Toward personalized management of chronic hypertension in pregnancy

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Chronic hypertension complicates 1% to 2% of pregnancies, and it is increasingly common. Women with chronic hypertension are an easily recognized group who are in touch with a wide variety of healthcare providers before, during, and after pregnancy, mandating that chronic hypertension in pregnancy be within the scope of many practitioners. We reviewed recent data on management to inform current care and future research. This study is a narrative review of published literature. Compared with normotensive women, women with chronic hypertension are at an increased risk of maternal and perinatal complications. Women with chronic hypertension who wish to be involved in their care can do by measuring blood pressure at home. Accurate devices for home blood pressure monitoring are now readily available. The diagnostic criteria for superimposed preeclampsia remain problematic because most guidelines continue to include deteriorating blood pressure control in the definition. It has not been established how angiogenic markers may aid in confirmation of the diagnosis of superimposed preeclampsia when suspected, over and above information provided by routinely available clinical data and laboratory results. Although chronic hypertension is a strong risk factor for preeclampsia, and aspirin decreases preeclampsia risk, the effectiveness specifically among women with chronic hypertension has been questioned. It is unclear whether calcium has an independent effect in preeclampsia prevention in such women. Treating hypertension with antihypertensive therapy halves the risk of progression to severe hypertension, thrombocytopenia, and elevated liver enzymes, but a reduction in preeclampsia or serious maternal complications has not been observed; however, the lack of evidence for the latter is possibly owing to few events. In addition, treating chronic hypertension neither reduces nor increases fetal or newborn death or morbidity, regardless of the gestational age at which the antihypertensive treatment is started. Antihypertensive agents are not teratogenic, but there may be an increase in malformations associated with chronic hypertension itself. At present, blood pressure treatment targets used in clinics are the same as those used at home, although blood pressure values tend to be inconsistently lower at home among women with hypertension. Although starting all women on the same antihypertensive medication is usually effective in reducing blood pressure, it remains unclear whether there is an optimal agent for such an approach or how best to use combinations of antihypertensive medications. An alternative approach is to individualize care, using maternal characteristics and blood pressure features beyond blood pressure level (eg, variability) that are of prognostic value. Outcomes may be improved by timed birth between 38 0/7 and 39 6/7 weeks' gestation based on observational literature; of note, confirmatory trial evidence is pending. Postnatal care is facilitated by the acceptability of most antihypertensives (including angiotensin-converting enzymes inhibitors) for use in breastfeeding. The evidence base to guide the care of pregnant women with chronic hypertension is growing and aligning with international guidelines. Addressing outstanding research questions would inform personalized care of chronic hypertension in pregnancy.

Key words: antihypertensive therapy, aspirin, chronic hypertension, pregnancy

Epidemiology

Hypertension complicates up to 10% of pregnancies and potentially twice that when considered per woman.[1] Chronic hypertension complicates 1% to 2% of pregnancies, and rates are rising.[2] Although this has been attributed to secular trends in age and body mass index,[1] a relationship with black race and rising maternal age, but not obesity or smoking, could be demonstrated in a population-based cross-sectional study of more than 150 million hospital deliveries in the United States.[2] This is a global phenomenon, with rates at least as high in resource-limited settings.[3]

Definition

Clinical practice guidelines define chronic hypertension as a blood pressure (BP) of ≥140/90 mm Hg before pregnancy or before 20 weeks' gestation.[4] Although this is consistent with how hypertension is generally defined outside pregnancy, the American College of Cardiology (ACC) and American Heart Association (AHA) have lowered their threshold for diagnosis to 130/80 mm Hg, with 130 to 139/80 to 89 mm Hg designated as stage 1 hypertension and ≥140/90 mm Hg as stage 2.[5] If 130/80 mm Hg was the threshold for diagnosing chronic hypertension in pregnancy,

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more women would be identified who have a heightened risk of preeclampsia (with risk being intermediate between those with a BP of <130/80 mm Hg [defined as normal if <120/80 mm Hg and "elevated" if systolic BP is 120–129 mm Hg] and stage 2 chronic hypertension), preterm birth, and gestational diabetes.[6] Furthermore, women with stage 1 hypertension would benefit from low-dose aspirin, based on a secondary analysis of a larger trial.[7]

Clinical significance

Women with chronic hypertension experience increased maternal and perinatal complications. According to a systematic review (55 studies, 795,221 pregnancies), women with chronic hypertension have high rates of superimposed preeclampsia (26%), cesarean delivery (41%), preterm delivery (28%), low birthweight (17%), perinatal death (4%), and neonatal intensive care unit (NICU) admission (21%).[8] Stillbirths occur earlier, at a median of 28 vs 35 weeks' gestation, with an absolute risk at 36 weeks' gestation (1/1000 births) that equates to the risk among low-risk nulliparous women at 41 weeks' gestation.[9,10] Chronic hypertension is a singular clinical risk factor for preeclampsia,[11] which itself accentuates risk for adverse pregnancy outcomes[12–15]; however, development of preeclampsia, defined traditionally by new proteinuria, inadequately accounts for the excess of complications. For example, preeclampsia accounts for <50% cases of chronic hypertension–associated prematurity, small-for-gestational-age (SGA) infants, and NICU admissions.[16–20]

Assessment and Blood Pressure Measurement

Early pregnancy evaluation

More than 90% of pregnant women with chronic hypertension have underlying primary (formerly called "essential") hypertension, related to genetics or lifestyle factors,[21] and most will have been identified before pregnancy. Extensive genetics studies have revealed 2 types of abnormalities: (1) <20 rare mutations that are primarily genes regulating mineralocorticoid or renal pathways, associated with substantial hypertension, and useful in a small number of families, and (2) hundreds of genetic variants associated with a very small increase in BP (ie, ≈1 mm Hg) that contribute to our understanding of the pathogenesis of hypertension but not to the care of individuals.[22] Excessive intake of sodium (ie, >3 g/d of sodium chloride) or alcohol or a sedentary lifestyle are all modifiable lifestyle risk factors for hypertension outside pregnancy; although little is known about altering salt intake in women with chronic hypertension in pregnancy and pregnant women are advised not to drink alcohol, encouraging physical activity is emerging as an important intervention in pregnancy to prevent preeclampsia.[23] Although less likely to be an issue in pregnancy, it is noteworthy that many medications can increase BP; oral contraceptives and nonsteroidal antiinflammatory drugs (NSAIDs) will have been stopped in pregnancy, but women may take over-the-counter decongestants, prescription drugs for medical indications (such as immunosuppressants or antidepressants), or consume illicit drugs such as cocaine.

An underlying, "secondary," cause of hypertension may be related to problems in the renal (eg, chronic kidney disease or renal artery stenosis), vascular (eg, coarctation of the aorta), endocrine (eg, primary aldosteronism, pheochromocytoma, Cushing syndrome, hypothyroidism, or thyrotoxicosis), or respiratory (eg, obstructive sleep apnea) systems. Although, collectively, they are thought to account for less than 10% of cases of hypertension, primary aldosteronism may be underrecognized. With systematic screening, including aldosterone-to-renin ratios, hyperaldosteronism is prevalent among individuals within stage 1 (16%) or stage 2 (22%) hypertension, compared with normotensive individuals (11%).[24]

It is not cost-effective to perform a workup for secondary causes of hypertension in all pregnant women or all adults outside pregnancy. However, it is considered prudent to perform a basic workup in early pregnancy if not performed before pregnancy. The objective is to rule out obvious secondary causes of hypertension and evaluate baseline cardiovascular risk, although most tests for the latter are not recommended in pregnancy given the differences in reference ranges and/or no resultant change in management in pregnancy (Table 1). Additional baseline tests may be useful for later comparison when superimposed preeclampsia is suspected (Table 1). Of note, this screening does not include hyperaldosteronism because associated hypertension usually improves in pregnancy and the most commonly used mineralocorticoid receptor antagonist (spironolactone) is not recommended for use in pregnancy owing to potential antiandrogen effects on male fetuses. Hypertension secondary to renal, vascular, or endocrine causes is suggested by age of onset <30 years, uncontrolled BP with 3 antihypertensives, or condition-specific symptoms; however, many symptoms are associated with normal pregnancy (eg, dizziness [pheochromocytoma]; snoring [obstructive sleep apnea]; palpitations and heat intolerance [thyrotoxicosis]; or edema, fatigue, and frequent urination [kidney disease]). Suspected secondary hypertension should initiate referral for specialist workup.[25]

The baseline risk of fetal malformations should be clarified numerically, as many women may not appreciate that 1% to 5% of all pregnancies are complicated by major birth defects. In addition, untreated chronic hypertension may further increase that risk, particularly for cardiovascular defects, cleft lip or palate, and hypospadias.[26–28] The mechanism is not understood, and even though antihypertensive agents neither seem to be responsible (as discussed below) nor do they seem to alter miscarriage risk (≈20%),[29,30] information is limited.

Because approximately half of pregnancies are unplanned, women with chronic hypertension who are of reproductive age would ideally be treated with antihypertensives that are safe in pregnancy. Although no antihypertensive medication is a proven human teratogen, initial associations between angiotensin-converting enzyme inhibitors (ACEIs) and birth defects may have suffered from

TABLE 1
Suggested workup of women with chronic hypertension

Explore lifestyle factors that could increase BP	
	Excessive salt intake
	Excessive alcohol intake
	Sedentary lifestyle
	Medications or illicit substances that can increase BP (eg, decongestants, NSAIDs, immunosuppressants, antidepressants, cocaine)
Rule out obvious secondary causes of hypertension	
	Serum electrolytes (including serum potassium and calcium)
	Serum creatinine
	Thyroid-stimulating hormone
	Urinalysis
Evaluate baseline cardiovascular risk	
	Fasting blood glucose
	Lipid profile[a]
	Electrocardiogram[b]
Establish results of baseline blood work critical to evaluation of superimposed preeclampsia	
	Complete blood count (particularly for platelet count)
	Serum creatinine[c]
	Liver enzymes (AST or ALT)

ALT, alanine aminotransferase; *AST*, aspartate aminotransferase; *BP*, blood pressure; *NSAID*, nonsteroidal antiinflammatory drug.

[a] Not performed in pregnancy as the normal range is higher and management would not be changed; [b] Not routinely performed in pregnancy but may be useful as part of a hemodynamically guided antihypertensive therapy; [c] Even if performed earlier to rule out secondary causes of hypertension.

