt oversecretion of placental antiangiogenic peptides capable of causing the diffuse end-organ preeclampsia manifestations [15]. Antiangiogenic peptides include soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng). There is concurrent underexpression of angiogenic peptides, including

Table 2 Risk factors for preeclampsia

Maternal	Age older than 40 years
	Black race
	Interpregnancy interval less than 2 years, or more than 10 years
	Mother born small for gestational age
	Nulliparity
	Preeclampsia or gestational hypertension in a prior pregnancy
	Chronic hypertension
	Hyperlipidemia [88]
	Obesity, insulin resistance, and/or prepregnancy diabetes [89]
	Chronic kidney disease
	Thrombophilia
	Systemic lupus erythematosus
	History of migraine [90]
	Use of SSRIs beyond the first trimester [91]
	Maternal infections (e.g., periodontal disease) [92]
	No baseline use of oral contraceptives [88]
Paternal	First pregnancy with partner
	Pregnancies following donor insemination or limited paternal sperm exposure
	Partner who fathered a preeclamptic pregnancy in another woman
Fetal	Multiparity
	Gestational trophoblastic disease
	Hydrops fetalis
	Triploidy

vascular endothelial growth factor (VEGF), placental growth factor (PlGF), placental protein 13 (PP-13) and pregnancy-associated plasma protein A (PAPP-A).

PP-13, also known as galectin 13, has been credited with a pathophysiologic role in trophoblastic invasion and the development of preeclampsia. Women who develop severe preeclampsia are more likely to have low levels of serum PP-13 between gestational weeks 6–10 [16]. The serum levels of both sFlt-1 and sEng are also elevated in preeclampsia [17–20]. Serum sFlt-1 levels also appear to be high in women with preeclampsia superimposed on systemic lupus erythematosus or glomerulonephritis, and are higher during nulliparous than multiparous pregnancies [20–22]. The reason for placental hypersecretion of these proteins remains unexplained. Conversely, VEGF is one of the underexpressed angiogenic peptides, and recombinant VEGF-121 infusion is effective in treating a rat model of preeclampsia [23].

Parallel lines of preeclampsia investigation include immunologic mechanisms, oxidative stress, and inflammation [24]. The immunologic privilege of the fetus and placenta that enables their nonmaternal cells to evade host immune destruction has been explored for decades. It is well established that a fourfold to fivefold excess of preeclampsia occurs in first pregnancies, and that parous women who are pregnant with a new partner lose the protective effect of a prior birth [25]. Furthermore, the protective effect of a prior abortion applies only to women who have conceived again with the same partner. A longer period of unprotected intercourse with the father also appears protective for preeclampsia, suggesting maternal exposure to paternal antigens may attenuate a key immune process in the disease [26]. Likewise, artificial donor insemination substantially increases preeclamptic risk [27]. These findings support immunologic intolerance between maternal and fetal tissues in the pathogenesis of preeclampsia. Links have now been made between immune mechanisms and endothelial dysfunction. Natural killer cells aggregate around the invading cytotrophoblasts until approximately 20 weeks and secrete cytokines such as VEGF and PlGF [28]. However preeclampsia does not ensue in all women with high sFlt-1 and low PlGF levels and does develop in some women with low sFlt-1 and high PlGF levels [29]. These recent pathophysiologic developments are reviewed in greater depth elsewhere [30•, 31].

Screening and Prevention of Preeclampsia

A British group recently established a first-trimester screening protocol that moved beyond the traditional reliance on the maternal history [32]. The prediction tool included baseline mean arterial pressure, uterine artery pulsatility index, and serum PAPP-A and PlGF concentrations. The risk of hypertension during pregnancy increased with higher mean arterial pressure and uterine artery pulsatility index at 11-13 weeks, or decreased serum PAPP-A and PlGF concentrations. The algorithm incorporated baseline maternal clinical data and identified 90 % of cases of early preeclampsia, with 5 % false positives. In contrast, maternal history alone has an estimated 30 % case detection for preeclampsia, with a false-positive rate of 5 % [33]. However, PAPP-A and PlGF levels did not perform as well in predicting late preeclampsia. More recently, among 287 women enrolled before 35 weeks' gestation, PlGF levels below the fifth centile demonstrated a 96 % sensitivity and 98 % negative predictive value for preeclampsia within 14 days; specificity was lower at 55 % [34•].