Magee. Personalized care of chronic hypertension. Am J Obstet Gynecol 2020.

residual confounding from the underlying hypertension, as discussed previously.[31] Subsequent work has not been consistently reassuring. In a prospective cohort (N=138 women), ACEIs and angiotensin receptor blockers (ARBs) were associated with miscarriage (but not malformations), compared with both hypertensive and normotensive controls; most women (79.8%) were exposed to ACEIs.[32] However, ACEIs, ARBs, and other antihypertensive agents have been associated with teratogenicity in a meta-analysis of 5 controlled cohort studies (786 infants exposed to ACEIs or ARBs, 1723 to other antihypertensives, and 1,091,472 unexposed).[33] The UK clinical practice guideline suggests that thiazides are teratogenic,[34] but this statement is not supported by animal or limited human studies.[35] Given the inconsistent literature, it is acceptable to continue antihypertensive agents, including ACEIs and ARBs, until conception; this practice may be particularly important for women taking ACEIs for renoprotection in chronic kidney disease (CKD). Conception may normally take up to 12 months, and women older than 30 years are at a greater risk for subfertility, so replacing medication prepregnancy can mean that such women's medication is suboptimal for 1 to 2 years.

The safety of antihypertensive agents beyond early pregnancy is further discussed under the Antihypertensive therapy section.

Home blood pressure monitoring

Home blood pressure monitoring (HBPM) is recommended by most guidelines for care of hypertension outside pregnancy, based on improved links between diagnoses and adverse outcomes, convenience, antihypertensive compliance, and BP control.[36] Therefore, women with chronic hypertension may have used HBPM preconceptionally; the coronavirus disease 2019 pandemic has broadened pregnancy HBPM implementation.[37]

In pregnancy, women using HBPM report greater awareness of risks and empowerment.[38,39] In a systematic review of pregnancies at risk of, or complicated by, hypertension (11 studies [5 randomized controlled trials]), HBPM (usually antenatal [9/11] with telemonitoring [8/11]) was associated with reductions in labor induction (odds ratio [OR], 0.55; 95% confidence interval [CI], 0.36–0.42; N=444 women), antepartum admission (OR, 0.31; 95% CI, 0.19–0.49; N=416 women), and preeclampsia (OR, 0.50; 95% CI, 0.31–0.81; N=725 women).[40] Another study suggested possible cost reductions.[41] In trials outside pregnancy and 1 postpartum (91 women), self-monitoring and self-titration of antihypertensives improved BP control[42–44]; ongoing trials have not raised safety concerns.[37]

HBPM is the established method to diagnose white coat hypertension in pregnancy, defined as an elevated office BP that is normal outside the office. The 30% of women with chronic hypertension in pregnancy with white coat hypertension do not require antihypertensives but warrant surveillance owing to increased preeclampsia, fetal growth restriction (FGR), and prematurity risk.[45–47] Used to monitor the BP of unselected and pregnant women with hypertension,[48] HBPM reduces false-positive diagnoses of severe hypertension and unnecessary interventions.[49]

Key considerations for HBPM use in pregnancy include pregnancy- and preeclampsia-validated BP devices, clear triggers for action by women, care pathways, and mechanisms for bidirectional communication between women and care providers.

BP measurements from up to 25% of devices differ from those taken using standard sphygmomanometry[50]; regularly updated lists of acceptable devices are available.[51,52] However, as even a grade A device will be accurate within 5 mm Hg of true BP only 60% of the time, it is wise to check a woman's home BP device against a calibrated sphygmomanometer or validated automated device.

Currently, similar BP targets should be used for HBPM and office BP to inform care pathways. Systematic review (7 studies, up to 140 women in late pregnancy) found that home BP is widely variable and probably lower than clinic BP for women with hypertension.[48] Of note, subgroup analyses before 20 weeks' gestation involved fewer than 100 women, and differences were seen primarily in systolic BP (up to 16 mm Hg vs 7 mm Hg for diastolic BP [dBP]).

Smartphone applications (apps) are emerging in pregnancy hypertension to facilitate bidirectional communication.[53] User involvement in development and evaluation, easy-to-use formats, portability, and multifunctionality support clinical decision support.[54] Typically, women enter self-measured BP values into an app that transmits values to the clinicians' dashboard. Women receive immediate feedback to call or present for urgent care, based on the level of BP relative to set thresholds, reported symptoms, and/or proteinuria testing.[41,49]

Digital technology may facilitate use of physiological variables other than BP level (eg, heart rate [HR], BP variability, hyperdynamic circulation, high vascular resistance) to predict preeclampsia and FGR; these are facilitated by the large numbers of recordings available through HBPM and availability of noninvasive cardiac output monitors.[55–57]

Prediction and Prevention of Preeclampsia

Prediction of preeclampsia

Chronic hypertension is a strong clinical risk factor for preeclampsia (relative risk [RR], 5.1; 95% CI, 4.0–6.5),[11,58,59] but clinical risk factors alone have poor sensitivity for preterm (≈40%) or term (≈40%) preeclampsia in general or among women with chronic hypertension specifically.[60–62] However, clinical risk factors do contribute independently to risk estimates when used in multivariable models.[63] The 11- to 14-week Fetal Medicine Foundation (FMF) model incorporates clinical risk factors, BP, uterine artery Doppler, and placental growth factor (PlGF); shows high sensitivity (≈80%) for preterm preeclampsia[60,61]; and has been validated prospectively in all continents outside Africa.[64–69] An online calculator is available.[70] A more detailed review can be found elsewhere.[71]

Aspirin

Chronic hypertension is a uniform indication for low-dose aspirin in practice guidelines,[4] but there are 2 major unanswered questions. First, there is uncertainty about the necessity of multivariable screening. Although women with strong clinical factors such as chronic hypertension who screen negative have a low background risk of preeclampsia (0.65%), almost all such women (94%) screen positive,[72] and the cost-effectiveness of early pregnancy multivariable screening is disputed.[73–75] Second, when multivariable screening identified women at high risk of preeclampsia, and they were administered 150 mg/evening of aspirin, the risk of preterm preeclampsia was substantially reduced,[76] but women with chronic hypertension were the only subgroup not to benefit.[76] This observation is consistent with subgroup analyses in the relevant individual participant data meta-analysis[77] and 2 randomized trials, although aspirin was used in low dose[78,79] and/or often started after 20 weeks' gestation[78]; a trial is planned (NCT04356326). No practice guideline currently recommends against administering aspirin to these women.[4] These issues are discussed in detail elsewhere.[80]

Calcium

Increasing calcium intake to ≥1 g/d reduces the likelihood of preeclampsia in women with low intake[81–83]; most women in more developed countries have adequate intake.[84] Unresolved controversies include whether calcium adds benefit to aspirin, whether high-dose (≥1.0 g/d) or low-dose calcium should be prescribed, and the effectiveness of calcium according to baseline preeclampsia risk. Prevention of preeclampsia is discussed in detail elsewhere.[80,85–87]

Antihypertensive Therapy

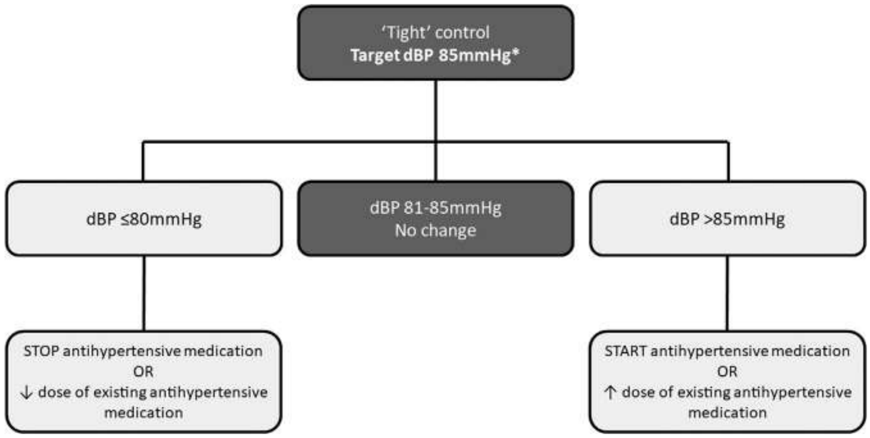
"Tight" blood pressure control

There have been concerns that antihypertensive treatment of nonsevere hypertension may decrease uteroplacental perfusion, leading to adverse perinatal outcomes; an argument strengthened by meta-regression analyses that associated greater antihypertensive-induced falls in BP with an increased risk of birthweight <10th percentile and lower mean birthweight.[88,89] Such concerns must be balanced by oral antihypertensive therapy halving the risk of severe hypertension (systematic review, 31 trials, 3485 women),[90] an outcome worthy of avoidance as a surrogate for adverse maternal and perinatal outcomes, independent of, and similar in magnitude to, the effects of preeclampsia.[91]

The international Control of Hypertension In Pregnancy Study (CHIPS) trial aimed to evaluate the impact of BP control on pregnancy outcomes. Overall, 987 women with chronic (75%) or gestational (25%) hypertension at 14 to 33 weeks' gestation were randomized to "tight" (target dBP, 85 mm Hg) or "less tight" (target dBP, 100 mm Hg) BP control, with labetalol as the drug of first choice. "Tight" (vs "less tight") control reduced the incidence of severe hypertension (27.5% vs 40.6%; adjusted OR, 0.56; 95% CI, 0.42−0.74), thrombocytopenia (platelet count, $<100\times10^9$/L; 1.6% vs 4.3%; adjusted OR, 0.38; 95% CI, 0.17−0.87), and symptomatic elevation of liver transaminases (1.8% vs 4.3%; adjusted OR, 0.43; 95% CI, 0.19−0.95), although there was no reduction in serious maternal complications (2.0% vs 3.7%; adjusted OR, 0.57; 95% CI, 0.26−1.27).[92] Women with comorbidities (eg, kidney disease, pregestational diabetes) were excluded, as "tight" control was an established practice to reduce the progression of underlying kidney or cardiovascular disease, as outside pregnancy.[5] Although women with preeclampsia at enrollment were also excluded, when preeclampsia developed in 30% based on new proteinuria or 48% based on a broad definition,[93] women remained in their randomized group and delivered an average of 2 weeks later, so the results have been considered to be relevant to women with preeclampsia.[94] Importantly, in the CHIPS trial, there was no impact of "tight" control on perinatal mortality or morbidity (pregnancy loss or high-level neonatal care for >48 hours, 30.7% vs 31.4%, respectively; adjusted OR, 0.98; 95% CI, 0.74−1.30) or either birthweight <10th percentile (19.7% vs 16.1%; adjusted OR, 1.28; 95% CI, 0.93−1.79) or preterm birth (31.5% vs 35.6%; adjusted OR, 0.85; 95% CI, 0.64−1.11)[95]; the effects of "tight" vs "less tight" control on perinatal outcome were balanced across the gestational ages at which women were recruited.[96] Women in "tight" (vs "less tight") control were equally satisfied with their care.[97] "Tight" control was probably cheaper (average $6000 [Canadian dollars]), based on lower NICU costs (P=.07).[98]

"Tight" BP control in the CHIPS trial was achieved by a simple algorithm of antihypertensive up- or down-titration

FIGURE 1
Tight BP control algorithm



Treatment algorithm for "tight" control of BP. The asterisk indicates the recommendation: if systolic BP is ≥160 mm Hg, increase dose of existing medication or start new antihypertensive medication to lower systolic BP to <160 mm Hg.
Adapted from Magee et al.[92]

BP, blood pressure; *dBP*, diastolic blood pressure.

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(Figure 1), using single or multiple medications. Importantly, antihypertensive therapy was decreased if dBP fell to 80 mm Hg or below, as frequently encountered in midpregnancy, and therapy increased if systolic BP were ≥160 mm Hg, regardless of dBP, for safety. The mean BP achieved in the "tight" control group, 133/85 mm Hg,[92] was in the lower half of the ACC and AHA "stage 1 hypertension" range,[5] and increasing antihypertensive medication when BP is "high normal" concurs with guidance from the Royal College of Obstetricians and Gynaecologists.[37] Also of note is that the BP achieved in "less tight" control was not particularly high, at 139/90 mm Hg; the dBP goal of 100 mm Hg was designed to minimize the use of antihypertensives that were nevertheless required by 73% of women after randomization. Although adherence to these algorithms was similar in "less tight" (74%) and "tight" controls (73%), adherence based on adjusting according to a range of ±5 mm Hg around the target dBP was lower in "less tight" control (77%) than "tight" control (82%) (P=.04), as clinicians tended to leave current dosing of medication in "tight" control when dBP was 86 to 89 mm Hg and tended to increase medication in "less tight" control when dBP was 96 to 99 mm Hg.[92] It seems unlikely that clinicians would be comfortable keeping BP below 130/80 mm Hg if ACC and AHA thresholds were adopted.

Four national and international practice guidelines (Canada, United Kingdom, Poland, and the International Society for the Study of Hypertension in Pregnancy [ISSHP]) now endorse "tight" BP control for all forms of pregnancy hypertension, based on the results of the CHIPS trial.[4] Other societies do not yet consider the evidence to be definitive. The Society of Maternal-Fetal Medicine (SMFM) considers as acceptable both "tight" and "less tight" controls, by giving advice to maintain BP at 120 to 159/80 to 104 mm Hg in women with low-risk chronic hypertension. The American College of Obstetricians and Gynecologists (ACOG) recommends treating BP emergently when it reaches severe levels (ie, ≥160/110 mm Hg) but not at all before then, unless there are comorbidities pending the results of the Chronic Hypertension and Pregnancy trial (CHAP, NCT02299414), as discussed below.[25]

There are 2 ongoing trials of an oral antihypertensive vs another for nonsevere pregnancy hypertension. One is studying nifedipine vs labetalol initiation to achieve a “tight” BP approach in each group (Giant PANDA, NIHR128721), with randomization minimized by race. There is 1 ongoing trial of antihypertensive therapy vs “treatment only when BP is severe” (CHAP) for women with chronic hypertension randomized to treatment approaches similar to the CHIPS trial, with a primary composite maternal and perinatal outcome and a coprimary of birthweight <10th percentile.[99] SMFM is looking to the CHAP trial to address 2 concerns. First, the average gestational age at recruitment to the CHIPS trial was >20 weeks (ie, 24 weeks’ gestation); although this was related in part to 25% of women recruited having gestational hypertension, the adverse effects of “less tight” control were seen in particular before 24 weeks’ gestation.[96] Second, most women in “less tight” control (77%) received an antihypertensive before birth; this should be anticipated in CHAP as the interventions are similar. Reporting in 2023, CHAP will be powered to address whether “tight” control benefits the mother (ie, fewer serious maternal complications) and baby (ie, fewer preterm births) or causes more newborn side effects (ie, more SGA infants).

Which antihypertensive to use?

Initial antihypertensive therapy should be a monotherapy from accepted first-line drugs; it has been reported that ≥60% of women take only 1 agent prenatally.[92] The most commonly used and recommended antihypertensive medications come from different drug classes. All cross the placenta.

Labetalol is a combined alpha- and (nonselective) beta-blocker, used in oral and parenteral forms; beta-blockade predominates, particularly when labetalol is administered parenterally. The overall effect is vasodilatation without reflex tachycardia or a reduction in cardiac output. Labetalol should be used with caution in women with mild-moderate asthma (or another contraindication to nonselective beta-blockade) and not at all in women with severe or decompensated asthma. Labetalol may increase the risk of neonatal bradycardia and hypoglycemia based on a large cohort study of Medicaid beneficiaries.[100]

Nifedipine is a dihydropyridine calcium channel blocker that acts on vascular smooth muscle to produce vasodilation and reduce systemic vascular resistance. Nifedipine comes in 3 oral formulations: capsule (“sublingual”), intermediate release (ie, prolonged action or modified release), and extended release (extended action or long acting). The capsule when punctured was associated with abrupt falls in BP and cardiovascular morbidity outside pregnancy, leading many organizations, including the ACOG, to recommend against its use when bitten.[25] The intermediate-release formulation can be used for nonsevere or severe hypertension over a shorter time frame, whereas the extended-release formulation is appropriate for nonsevere hypertension. Nifedipine may result in reflex tachycardia, flushing, and/or headache (particularly among those predisposed), and peripheral edema when used in a high dose.

Hydralazine is a direct-acting vasodilator that is available in oral and parenteral formulations, but it is used most commonly intravenously because of reflex tachycardia when used as an oral monotherapy. The drug reduces peripheral vascular resistance, after metabolism in the vessel wall, which may account for variability in the onset of effect between individuals and a longer time to onset (10−20 minutes). The side effects are similar to nifedipine, another vasodilator. Although previous meta-analyses have raised concerns about more maternal hypotension with hydralazine, this was not substantiated in a 2018 network meta-analysis that also failed to show an excess of other side effects, such as headache, maternal tachycardia, or stillbirth.[101]

Methyldopa is a centrally acting alpha-receptor antagonist that decreases sympathetic tone and reduces peripheral vascular resistance. It is available only in an oral formulation. Although much has been written about the central nervous system side effects of methyldopa use in pregnancy (eg, drowsiness, depression), women did not change drugs more frequently in methyldopa (0/133 women) vs beta-blocker trials (1/139 women) in randomized trials.[90]

Hydrochlorothiazide used as a second-line agent is supported by the ACOG. Ongoing use is not associated with volume depletion, and concerns about neonatal side effects are not supported by trials of thiazide use for preeclampsia prevention.[102]

In a 2017 meta-analysis (15 trials [11 in common], N=1166 women), antihypertensive therapy (vs placebo or no therapy) for women with chronic hypertension decreased severe hypertension without differences in other outcomes or among agents.[103] In a 2020 network meta-analysis (14 trials, 1956 women with chronic hypertension, usually without comorbidities) of numerous agents (including placebo or no therapy),[104] many agents decreased the incidence of severe hypertension compared with placebo or no therapy: nifedipine, methyldopa, pindolol, and ketanserin; nifedipine decreased severe hypertension compared with furosemide, as did pindolol compared with furosemide or amlodipine. Both nifedipine and methyldopa decreased the incidence of placental abruption compared with placebo or no therapy. Atenolol increased the incidence of SGA infants compared with placebo or no therapy and other antihypertensives (labetalol, nifedipine, methyldopa, and ketanserin). No differences were seen in preeclampsia, cesarean delivery, preterm birth, or perinatal death. The 95% CIs around estimates of effect were often very wide, and 1 trial was counted twice.[105,106] However, the results suggest that nifedipine and methyldopa are most beneficial. Vitamin D may enhance the effectiveness of nifedipine.[107]

These data concur with the broader systematic review of antihypertensive vs placebo or no therapy in pregnancy (31 trials, N=3485 women) and head-to-head comparisons of different antihypertensives (29 trials, N=2774 women); generally, the type of hypertensive disorder was unspecified.[90] Multiple agents reduce the incidence of severe hypertension compared with no antihypertensive. However, neither nifedipine nor methyldopa had previously been recognized to reduce abruption. Although comparison with methyldopa as the gold standard has been reported to show that beta-blockers (any, including labetalol) and calcium channel blockers taken together may reduce the risk of severe hypertension, results were more different than could be expected by chance alone. In addition, beta-blockers, but not calcium channel blockers, may decrease the risk of preeclampsia compared with placebo or no therapy; however, when beta-blockers and calcium channel blockers were compared directly, beta-blockers did not decrease preeclampsia as anticipated. Of note, in the CHIPS trial, women treated with methyldopa (vs labetalol) may have had better maternal and perinatal outcomes, although there may have been residual confounding.[108]

Other relevant short- and long-term outcomes have been understudied. An example is an unsubstantiated belief that both oral labetalol and methyldopa may alter fetal heart rate (FHR) patterns[109]; prudently, changes in FHR or pattern should be ascribed to the evolution of underlying disease and not prescribed antihypertensives. Importantly, studies of the potential long-term developmental effects of antihypertensive therapy in pregnancy are limited, are not of high quality, and do not address important confounders of the antihypertensive-outcome relationship. Key among these is the type of pregnancy hypertension; in a relevant systematic review, only 16 of 47 primary studies reported on the hypertensive disorder of included women, chronic hypertension in 8 of 16.[110] Although most studies were reassuring, some reported associations between in utero exposure to labetalol and attention deficit hyperactivity disorder and methyldopa or clonidine and sleep disorder. However, as only 5 of 47 studies were of high quality; all were small and underpowered, and no strong conclusions could be drawn.