PP-13 is another biomarker candidate. Maternal serum PP-13 levels normally increase during pregnancy, but lower levels at 9-12 weeks are seen in women who progress to preeclampsia [35]. Several investigators have found utility in combining maternal serum PP-13 levels with uterine artery Doppler ultrasonography for early preeclampsia prediction, citing a 90 % detection rate with 6 % false positivity [36]. However, one group concluded that the use of first-trimester PP-13 and PAPP-A levels and uterine artery pulsatility index in combination did not offer enhanced predictive value compared with measurement of these parameters individually [37]. Additional proposed preeclampsia biomarkers include sFlt-1 and sEng (as outlined earlier) and also adiponectin, urine orosomucoid, inhibin A, and activin A [15, 38]. Uric acid may be a useful predictor specifically in women with gestational hypertension who progress to preeclampsia [39]. Although these biomarker developments are very encouraging, the only currently recommended preeclampsia screening tool per the ACOG Task Force on Hypertension in Pregnancy is a detailed maternal history.

A greater role for screening would require proven interventions to prevent development of preeclampsia in high-risk women. Several therapies have been proposed and studied. Aspirin may address an imbalance between prostacyclin and thromboxane arising early in the preeclampsia process. A Cochrane review of 36,500 women in 59 trials revealed a 17 % risk reduction for preeclampsia, with a number needed to treat of 72 [40]. Patients with high-risk histories, including prior preeclampsia necessitating delivery at 34 weeks or earlier, are advised to take low-dose aspirin daily from late in the first trimester by the NHBPEP, National Institute for Health and Clinical Excellence (NICE), and ACOG guidelines.

Studies of calcium supplementation suggest that it is beneficial in women who have a high preeclampsia risk and a low dietary calcium intake [41, 42]. Preliminary trials demonstrated benefit from vitamins C and E [43], but adequately powered studies did not support this hypothesis [44, 45]. Trials of magnesium and zinc supplements, fish oils, garlic, a low-salt diet, and folic acid have shown no impact on preeclampsia risk. Other agents specifically recommended against by the guidelines are nitric oxide donors, progesterone,

and low molecular weight heparin [46•]. Women who smoke during pregnancy have poorer obstetric outcomes overall, but smoking may actually be protective for hypertensive complications of pregnancy [47]. However a substudy of one of the large calcium trials demonstrated that in smokers who quit before conception there was no change in the risk of gestational hypertension or preeclampsia [48].

Clinical Course and Prognosis

Chronic and gestational hypertension is usually associated with good outcomes, although there is an increased risk of maternal intracerebral hemorrhage and poor fetal outcomes, and up to a quarter of women with chronic hypertension will develop superimposed preeclampsia [49]. Even without preeclampsia development, the likelihood of preterm birth is elevated fivefold, and there is a 50 % excess risk of a small-for-gestational-age neonate for women with chronic hypertension [50]. Elevated BP early in pregnancy is also associated with a significantly increased risk of gestational diabetes even after adjustment for age, race, obesity, and parity [51].

Preeclampsia represents a third of cases of severe obstetric morbidity [52], and is a major predisposing factor in pregnancies resulting in stillbirth of an otherwise viable neonate [53]. Preeclampsia is also strongly associated with intrauterine growth restriction, low birth weight, preterm delivery, and neonatal respiratory distress syndrome. The mortality associated with preeclampsia and eclampsia remains significant; in 2006–2008 the mortality rate in the UK was 0.83 per 100,000 maternities, which amounted to 22 deaths, 14 of which were due to cerebral diseases [1•]. Combining the UK Obstetric Surveillance System data [11] and the data from the eighth report of the Confidential Enquiries into Maternal Deaths results in an estimated case fatality rate from eclampsia of 3.1 %. Encouragingly, the incidence of eclamptic seizures has halved in the UK since 1992, presumably due to adoption of magnesium sulfate prophylaxis.