Most clinical practice guidelines recommend oral labetalol, nifedipine, or methyldopa as first-line antihypertensives[4,90,111]; all were used in the CHIPS trial, with <15% of women overall taking another antihypertensive.[92]

Additional antihypertensive drugs, required in 8% to 40% of women,[90,92] should be used if target BP levels are not achieved with midrange dose monotherapy.[94] Based on nonpregnancy care, add-on drugs should be from a different drug class.[94] The focus has been initial choice and dose and maximal dose of antihypertensives and less on dose escalation and addition of a second agent. Table 2 presents a dose escalation protocol suggested by the ISSHP Guidelines Committee.[112] This may prove useful as oral antihypertensives effectively resolve episodes of severe hypertension.[113] When severe hypertension has developed on large doses of a medication, a single dose of that medication is unlikely to be as effective as a single dose of a drug from another class.

Most guidelines recommend intravenous (IV) labetalol, oral nifedipine, or IV hydralazine for treating severe hypertension.[4] Trials have focused on BP level for inclusion; none were restricted to women with chronic hypertension. By network meta-analysis (51 trials), target BP was achieved in a similar number of women with these medications (or others evaluated) (32 trials, N=3236 women), although more efficiently with nifedipine than IV hydralazine.[101] Using a minimally important RR reduction of 10% among groups, an associated trial sequential analysis concluded that there was no difference in effectiveness between IV labetalol and oral nifedipine or IV hydralazine, but more data were needed to compare nifedipine and hydralazine. A second network meta-analysis of first-line agents (17 trials, N=1591 women) found that nifedipine more successfully treated severe hypertension than IV hydralazine.[114]

Oral labetalol and oral methyldopa compared favorably with oral nifedipine in a recent Indian trial for severe pregnancy hypertension[113]; an in-target BP (ie, 120−150/70−100 mm Hg) was achieved without fetal compromise at 6 hours in ≥75% of women in each group, similarly in the nifedipine (84%) and labetalol (84%) groups, but slightly more often in the nifedipine vs methyldopa comparison (76%; absolute difference, 7.1%, 95% CI, 0.8−13.5). However, more babies in the nifedipine group received neonatal intensive care (for low birthweight) (18%) than in the labetalol (10%) or methyldopa group (10%).

Table 3 presents a dose escalation protocol consistent with recommendations by the Society of Obstetricians and Gynaecologists of Canada and the ACOG and incorporating oral treatment.[25,113,115] The protocol is more conservative in places with regard to dosing (at the lower limit of published ranges) and/or time for repeat dosing (at or beyond the upper limit of recommendations) to harmonize between medications for ease of implementation in urgent care and to minimize the risk of maternal hypotension. Of note, a third dose of oral nifedipine capsules is given at 90 minutes because a dose of 20 mg is not used, and when another agent is needed, one should choose from a different drug class and not hydralazine if nifedipine failed (or vice versa). Successful treatment is resolution of severe hypertension. Consistent with the ACOG guidelines, routine antihypertensive therapy should be instituted to avoid further episodes of severe hypertension.[25]

Which antihypertensives not to use

No antihypertensive medication is a proven human teratogen. However, some agents may be best avoided in pregnancy, given the possible or proven concerns about fetotoxicity and the availability of alternative agents.

Atenolol, a cardioselective beta-blocker, may reduce fetal growth velocity.[56,104,116−119] Many practitioners are uncomfortable using thiazides and thiazide-like diuretics owing to theoretical concerns about reducing gestational plasma volume expansion[102]; however, diuretics were not associated with adverse outcomes when used throughout pregnancy for preeclampsia prevention. Their use is probably best limited to specific circumstances (eg, medullary sponge kidney).

TABLE 2
Suggested dose titration of antihypertensive therapy for nonurgent control of hypertension in pregnancy

	Dosage (mg)					
	Low[a]	If BP not controlled	Medium	If BP not controlled on medium dosage	High[b]	Maximum
First line		Proceed to medium dose of same low-dose medication		Consider adding another low-dose medication rather than going to a high dose of the same medication, for a maximum of 3 medications		
Labetalol	100 TID—QID		200 TID—QID		300 TID—QID	1200/d
Nifedipine (PA or MR)	10 BID—TID		20 BID—TID		30 BID—TID	120/d
Nifedipine (XL or LA)	30 OD		30 BID or 60 OD		30 QAM and 60 QPM	120/d
Methyldopa	250 TID—QID		500 TID—QID		750 TID	2500/d

BID, twice per day; *BP*, blood pressure; *LA*, long acting; *MR*, modified release; *PA*, prolonged action; *QAM*, every morning; *QID*, 4 times per day; *QPM*, every evening; *TID*, 3 times per day; *XL*, extended release.

[a] Starting doses are higher than generally recommended for adults given more rapid clearance in pregnancy; [b] When a medication is at high (or maximum) dose, consider using a different medication to treat any severe hypertension that may develop.

Adapted from Magee et al.[55]

Magee. Personalized care of chronic hypertension. Am J Obstet Gynecol 2020.

ACEIs and ARBs should not be used in women once pregnant (grades C and D, respectively)[94]; although they do not seem to be teratogenic,[33,120,121] there may be an excess of miscarriage, FGR, and neonatal morbidity following use in early pregnancy, even when the medication is stopped in early pregnancy.[122] However, such associations have been based on low-quality data (eg, case reports and series), inconsistently observed, and may relate to underlying hypertension.[27,123,124]

Individualized antihypertensive therapy

Outside pregnancy, age and race reflect different hemodynamic profiles in hypertension and response to antihypertensive therapy[125,126]; high renin hypertension is associated with young age and higher HR or volume expansion, and low renin hypertension is associated with the black race.[125] Antihypertensive therapy guided by these phenotypes halves poor BP control, by giving ACEIs or ARBs to young and white patients and calcium channel blockers to black patients,[127] and is recommended outside pregnancy for adult hypertension.[128]

In observational work, demographic and hemodynamic parameters identify individual pregnant women less likely to achieve BP control with oral labetalol.[129] These women were more often black, with lower HR and cardiac stroke volume (SV) ("vasoconstricted" or "high resistance" phenotype associated with more severe hypertension and FGR), and more likely to respond to a vasodilator. In contrast, women with nonblack race and higher HR and SV ("hyperdynamic" phenotype) were more successfully treated with oral labetalol. Importantly, maternal race alone was a poor predictor of BP response to labetalol (area under the receiver operating characteristic curve is only 0.65). In a subsequent observational study of 84 pregnancies with hypertension, initiation and titration of antihypertensive therapy (for BP ≥140/90 mm Hg) guided by this model resulted in a change in care for 51% of women taking oral labetalol; 30% initially given labetalol required additional nifedipine, and 20% initially given nifedipine required additional labetalol. Severe hypertension requiring admission to a high dependency unit was reduced by 60%, without FGR.[130]

Personalized hemodynamic assessment holds promise to deliver "tight" BP control while optimizing fetal growth and highlighting potential perinatal benefits. Neither of the 2 ongoing trials of hemodynamic-guided antihypertensive therapy in pregnancy incorporates race into antihypertensive therapy choice, and both trials compare hemodynamic-guided therapy with "less tight" control (NCT03245970, NCT02531490).

Shared decision making

Considering women's views contributes to management planning for antihypertensive therapy in pregnancy. A stated preference study (N=183) found that women who preferred tight control (49%) were more often white (OR, 2.4; 95% CI, 1.2—4.6), university educated or professionally qualified (OR, 2.0; 95% CI, 1.0—3.7), and more knowledgeable about pregnancy hypertension and complications (OR, 1.4; 95% CI, 1.2—1.7).[131] Most

TABLE 3
Suggested dose titration of antihypertensive therapy for urgent control of hypertension in pregnancy[a]

Medication	T 0 min	T 30 min	T 60 min	T 90 min	T 120 min	T 150 min[b]	T 180 min
Labetalol (oral)	200 mg	—	200 mg	—	200 mg	—	Use an alternative drug from a different drug class[c]
Labetalol (IV intermittent)	10–20 mg	20–40 mg[d]	40–80 mg	40–80 mg	40–80 mg	40–80 mg	
Labetalol (IV infusion)	0.5–2 mg/min	→	→	→	→	→[c]	
Nifedipine (oral capsule)[e]	10 mg	10 mg	—	10 mg	—	10 mg	
Nifedipine (oral PA or MR)	10 mg	—	10 mg	—	10 mg	—	
Methyldopa (oral)	1000 mg	—	—	—	—		
Hydralazine (IV)	5 mg	5–10 mg	5–10 mg[f]	5–10 mg[f]			

IV, intravenous; *MR*, modified release; *PA*, prolonged action; *T 0*, time zero, meaning the start of treatment.

[a] When severe hypertension has been resolved, switch to routine oral medication; [b] Do not exceed the maximum dose of IV labetalol, which is 300 mg total in a treatment course; [c] If nifedipine or hydralazine were the initial drug used, choose oral labetalol or oral methyldopa as the alternative drug; [d] Double the initial dose of IV labetalol; [e] To be swallowed whole, not bitten; [f] Do not exceed the maximum dose of IV hydralazine of 20 mg.

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women (62%) expressed equal prioritization of treatment outcomes, and 23% prioritized avoidance of birth at <34 weeks' gestation; however, 14% of women prioritized minimizing medication use, and for them, "less tight" control would best fit their values. Two decision aids are available.[132,133]

Superimposed Preeclampsia

Definition

Superimposed preeclampsia is defined by most guidelines as the "development of preeclampsia."[4] Three guidelines specifically exclude deteriorating BP control from the definition because of subjectivity,[134–136] so the diagnosis may be made only when there is new-onset proteinuria or another indication of maternal end-organ or fetoplacental involvement.

Angiogenic markers are not yet part of the definition of superimposed preeclampsia, but this may be the case in the future based on evidence to date. Among unselected women with "suspected preeclampsia," a normal PlGF (<5th percentile or <100 pg/mL) or soluble fms-like tyrosine kinase-1 (sFlt-1) to PlGF ratio (<38) makes significantly less likely development of preeclampsia (defined by new proteinuria) within 7 days or the need for delivery for preeclampsia (defined broadly) within 14 days, and these markers are recommended for such use in the United Kingdom.[137–141] Three studies using commercial assays (268 women with chronic hypertension; 114 with superimposed preeclampsia) identified that either low maternal plasma PlGF or elevated sFlt-1, endoglin, or sFlt-1/PlGF ratio were associated with a greater likelihood of preeclampsia (defined by new proteinuria), preeclampsia that was more severe, early delivery, and adverse maternal and perinatal outcomes.[142–144] In addition, 1 study confirmed the observations in a cohort of 123 women with chronic hypertension and CKD.[143] As angiogenic imbalance is associated with risks for both placental FGR and stillbirth, it is possible that defining preeclampsia broadly would improve the diagnostic test performance of angiogenic markers.[145–149]

Prediction of complications

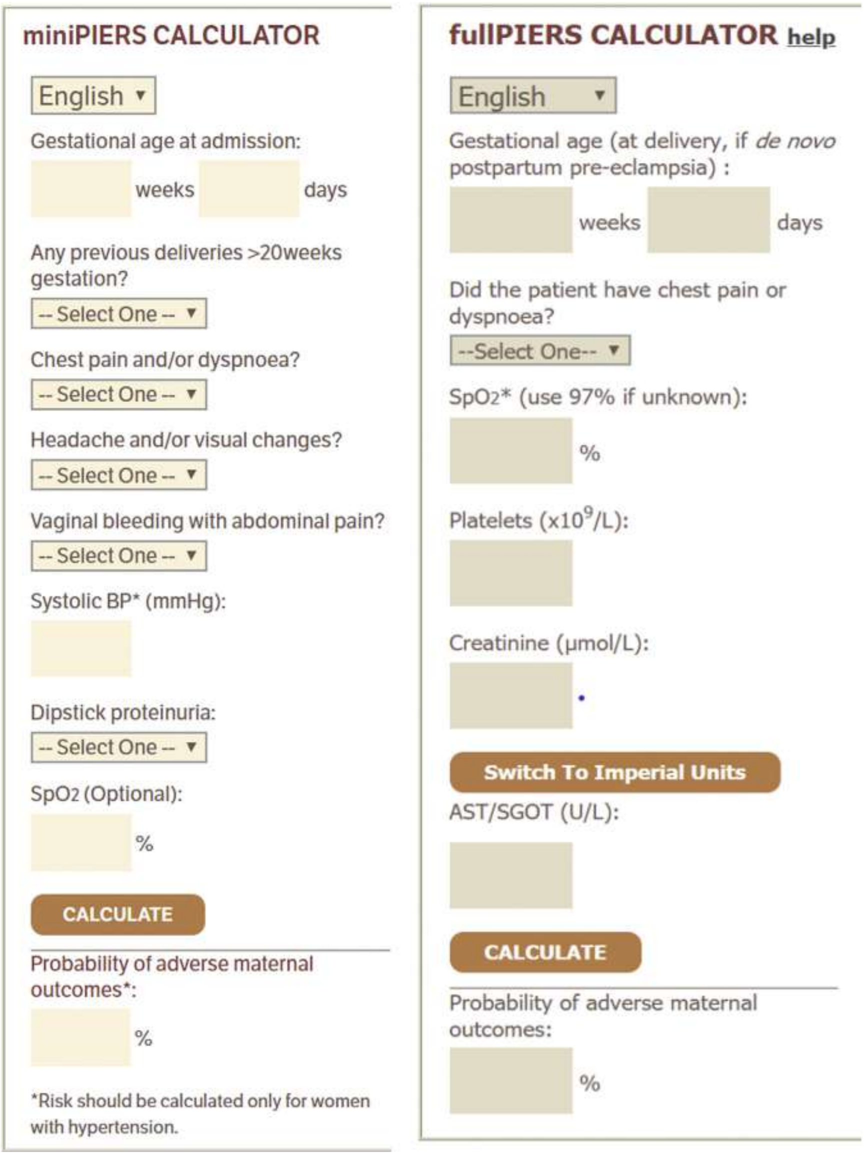
Detecting progression to preeclampsia when it occurs is the reason why many professional organizations emphasize evaluating maternal symptoms.[111] In a systematic review of maternal risk stratification in pregnancy hypertension (32 studies), the miniPIERS (Preeclampsia Integrated Estimate of Risk Score) was the only model for all pregnancy hypertension types; this has been externally validated[150] and quantifies the risk of adverse maternal outcome by BP, symptoms, urinalysis (if performed), gestational age, and parity (of particular importance for nulliparous women). Women who are at a "high-risk" have a predicted risk ≥25%, as a "rule-in" test for adverse maternal outcome within 48 hours (likelihood ratio [LR] of 5.1) and correct classification (86%). An online calculator is available (Figure 2).[151]

If preeclampsia develops, the adverse maternal outcomes can be predicted by the fullPIERS model, incorporating gestational age, chest pain or dyspnea, pulse oximetry, platelet count, serum creatinine, and aspartate aminotransferase or serum glutamic-oxaloacetic transaminase or alanine aminotransferase or serum glutamic-pyruvic transaminase).[152] Using ≥10% to define high risk, fullPIERS can be used as a "rule-in" test for adverse maternal outcome within 48 hours, based on a good LR (9.2). An online calculator is available (Figure 2).[153] Determining the added value of angiogenic markers is warranted.[154,155]

Timed Birth

Practice related to the timing of birth for women with chronic hypertension varies widely. In a previously unpublished site survey of CHIPS trial investigators, 70

FIGURE 2
fullPIERS and miniPIERS online calculators



Online calculators for calculation of the fullPIERS (preeclampsia integrated estimate of risk score, https://pre-empt.obgyn.ubc.ca/evidence/fullpiers) and miniPIERS (https://pre-empt.obgyn.ubc.ca/evidence/minipiers) for risk of adverse maternal outcomes in preeclampsia.

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respondents highlighted variable practice, with delivery currently offered at 37 (16%), 38 (33%), 39 (20%), 40 (20%), and 41 (12%) weeks' gestation. Observational data suggest that delivery between 38 0/7 and 39 6/7 weeks' gestation may optimize perinatal outcomes, by balancing stillbirth and neonatal morbidity risks.[9,156] These observational data are complemented by limited trial data related to 50 Egyptian women with chronic hypertension[157] that suggest that earlier term delivery may benefit women without increasing perinatal risks or cesarean deliveries. However, there are insufficient data available to assess the impact of planned delivery at term (ie, between 37 0/7 and 41 6/7 weeks' gestation) on maternal morbidity or cesarean delivery.[158]

The When to Induce Labour to Limit trial (WILL risk in pregnancy hypertension; ISRCTN 77258279) is randomizing women with chronic hypertension and gestational hypertension to either a policy of delivery at 38 0/7 to 38 3/7 weeks' gestation or expectant care until ≥40 0/7 weeks' gestation (or as clinical need dictates). The coprimary outcomes are maternal death or serious morbidity (fullPIERS outcome[152]; superiority) and NICU admission for ≥4 hours (noninferiority); cesarean delivery rate is the core secondary outcome.

Postpartum Care

As most trials have evaluated antepartum, rather than postpartum, antihypertensive therapy, evidence is insufficient to guide clinical practice; however, it is reasonable to continue "tight" BP control after delivery. BP is likely to rise after a woman leaves the hospital (peaking on postpartum days 3–6), postnatal stroke is increasing in incidence, and most antihypertensives are acceptable for use in breastfeeding (searchable information in LactMed[159]). The choice of antihypertensives is similar to antepartum, with 2 caveats. First, methyldopa is not recommended for use after delivery in the United Kingdom, based on unsubstantiated concerns that it may increase the risk of postpartum depression.[34] Second, 2 antihypertensives are not recommended for use during breastfeeding: oral clonidine (high serum drug levels are documented in breastfed infants) and sodium nitroprusside (thiocyanate and cyanide [toxic metabolites] may cross into breast milk).[159] Of note, captopril, enalapril, and quinapril drug levels in breast milk are low, and any may be prescribed after delivery with appropriate monitoring of maternal serum potassium and creatinine. Neonatologists may have theoretical reservations in preterm or FGR babies; we are unaware of any reported adverse effects. Nifedipine may be more effective postnatally when administered with furosemide.[160]

Conclusion

Women with chronic hypertension are at a high risk of pregnancy complications, but they are an easily recognized group in touch with a wide variety of healthcare providers before, during, and after pregnancy. We know that these women are at an increased risk of maternal and perinatal complications, that they are capable of measuring their BP values at home with accurate devices, that treating their hypertension with antihypertensive therapy halves the risk of progression to severe hypertension, and that they wish to be involved in their care. Priorities for future research include whether (1) additional characteristics of BP and other physiological variables can be used to predict preeclampsia; (2) low-dose aspirin reduces their risk of preeclampsia specifically and calcium has an independent preventive effect; (3) use of angiogenic markers with clinical factors and routine laboratory testing improves care; (4) hemodynamically guided care improves outcomes in comparison with antihypertensive therapy titrated to BP level and, if the latter, with which antihypertensive agent is best to initiate treatment from among labetalol, nifedipine, and methyldopa, in addition to optimal timing of birth. All of this will bring us closer to offering women more personalized care for their chronic hypertension in pregnancy. ■

REFERENCES

1. Garovic VD, White WM, Vaughan L, et al. Incidence and long-term outcomes of hypertensive disorders of pregnancy. J Am Coll Cardiol 2020;75:2323–34.

2. Ananth CV, Duzyj CM, Yadava S, Schwebel M, Tita ATN, Joseph KS. Changes in the prevalence of chronic hypertension in pregnancy, United States, 1970 to 2010. Hypertension 2019;74:1089–95.

3. Magee LA, Sharma S, Nathan HL, et al. The incidence of pregnancy hypertension in India, Pakistan, Mozambique, and Nigeria: a prospective population-level analysis. PLoS Med 2019;16:e1002783.

4. Scott G, Gillon TE, Pels A, von Dadelszen P, Magee LA. Guidelines—similarities/dissimilarities. A systematic review of international clinical practice guidelines for pregnancy hypertension. Am J Obstet Gynecol [In press].

5. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice guidelines. Hypertension 2018;71:e13–115.

6. Sutton EF, Hauspurg A, Caritis SN, Powers RW, Catov JM. Maternal outcomes associated with lower range stage 1 hypertension. Obstet Gynecol 2018;132:843–9.

7. Hauspurg A, Sutton EF, Catov JM, Caritis SN. Aspirin effect on adverse pregnancy outcomes associated with stage 1 hypertension in a high-risk cohort. Hypertension 2018;72:202–7.

8. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. BMJ 2014;348:g2301.