Hypertension due to preeclampsia typically improves within days of delivery and BP should return to the baseline level by 12 weeks postpartum. However, a 2013 Cochrane review noted that BP peaks 3-6 days after birth, when most women have been discharged home [54]. Antihypertensive therapy is currently recommended for women with persistent postpartum BP of 150/100 mmHg or greater [7••], although the Cochrane review found no data to support this practice [54]. For women who were diagnosed with preeclampsia, there is a 16 % rate of preeclampsia recurrence with subsequent pregnancy. The rate of recurrence rises to 25 % if preeclampsia mandated delivery before 34 weeks, and rises to 55 % if delivery occurred before 28 weeks [55, 56]. Preeclampsia confers a 13-53 % risk of gestational hypertension in a future pregnancy. For women who had gestational hypertension, the risk of recurrence during future pregnancy is 16-47 %. A 2-7 % risk of preeclampsia in future pregnancies can also be expected [46•].

Impact on Future Cardiovascular Risk

Hypertension during pregnancy, regardless of the type and even without known risk factors, confers a high risk of later hypertension, cardiovascular disease, chronic kidney disease, and diabetes mellitus [57–59]. Preeclampsia elevates the risk of future hypertension threefold to fourfold [60]. There is also an increased risk of stroke in the adult offspring from preeclamptic pregnancies [61]. Severe hypertensive disease in pregnancy has a stronger association with the later development of ischemic heart disease than mild hypertensive disease, and recurrent hypertensive disease in pregnancy is more strongly associated with future heart disease than is nonrecurrent disease [62]. It is possible that the association with future cardiovascular events is primarily due to shared risk factors rather than a direct influence of pregnancy complications on the heart or vasculature [63–65]. Cardiologists should routinely take a pregnancy history when evaluating cardiovascular risk for female patients who have been pregnant [66, 67].

Management Goals and Guidelines

Significant uncertainty remains regarding optimal management of chronic and gestational hypertension in the absence of preeclamptic features. There is general agreement, reflected in the NHBPEP and ACOG guidelines, that BP of 150-160/100-110 mmHg or greater should be treated. Treatment is aimed at minimizing maternal end-organ damage, for which systolic (rather than diastolic) pressure is the strongest predictor [68].

Mild-to-moderate chronic or gestational hypertension is less likely to exert end-organ disease, and treatment has been shown to neither improve neonatal outcomes nor prevent superimposed preeclampsia. A Cochrane review of 46 trials, encompassing 4,282 patients with modest BP elevations, demonstrated no benefits of treatment in terms of stillbirth, preterm birth, or small-for-gestational-age neonates [69]. Excessive BP lowering in such patients may even harm fetal growth via placental hypoperfusion [70].

There are very few adequately powered, randomized trials of antihypertensive medications in pregnancy [71]. The US Food and Drug Administration (FDA) grades the risk of medications in pregnancy mainly on the basis of available animal studies, postmarketing surveillance, and case reports. It is recognized that randomized, large-scale studies to determine both the optimal BP targets and drug regimens for pregnant women with hypertension are urgently needed. A

pilot study that is beginning to address this deficit was recently published [72]. The Control of Hypertension in Pregnancy Study (CHIPS; ClinicalTrials.gov identifier NCT01192412) is the largest prospective, randomized, multicenter trial evaluating the impact of a diastolic BP target of 100 mmHg versus 85 mmHg on maternal and neonatal outcomes. Trial completion is expected in March 2014. Meanwhile, there is no consensus on BP treatment targets during preeclampsia, although the 2013 AGOC Task Force on Hypertension in Pregnancy recommends 120–160/80–105 mmHg for pregnant women with chronic hypertension.

Management of Chronic and Gestational Hypertension

BP typically falls by 10 mmHg by the end of the second trimester compared with before conception, owing to decreased systemic vascular resistance. Therefore, the 2000 NHBPEP report supports stopping antihypertensive medications in women with preexisting hypertension and no target organ involvement, with plans for reinstating appropriate medications should the BP exceed 150-160/100-110 mmHg. The NHBPEP report endorsed the use the central adrenergic inhibitor methyldopa as the first-line medication, on the basis of three decades of postmarketing surveillance and 7.5 years of neonatal follow-up [73]. Orally administered methyldopa carries an FDA category B designation, meaning either that animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or that animal reproduction studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester. However, the NICE guidelines from the UK highlight potential precipitation of maternal depression with this medication and specifically advise against the continuation of methyldopa beyond the second day postpartum. Other commonly used oral medications such as labetalol, hydralazine, and nifedipine are all category C agents, implying either that animal studies have revealed adverse effects on the fetus and there are no controlled studies in women, or that studies in women are not available. The FDA advises that category C drugs should be given only if the potential benefits outweigh the fetal risks.