9. Hutcheon JA, Lisonkova S, Magee LA, et al. Optimal timing of delivery in pregnancies with pre-existing hypertension. BJOG 2011;118:49–54.

10. Panaitescu AM, Syngelaki A, Prodan N, Akolekar R, Nicolaides KH. Chronic hypertension and adverse pregnancy outcome: a cohort study. Ultrasound Obstet Gynecol 2017;50:228–35.

11. Bartsch E, Medcalf KE, Park AL, Ray JG. High Risk of Pre-eclampsia Identification Group. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ 2016;353:i1753.

12. Boriboonhirunsarn D, Pradyachaipimol A, Viriyapak B. Incidence of superimposed preeclampsia among pregnant Asian women with chronic hypertension. Hypertens Pregnancy 2017;36:226–31.

13. Chappell LC, Enye S, Seed P, Briley AL, Poston L, Shennan AH. Adverse perinatal outcomes and risk factors for preeclampsia in women with chronic hypertension: a prospective study. Hypertension 2008;51:1002–9.

14. 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 2017;34:403–8.

15. Nakanishi S, Aoki S, Nagashima A, Seki K. Incidence and pregnancy outcomes of superimposed preeclampsia with or without proteinuria among women with chronic hypertension. Pregnancy Hypertens 2017;7:39–43.

16. Rey E, Couturier A. The prognosis of pregnancy in women with chronic hypertension. Am J Obstet Gynecol 1994;171:410–6.

17. Sibai BM, Lindheimer M, Hauth J, et al. Risk factors for preeclampsia, abruptio placentae, and adverse neonatal outcomes among women with chronic hypertension. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. N Engl J Med 1998;339:667–71.

18. Magee LA, von Dadelszen P, Chan S, et al. The Control of Hypertension In Pregnancy Study pilot trial. BJOG 2007;114:770. e13—20.

19. McCowan LM, Buist RG, North RA, Gamble G. Perinatal morbidity in chronic hypertension. Br J Obstet Gynaecol 1996;103:123–9.

20. Chappell MC, Westwood BM, Yamaleyeva LM. Differential effects of sex steroids in young and aged female mRen2.Lewis rats: a model of estrogen and salt-sensitive hypertension. Gend Med 2008;5(Suppl A):S65–75.

21. Bateman BT, Bansil P, Hernandez-Diaz S, Mhyre JM, Callaghan WM, Kuklina EV. Prevalence, trends, and outcomes of chronic hypertension: a nationwide sample of delivery admissions. Am J Obstet Gynecol 2012;206:134.e1–8.

22. Ehret GB, Bakris GL, Forman JP. Genetic factors in the pathogenesis of hypertension. 2020. Available at: https://www.uptodate.com/contents/genetic-factors-in-the-pathogenesis-of-hypertension. Accessed June 19, 2020.

23. Mottola MF, Davenport MH, Ruchat SM, et al. No. 367-2019 Canadian guideline for physical activity throughout pregnancy. J Obstet Gynaecol Can 2018;40:1528–37.

24. Brown JM, Siddiqui M, Calhoun DA, et al. The unrecognized prevalence of primary aldosteronism: a cross-sectional study. Ann Intern Med 2020;173:10–20.

25. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin no. 203: chronic hypertension in pregnancy. Obstet Gynecol 2019;133:e26–50.

26. Ramakrishnan A, Lee LJ, Mitchell LE, Agopian AJ. Maternal hypertension during pregnancy and the risk of congenital heart defects in offspring: a systematic review and meta-analysis. Pediatr Cardiol 2015;36:1442–51.

27. 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 2015;212:337.e1–14.

28. van Gelder MM, Van Bennekom CM, Louik C, Werler MM, Roeleveld N, Mitchell AA. Maternal hypertensive disorders, antihypertensive medication use, and the risk of birth defects: a case-control study. BJOG 2015;122:1002–9.

29. Moorthie S, Blencowe H, Darlison MW, et al. Estimating the birth prevalence and pregnancy outcomes of congenital malformations worldwide. J Community Genet 2018;9:387–96.

30. Mukherjee S, Velez Edwards DR, Baird DD, Savitz DA, Hartmann KE. Risk of miscarriage among black women and white women in a U.S. prospective cohort study. Am J Epidemiol 2013;177:1271–8.

31. Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med 2006;354:2443–51.

32. Moretti ME, Caprara D, Drehuta I, et al. The fetal safety of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers. Obstet Gynecol Int 2012;2012:658310.

33. Walfisch A, Al-maawali A, Moretti ME, Nickel C, Koren G. Teratogenicity of angiotensin converting enzyme inhibitors or receptor blockers. J Obstet Gynaecol 2011;31:465–72.
34. National Institute for Health and Care Excellence. Hypertension in pregnancy: diagnosis and management. NICE guideline [NG133]. 2019. Available at: https://www.nice.org.uk/guidance/ng133. Accessed May 20, 2020.
35. Reprotox. Hydrochlorothiazide. 2020. Available at: https://wwwreprotoxorg/member/agents/17401. Accessed June 25, 2020.
36. Muntner P, Carey RM, Jamerson K, Wright JT Jr, Whelton PK. Rationale for ambulatory and home blood pressure monitoring thresholds in the 2017 American College of Cardiology/American Heart Association Guideline. Hypertension 2019;73:33–8.
37. Self-monitoring of blood pressure in pregnancy. Information for healthcare professionals. London: Royal College of Obstetricians & Gynaecologists; 2020. Available at: https://www.rcog.org.uk/globalassets/documents/guidelines/2020-03-30-self-monitoring-of-blood-pressure-in-pregnancy.pdf. Accessed May 20, 2020.
38. Taylor RS, Freeman L, North RA. Evaluation of ambulatory and self-initiated blood pressure monitors by pregnant and postpartum women. Hypertens Pregnancy 2001;20:25–33.
39. Pealing LM, Tucker KL, Mackillop LH, et al. A randomised controlled trial of blood pressure self-monitoring in the management of hypertensive pregnancy. OPTIMUM-BP: a feasibility trial. Pregnancy Hypertens 2019;18:141–9.
40. Kalafat E, Benlioglu C, Thilaganathan B, Khalil A. Home blood pressure monitoring in the antenatal and postpartum period: a systematic review meta-analysis. Pregnancy Hypertens 2020;19:44–51.
41. Xydopoulos G, Perry H, Sheehan E, Thilaganathan B, Fordham R, Khalil A. Home blood-pressure monitoring in a hypertensive pregnant population: cost-minimization study. Ultrasound Obstet Gynecol 2019;53:496–502.
42. McManus RJ, Mant J, Bray EP, et al. Telemonitoring and self-management in the control of hypertension (TASMINH2): a randomised controlled trial. Lancet 2010;376:163–72.
43. McManus RJ, Mant J, Haque MS, et al. Effect of self-monitoring and medication self-titration on systolic blood pressure in hypertensive patients at high risk of cardiovascular disease: the TASMIN-SR randomized clinical trial. JAMA 2014;312:799–808.
44. Cairns AE, Tucker KL, Leeson P, et al. Self-management of postnatal hypertension: the SNAP-HT trial. Hypertension 2018;72:425–32.
45. Brown MA, Mangos G, Davis G, Homer C. The natural history of white coat hypertension during pregnancy. BJOG 2005;112:601–6.
46. Rodrigues Â, Barata C, Marques I, Almeida MC. Diagnosis of white coat hypertension and pregnancy outcomes. Pregnancy Hypertens 2018;14:121–4.
47. Johnson S, Liu B, Kalafat E, Thilaganathan B, Khalil A. Maternal and perinatal outcomes of white coat hypertension during pregnancy: a systematic review and meta-analysis. Hypertension 2020;76:157–66.
48. Tucker KL, Bankhead C, Hodgkinson J, et al. How do home and clinic blood pressure readings compare in pregnancy? Hypertension 2018;72:686–94.
49. Kalafat E, Mir I, Perry H, Thilaganathan B, Khalil A. Is home blood-pressure monitoring in hypertensive disorders of pregnancy consistent with clinic recordings? Ultrasound Obstet Gynecol 2018;52:515–21.
50. Tremonti C, Beddoe J, Brown MA. Reliability of home blood pressure monitoring devices in pregnancy. Pregnancy Hypertens 2017;8:9–14.
51. STRIDE BP. Validated blood pressure monitors. 2020. Available at: https://STRIDEBP.org/BP-monitors. Accessed May 20, 2020.
52. British and Irish Hypertension Society. BP monitors. 2020. Available at: https://bihsoc.org/bp-monitors/. Accessed May 20, 2020.
53. NHS Innovation Accelerator. My Story: enabling home monitoring of hypertension in pregnancy. 2018. Available at: https://nhsaccelerator.com/story-enabling-home-monitoring-hypertension-pregnancy/. Accessed May 20, 2020.
54. Carter J, Sandall J, Shennan AH, Tribe RM. Mobile phone apps for clinical decision support in pregnancy: a scoping review. BMC Med Inform Decis Mak 2019;19:219.
55. Magee LA, Singer J, Lee T, et al. Are blood pressure level and variability related to pregnancy outcome? Analysis of control of hypertension in pregnancy study data. Pregnancy Hypertens 2020;19:87–93.
56. Easterling TR, Brateng D, Schmucker B, Brown Z, Millard SP. Prevention of preeclampsia: a randomized trial of atenolol in hyperdynamic patients before onset of hypertension. Obstet Gynecol 1999;93:725–33.
57. Bijl RC, Valensise H, Novelli GP, et al. Methods and considerations concerning cardiac output measurement in pregnant women: recommendations of the International Working Group on Maternal Hemodynamics. Ultrasound Obstet Gynecol 2019;54:35–50.
58. Giannakou K, Evangelou E, Papatheodorou SI. Genetic and non-genetic risk factors for pre-eclampsia: umbrella review of systematic reviews and meta-analyses of observational studies. Ultrasound Obstet Gynecol 2018;51:720–30.
59. Townsend R, Khalil A, Premakumar Y, et al. Prediction of pre-eclampsia: review of reviews. Ultrasound Obstet Gynecol 2019;54:16–27.
60. O'Gorman N, Wright D, Poon LC, et al. Multicenter screening for pre-eclampsia by maternal factors and biomarkers at 11–13 weeks' gestation: comparison with NICE guidelines and ACOG recommendations. Ultrasound Obstet Gynecol 2017;49:756–60.
61. Tan MY, Wright D, Syngelaki A, et al. Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. Ultrasound Obstet Gynecol 2018;51:743–50.
62. Magee LA, von Dadelszen P, Singer J, et al. Can adverse maternal and perinatal outcomes be predicted when blood pressure becomes elevated? Secondary analyses from the CHIPS (Control of Hypertension In Pregnancy Study) randomized controlled trial. Acta Obstet Gynecol Scand 2016;95:763–76.
63. Al-Rubaie Z, Askie LM, Ray JG, Hudson HM, Lord SJ. The performance of risk prediction models for pre-eclampsia using routinely collected maternal characteristics and comparison with models that include specialised tests and with clinical guideline decision rules: a systematic review. BJOG 2016;123:1441–52.
64. Chaemsaithong P, Pooh RK, Zheng M, et al. Prospective evaluation of screening performance of first-trimester prediction models for preterm preeclampsia in an Asian population. Am J Obstet Gynecol 2019;221:650.e1–16.
65. Guizani M, Valsamis J, Dutemeyer V, et al. First-trimester combined multimarker prospective study for the detection of pregnancies at a high risk of developing preeclampsia using the Fetal Medicine Foundation-algorithm. Fetal Diagn Ther 2018;43:266–73.
66. Mosimann B, Pfiffner C, Amylidi-Mohr S, Risch L, Surbek D, Raio L. First trimester combined screening for preeclampsia and small for gestational age - a single centre experience and validation of the FMF screening algorithm. Swiss Med Wkly 2017;147:w14498.
67. Park FJ, Leung CH, Poon LC, Williams PF, Rothwell SJ, Hyett JA. Clinical evaluation of a first trimester algorithm predicting the risk of hypertensive disease of pregnancy. Aust N Z J Obstet Gynaecol 2013;53:532–9.
68. Skråstad RB, Hov GG, Blaas HG, Romundstad PR, Salvesen KÅ. Risk assessment for preeclampsia in nulliparous women at 11-13 weeks gestational age: prospective evaluation of two algorithms. BJOG 2015;122:1781–8.
69. Sonek J, Krantz D, Carmichael J, et al. First-trimester screening for early and late preeclampsia using maternal characteristics, biomarkers, and estimated placental volume. Am J Obstet Gynecol 2018;218:126.e1–13.
70. The Fetal Medicine Foundation. Risk assessment: risk for preeclampsia. 2018. Available at: https://fetalmedicine.org/research/assess/preeclampsia/first-trimester. Accessed May 20, 2020.
71. Poon L. Preeclampsia screening and prediction. Am J Obstet Gynecol 2020.
72. Poon LC, Rolnik DL, Tan MY, et al. ASPRE trial: incidence of preterm pre-eclampsia in patients fulfilling ACOG and NICE criteria according to risk by FMF algorithm. Ultrasound Obstet Gynecol 2018;51:738–42.