Labetalol, a combined alpha-blocker and beta-blocker, has gained popularity in pregnancy and is the first-line treatment for gestational or preeclamptic hypertension in the 2010 NICE guidelines, on the basis of expert opinion. The 2013 ACOG Task Force on Hypertension in Pregnancy supports labetalol, nifedipine or methyldopa as first-line treatment [7••]. Slow-release nifedipine is the most commonly used calcium channel blocker in pregnancy. Animal studies have raised concerns of teratogenicity, but postmarketing data have not revealed any association with congenital abnormalities. Concurrent administration of calcium channel blockers and magnesium sulfate has traditionally been avoided because of potentially synergistic BP effects, although the 2008 Society of Obstetricians and Gynaecologists of Canada guidelines support contemporaneous use [4].

Atenolol carries a category D classification owing to its association with low birth weight, preterm delivery, and neonatal hypoglycemia and bradycardia. Metoprolol received a class C designation primarily on the basis of studies in rats. One human study compared the outcomes in 101 pregnant women receiving metoprolol alone or in combination with hydralazine with the outcomes for 97 hypertensive pregnant women receiving hydralazine. Perinatal mortality was lower in the metoprolol group (2.0 %) than in the hydralazine group (8.0 %), and the rate of fetal growth restriction was also lower with metoprolol [74]. There are possible associations between first-trimester hydralazine use and hypospadias, third-trimester use and neonatal thrombocytopenia, and maternal or neonatal lupus-like syndrome. The use of diuretics for BP control during pregnancy remains controversial, even though hydrochlorothiazide is an FDA category B drug. The total body volume is reduced in preeclampsia and hence diuresis can precipitate hypovolemia and placental hypoperfusion. Diuretics may reduce milk volume, although the American Academy of Pediatrics considers their use compatible with breastfeeding.

A recent retrospective cohort study detailed outcomes for 1,964 pregnant women with chronic hypertension. Six hundred twenty neonates were exposed to either methyldopa or atenolol during pregnancy. Higher rates of intrauterine growth restriction, small size for gestational age, and preterm delivery (before 37 weeks) occurred in pregnancies in which there was exposure to antihypertensives in the third trimester. Importantly though, a similar association was detected in comparing women with chronic hypertension who were untreated during pregnancy (n=1,074) with women who had no chronic hypertension or antihypertensive exposures (n=97,820) [75].

Hypertensive emergencies during pregnancy necessitate the use of medications with more rapid onset of action. In severe hypertension, or with evidence of maternal or fetal compromise, the systolic BP should be lowered by approximately 25 % over minutes to hours. Common strategies are intravenously administered labetalol, hydralazine or sodium nitroprusside. Rapidly acting sublingually administered nifedipine carries a substantial risk of precipitating severe hypotension and cerebral infarction and should not be used. Nimodipine should also be avoided [76••]. Intravenously administered nitroglycerin is a good choice in the setting of pulmonary edema [77]. If posterior reversible encephalopathy syndrome is suspected, labetalol may be a good choice, as it does not cerebrally vasodilate. The role of intravenously administered hydralazine was questioned by a meta-analysis that reported poorer maternal and perinatal outcomes for

hydralazine compared with other antihypertensives, particularly labetalol and nifedipine. Hydralazine was associated with excess maternal hypotension and oliguria, placental abruption, caesarean delivery, and low Apgar scores at 1 min [78]. Sodium nitroprusside can be used cautiously; women with renal impairment require thiocyanate levels to avoid cyanide toxicity [79]. An updated Cochrane review of 35 drug trials for severe hypertension in pregnancy (3,573 women) concluded there was insufficient evidence to make practice recommendations, but that the choice of antihypertensive drug should be based on the clinician's experience and familiarity with a particular drug, its known adverse effects, and patient preferences [76••].