73. Ortved D, Hawkins TL, Johnson JA, Hyett J, Metcalfe A. Cost-effectiveness of first-trimester screening with early preventative use of aspirin in women at high risk of early-onset pre-eclampsia. Ultrasound Obstet Gynecol 2019;53:239–44.
74. Mone F, O'Mahony JF, Tyrrell E, et al. Preeclampsia prevention using routine versus screening test-indicated aspirin in low-risk women. Hypertension 2018;72:1391–6.
75. Mallampati D, Grobman W, Rouse DJ, Werner EF. Strategies for prescribing aspirin to prevent preeclampsia: a cost-effectiveness analysis. Obstet Gynecol 2019;134:537–44.
76. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. N Engl J Med 2017;377:613–22.
77. Askie LM, Duley L, Henderson-Smart DJ, Stewart LA; PARIS Collaborative Group. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. Lancet 2007;369:1791–8.
78. Caritis S, Sibai B, Hauth J, et al. Low-dose aspirin to prevent preeclampsia in women at high risk. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. N Engl J Med 1998;338:701–5.
79. Viinikka L, Hartikainen-Sorri AL, Lumme R, Hiilesmaa V, Ylikorkala O. Low dose aspirin in hypertensive pregnant women: effect on pregnancy outcome and prostacyclin-thromboxane balance in mother and newborn. Br J Obstet Gynaecol 1993;100:809–15.
80. Poon LC. Prevention with aspirin. Am J Obstet Gynecol 2020.
81. Hofmeyr GJ, Lawrie TA, Atallah AN, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev 2018;10:CD001059.
82. Hofmeyr GJ, Belizán JM, von Dadelszen P. Calcium and Pre-eclampsia (CAP) Study Group. Low-dose calcium supplementation for preventing pre-eclampsia: a systematic review and commentary. BJOG 2014;121:951–7.
83. Hofmeyr GJ, Betrán AP, Singata-Madliki M, et al. Prepregnancy and early pregnancy calcium supplementation among women at high risk of pre-eclampsia: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet 2019;393:330–9.
84. Hoy MK, Goldman JD. Calcium intake of the U.S. population. What We Eat in America, NHANES 2009-2010. Available at: https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/DBrief/13_calcium_intake_0910.pdf. Accessed May 20, 2020.
85. Tong S. New interventions for the prevention and treatment of preeclampsia. Am J Obstet Gynecol 2020.
86. Llurba E. Prevention with heparin. Am J Obstet Gynecol 2020.
87. Costantine M. The role of statins for the prevention of preeclampsia. Am J Obstet Gynecol 2020.
88. von Dadelszen P, Magee LA. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: an updated metaregression analysis. J Obstet Gynaecol Can 2002;24:941–5.
89. von Dadelszen P, Ornstein MP, Bull SB, Logan AG, Koren G, Magee LA. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: a meta-analysis. Lancet 2000;355:87–92.
90. Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev 2018;10:CD002252.
91. Magee LA, von Dadelszen P, Singer J, et al. The CHIPS randomized controlled trial (Control of Hypertension In Pregnancy Study): is severe hypertension just an elevated blood pressure? Hypertension 2016;68:1153–9.
92. Magee LA, von Dadelszen P, Rey E, et al. Less-tight versus tight control of hypertension in pregnancy. N Engl J Med 2015;372:407–17.
93. Brown MA, Magee LA, Kenny LC, et al. Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. Hypertension 2018;72:24–43.
94. Butalia S, Audibert F, Côté AM, et al. Hypertension Canada's 2018 guidelines for the management of hypertension in pregnancy. Can J Cardiol 2018;34:526–31.
95. Magee LA, Rey E, Asztalos E, et al. Management of non-severe pregnancy hypertension - a summary of the CHIPS trial (Control of Hypertension In Pregnancy Study) research publications. Pregnancy Hypertens 2019;18:156–62.
96. Pels A, Mol BWJ, Singer J, et al. Influence of gestational age at initiation of antihypertensive therapy: secondary analysis of CHIPS trial data (Control of Hypertension In Pregnancy Study). Hypertension 2018;71:1170–7.
97. Vidler M, Magee LA, von Dadelszen P, et al. Women's views and postpartum follow-up in the CHIPS trial (Control of Hypertension In Pregnancy Study). Eur J Obstet Gynecol Reprod Biol 2016;206:105–13.
98. Ahmed RJ, Gafni A, Hutton EK, et al. The cost implications of less tight versus tight control of hypertension in pregnancy (CHIPS trial). Hypertension 2016;68:1049–55.
99. SMFM Publications Committee. SMFM statement: benefit of antihypertensive therapy for mild-to-moderate chronic hypertension during pregnancy remains uncertain. Am J Obstet Gynecol 2015;213:3–4.
100. Bateman BT, Patorno E, Desai RJ, et al. Late pregnancy β blocker exposure and risks of neonatal hypoglycemia and bradycardia. Pediatrics 2016;138:e20160731.
101. Sridharan K, Sequeira RP. Drugs for treating severe hypertension in pregnancy: a network meta-analysis and trial sequential analysis of randomized clinical trials. Br J Clin Pharmacol 2018;84:1906–16.
102. Churchill D, Beevers GD, Meher S, Rhodes C. Diuretics for preventing pre-eclampsia. Cochrane Database Syst Rev 2007;1:CD004451.
103. Webster LM, Conti-Ramsden F, Seed PT, Webb AJ, Nelson-Piercy C, Chappell LC. Impact of antihypertensive treatment on maternal and perinatal outcomes in pregnancy complicated by chronic hypertension: a systematic review and meta-analysis. J Am Heart Assoc 2017;6:e005526.
104. Bellos I, Pergialiotis V, Papapanagiotou A, Loutradis D, Daskalakis G. Comparative efficacy and safety of oral antihypertensive agents in pregnant women with chronic hypertension: a network metaanalysis. Am J Obstet Gynecol 2020 [Epub ahead of print].
105. Mutch LM, Moar VA, Ounsted MK, Redman CW. Hypertension during pregnancy, with and without specific hypotensive treatment. II. The growth and development of the infant in the first year of life. Early Hum Dev 1977;1:59–67.
106. Mutch LM, Moar VA, Ounsted MK, Redman CW. Hypertension during pregnancy, with and without specific hypotensive treatment. I. Perinatal factors and neonatal morbidity. Early Hum Dev 1977;1:47–57.
107. Shi DD, Wang Y, Guo JJ, Zhou L, Wang N. Vitamin D enhances efficacy of oral nifedipine in treating preeclampsia with severe features: a double blinded, placebo-controlled and randomized clinical trial. Front Pharmacol 2017;8:865.
108. Magee LA, ; CHIPS Study Group, von Dadelszen P, et al. Do labetalol and methyldopa have different effects on pregnancy outcome? Analysis of data from the Control of Hypertension In Pregnancy Study (CHIPS) trial. BJOG 2016;123:1143–51.
109. Waterman EJ, Magee LA, Lim KI, Skoll A, Rurak D, von Dadelszen P. Do commonly used oral antihypertensives alter fetal or neonatal heart rate characteristics? A systematic review. Hypertens Pregnancy 2004;23:155–69.
110. Fitton CA, Steiner MFC, Aucott L, et al. In-utero exposure to antihypertensive medication and neonatal and child health outcomes: a systematic review. J Hypertens 2017;35:2123–37.
111. Webster K, Fishburn S, Maresh M, Findlay SC, Chappell LC; Guideline Committee. Diagnosis and management of hypertension in pregnancy: summary of updated NICE guidance. BMJ 2019;366:l5119.
112. Magee LA, Khalil A, von Dadelszen P. Pregnancy hypertension diagnosis and care in COVID-19 era and beyond. Ultrasound Obstet Gynecol 2020 [Epub ahead of print].
113. Easterling T, Mundle S, Bracken H, et al. Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomised controlled trial. Lancet 2019;394:1011–21.
114. Alavifard S, Chase R, Janoudi G, et al. First-line antihypertensive treatment for severe hypertension in pregnancy: a systematic review