ACE inhibitors and angiotensin receptor blockers are strictly contraindicated throughout pregnancy. Fetal effects include oligohydramnios, intrauterine growth restriction, hypocalvaria, renal dysplasia, anuria, and death [80]. Direct renin inhibitors have a related mechanism of action and are therefore best avoided, although aliskiren has been assigned FDA pregnancy categories C (first trimester) and D (second and third trimesters). Labetalol, nifedipine, enalapril, captopril, and metoprolol are considered to have little effect or no effects on breastfed neonates. Angiotensin receptor blockers, amlodipine, and ACE inhibitors other than enalapril and captopril should not be prescribed during lactation [46•]; atenolol should also be avoided if possible [81].

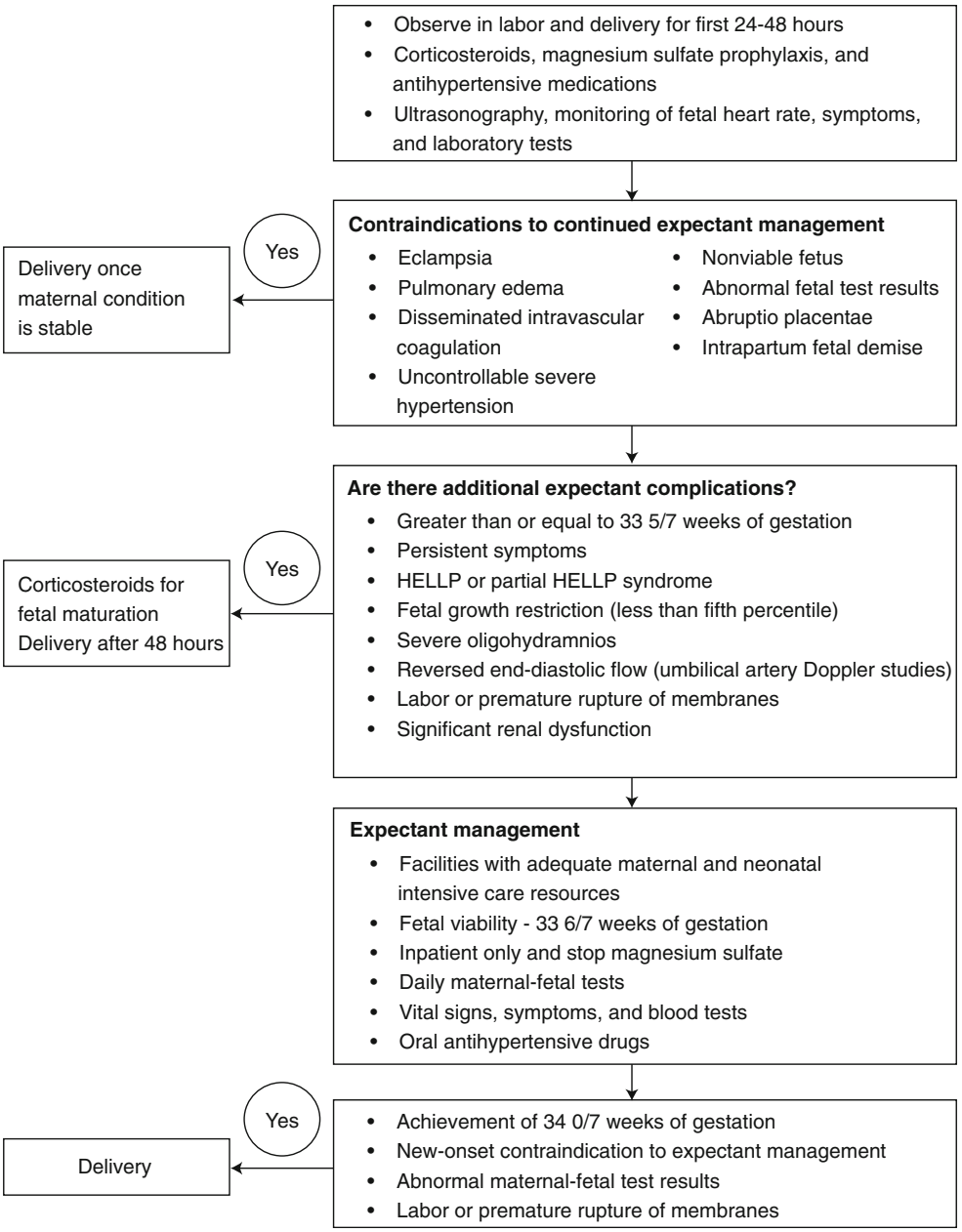

Fig. 1 Recommended management of severe preeclampsia at less than 34 weeks' gestation. (Copyright the American College of Obstetricians and Gynecologists [7••], 2013)

Management of Preeclampsia and Eclampsia

Preeclampsia and eclampsia necessitate much more complex management decisions than BP control alone. Intravenously administered magnesium sulfate has a crucial role in the prevention of seizures in preeclamptic women by slowing neuromuscular conduction and raising the seizure threshold. A loading dose of 4–6 g is usually diluted in 100 mL of normal saline and infused over 15–20 min, followed by a 2 g/h infusion. The therapeutic range for magnesium is 4-7 mg/dL; serum levels are advised in renal impairment [82]. The antidote is intravenously administered calcium gluconate. Seizure prophylaxis with magnesium should continue for 12–24 h postpartum. The Magpie trial clearly demonstrated the benefits of magnesium in the preeclamptic patient [83]. This study recruited 10,141 pregnant women with BP greater than 140/90 mmHg and protein grading of 1+ (30 mg/dL). Magnesium halved the risk of eclampsia without significant adverse maternal or fetal effects. The 2013 ACOG guidelines recommend magnesium sulfate in cases of severe preeclampsia, eclampsia, or HELLP syndrome [7••].

Combined oxytocin and ergometrine (Syntometrine) should not be used to precipitate placental delivery and prevent postpartum hemorrhage in hypertensive women [1•]. Ergometrine is a powerful vasoconstrictor and has been implicated in immediate postpartum hypertensive events. Intramuscular oxytocin without ergometrine is acceptable instead [84]. Neither the routine use of intravenous fluids nor the routine administration of diuretics is an appropriate response to maternal oliguria [4].