and network meta-analysis. Pregnancy Hypertens 2019;18:179–87.
115. Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P; Canadian Hypertensive Disorders of Pregnancy (HDP) Working Group. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens 2014;4:105–45.
116. Churchill D, Bayliss H, Beevers G. Fetal growth restriction. Lancet 2000;355:1366–7.
117. Easterling TR, Carr DB, Brateng D, Diederichs C, Schmucker B. Treatment of hypertension in pregnancy: effect of atenolol on maternal disease, preterm delivery, and fetal growth. Obstet Gynecol 2001;98:427–33.
118. Lip GY, Beevers M, Churchill D, Shaffer LM, Beevers DG. Effect of atenolol on birth weight. Am J Cardiol 1997;79:1436–8.
119. Lydakis C, Lip GY, Beevers M, Beevers DG. Atenolol and fetal growth in pregnancies complicated by hypertension. Am J Hypertens 1999;12:541–7.
120. Ahmed B, Tran DT, Zoega H, Kennedy SE, Jorm LR, Havard A. Maternal and perinatal outcomes associated with the use of renin-angiotensin system (RAS) blockers for chronic hypertension in early pregnancy. Pregnancy Hypertens 2018;14:156–61.
121. Bateman BT, Patorno E, Desai RJ, et al. Angiotensin-converting enzyme inhibitors and the risk of congenital malformations. Obstet Gynecol 2017;129:174–84.
122. Bullo M, Tschumi S, Bucher BS, Bianchetti MG, Simonetti GD. Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists: a systematic review. Hypertension 2012;60:444–50.
123. Fisher SC, Van Zutphen AR, Werler MM, et al. Maternal antihypertensive medication use and congenital heart defects: updated results from the National Birth Defects Prevention Study. Hypertension 2017;69:798–805.
124. Li DK, Yang C, Andrade S, Tavares V, Ferber JR. Maternal exposure to angiotensin converting enzyme inhibitors in the first trimester and risk of malformations in offspring: a retrospective cohort study. BMJ 2011;343:d5931.
125. Brown MJ. Hypertension and ethnic group. BMJ 2006;332:833–6.
126. Gupta AK, Poulter NR, Dobson J, et al. Ethnic differences in blood pressure response to first and second-line antihypertensive therapies in patients randomized in the ASCOT Trial. Am J Hypertens 2010;23:1023–30.
127. Smith RD, Levy P, Ferrario CM; Consideration of Noninvasive Hemodynamic Monitoring to Target Reduction of Blood Pressure Levels Study Group. Value of noninvasive hemodynamics to achieve blood pressure control in hypertensive subjects. Hypertension 2006;47:771–7.
128. National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management. NICE guideline [NG136]. 2019. Available at: https://www.nice.org.uk/guidance/ng136/chapter/recommendations. Accessed May 20, 2020.
129. Stott D, Bolten M, Salman M, Paraschiv D, Douiri A, Kametas NA. A prediction model for the response to oral labetalol for the treatment of antenatal hypertension. J Hum Hypertens 2017;31:126–31.
130. Stott D, Bolten M, Paraschiv D, Papastefanou I, Chambers JB, Kametas NA. Longitudinal hemodynamics in acute phase of treatment with labetalol in hypertensive pregnant women to predict need for vasodilatory therapy. Ultrasound Obstet Gynecol 2017;49:85–94.
131. Metcalfe RK, Harrison M, Hutfield A, et al. Patient preferences and decisional needs when choosing a treatment approach for pregnancy hypertension: a stated preference study. Can J Cardiol 2020;36:775–9.
132. University of British Columbia, Centre for Health Evaluation and Outcome Sciences, King's College London. Pregnancy hypertension decision aid. 2020. Available at: https://dcida2.cheos.ubc.ca/#/decision_aid/pregnancyhypertensionptda/intro?curr_intro_page_order=1. Accessed May 20, 2020.
133. National Institute of Health and Care Excellence. Endorsed resource—high blood pressure in pregnancy decision aid and infographic. 2019. Available at: https://www.nice.org.uk/guidance/ng133/resources/endorsed-resource-high-blood-pressure-in-pregnancy-decision-aid-and-infographic-6958842157. Accessed May 20, 2020.
134. Brown MA, Magee LA, Kenny LC, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens 2018;13:291–310.
135. Malachias MV, Figueiredo CE, Sass N, Antonello IC, Torloni MR, Bortolotto MRFL. 7th Brazilian guideline of arterial hypertension: chapter 9 - arterial hypertension in pregnancy. Arq Bras Cardiol 2016;107(3 Suppl 3):49–52.
136. Mounier-Vehier C, Amar J, Boivin JM, et al. Hypertension and pregnancy. Expert consensus statement from the French Society of Hypertension, an affiliate of the French Society of Cardiology. Presse Med 2016;45:682–99.
137. Bian X, Biswas A, Huang X, et al. Short-term prediction of adverse outcomes using the sFlt-1 (soluble fms-like tyrosine kinase 1)/PlGF (placental growth factor) ratio in Asian women with suspected preeclampsia. Hypertension 2019;74:164–72.
138. Chappell LC, Duckworth S, Seed PT, et al. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study. Circulation 2013;128:2121–31.
139. National Institute for Health and Care Excellence. PlGF-based testing to help diagnose suspected pre-eclampsia (Triage PlGF test, Elecsys immunoassay sFlt-1/PlGF ratio, DELFIA Xpress PlGF 1-2-3 test, and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio). Diagnostics guidance [DG23]. 2016. Available at: https://www.nice.org.uk/guidance/dg23. Accessed May 20, 2020.
140. Zeisler H, Llurba E, Chantraine F, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. N Engl J Med 2016;374:13–22.
141. Zeisler H, Llurba E, Chantraine FJ, et al. Soluble fms-like tyrosine kinase-1 to placental growth factor ratio: ruling out pre-eclampsia for up to 4 weeks and value of retesting. Ultrasound Obstet Gynecol 2019;53:367–75.
142. Perni U, Sison C, Sharma V, et al. Angiogenic factors in superimposed preeclampsia: a longitudinal study of women with chronic hypertension during pregnancy. Hypertension 2012;59:740–6.
143. Bramham K, Seed PT, Lightstone L, et al. Diagnostic and predictive biomarkers for pre-eclampsia in patients with established hypertension and chronic kidney disease. Kidney Int 2016;89:874–85.
144. Heimberger S, Mueller A, Ratnaparkhi R, Perdigao JL, Rana S. Angiogenic factor abnormalities and risk of peripartum complications and prematurity among urban predominantly obese parturients with chronic hypertension. Pregnancy Hypertens 2020;20:124–30.
145. Benton SJ, Hu Y, Xie F, et al. Can placental growth factor in maternal circulation identify fetuses with placental intrauterine growth restriction? Am J Obstet Gynecol 2012;206:163.e1–7.
146. Benton SJ, McCowan LM, Heazell AE, et al. Placental growth factor as a marker of fetal growth restriction caused by placental dysfunction. Placenta 2016;42:1–8.
147. Griffin M, Seed PT, Webster L, et al. Diagnostic accuracy of placental growth factor and ultrasound parameters to predict the small-for-gestational-age infant in women presenting with reduced symphysis-fundus height. Ultrasound Obstet Gynecol 2015;46:182–90.
148. Ukah UV, Mbofana F, Rocha BM, et al. Diagnostic performance of placental growth factor in women with suspected pre-eclampsia attending antenatal facilities in Maputo, Mozambique. Hypertension 2017;69:469–74.
149. Manriquez Rocha B, Mbofana F, Loquiha O, et al. Early diagnosis of preeclampsia using placental growth factor: an operational pilot study in Maputo, Mozambique. Pregnancy Hypertens 2018;11:26–31.
150. Payne BA, Hutcheon JA, Ansermino JM, et al. A risk prediction model for the assessment and triage of women with hypertensive disorders of pregnancy in low-resourced settings: the miniPIERS (Pre-eclampsia Integrated Estimate of RiSk) multi-country prospective cohort study. PLoS Med 2014;11:e1001589.
151. PREgnancy Evidence. Monitoring, Partnerships and Treatment (PRE-EMPT). Evidence:

miniPIERS. 2014. Available at: https://pre-empt.obgyn.ubc.ca/evidence/minipiers. Accessed May 20, 2020.

152. von Dadelszen P, Payne B, Li J, et al. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. Lancet 2011;377:219–27.

153. PREgnancy Evidence. Monitoring, Partnerships and Treatment (PRE-EMPT). Evidence: fullPIERS. 2011. Available at: https://pre-empt.obgyn.ubc.ca/evidence/fullpiers. Accessed May 20, 2020.

154. Rana S, Karumanchi SA, Lindheimer MD. Angiogenic factors in diagnosis, management, and research in preeclampsia. Hypertension 2014;63:198–202.

155. Perry H, Binder J, Kalafat E, Jones S, Thilaganathan B, Khalil A. Angiogenic marker prognostic models in pregnant women with hypertension. Hypertension 2020;75:755–61.

156. Ram M, Berger H, Geary M, et al. Timing of delivery in women with chronic hypertension. Obstet Gynecol 2018;132:669–77.

157. Hamed HO, Alsheeha MA, Abu-Elhasan AM, Abd Elmoniem AE, Kamal MM. Pregnancy outcomes of expectant management of stable mild to moderate chronic hypertension as compared with planned delivery. Int J Gynaecol Obstet 2014;127:15–20.

158. Cluver C, Novikova N, Koopmans CM, West HM. Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term. Cochrane Database Syst Rev 2017;1:CD009273.

159. National Library of Medicine. Drugs and lactation database (LactMed). 2020. Available at: https://www.ncbi.nlm.nih.gov/books/NBK501922/. Accessed May 20, 2020.

160. Veena P, Perivela L, Raghavan SS. Furosemide in postpartum management of severe preeclampsia: a randomized controlled trial. Hypertens Pregnancy 2017;36:84–9.