The definitive treatment of preeclampsia or eclampsia is delivery of the fetus. Delivery dramatically reduces the risk of complications such as seizures, cerebral edema, placental abruption, pulmonary edema, and dissemination intravascular coagulopathy, although potentially at the expense of poorer fetal outcomes. In preeclampsia without severe features, more conservative management with close monitoring for uteroplacental insufficiency is appropriate. In these patients, delivery is generally not indicated until at least 37 weeks [7••]. Bed rest is no longer routinely recommended in gestational hypertension or preeclampsia without severe features. Four small trials, involving 449 subjects, were evaluated by a Cochrane review [85]. One trial associated bed rest with reduced risks of severe hypertension and prematurity, but none of the studies evaluated the potential for deep vein thrombosis, or social and economic implications. The reviewers concluded that current evidence is insufficient to provide clinical guidance and bed rest should not be routinely recommended.

In severer forms of preeclampsia, hospital admission for prophylaxis of seizures and tight BP control is essential. If features of severe preeclampsia are detected before 34 weeks, expedited delivery may be indicated at specialized centers as outlined in Fig. 1 [86]. Expert opinion supports delivery within 24 h for women with treatment-resistant hypertension or maternal or fetal compromise, regardless of gestational age or fetal lung maturity. Beyond 34 weeks' gestation, or in cases where fetal lung maturity has been achieved, delivery should occur as soon as the mother has been urgently stabilized [7••, 87].

Conclusion

Hypertension during pregnancy complicates 5-10 % of pregnancies and is a common cause of maternal death. The pathogenesis of hypertension involves inadequate cytotrophoblastic invasion of the myometrium, resulting in placental hypoperfusion and diffuse maternal endothelial dysfunction. The goal of early diagnosis and treatment and learning how to recognize potentially dangerous conditions will help prevent fetal and maternal deaths.

Compliance with Ethics Guidelines

Conflict of Interest Amanda R. Vest and Leslie S. Cho declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of particular importance

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