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# Toward personalized management of chronic hypertension in pregnancy

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## Epidemiology

Hypertension complicates up to 10% of pregnancies and potentially twice that when considered per woman.<sup>1</sup> Chronic hypertension complicates 1% to 2% of pregnancies, and rates are rising.<sup>2</sup> Although this has been attributed to secular trends in age and body mass index,<sup>1</sup> 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.<sup>2</sup> This is a global phenomenon, with rates at least as high in resource-limited settings.<sup>3</sup>

## Definition

Clinical practice guidelines define chronic hypertension as a blood pressure (BP) of  $\geq 140/90$  mm Hg before pregnancy or before 20 weeks' gestation.<sup>4</sup> 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

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Received June 1, 2020; revised June 27, 2020; accepted July 15, 2020.

A.K. was the developer of the HaMpton blood pressure app for use in pregnancy. The other authors report no conflict of interest.

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0002-9378/\$36.00

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<https://doi.org/10.1016/j.ajog.2020.07.026>

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

threshold for diagnosis to 130/80 mm Hg, with 130 to 139/80 to 89 mm Hg designated as stage 1 hypertension and  $\geq 140/90$  mm Hg as stage 2.<sup>5</sup> If 130/80 mm Hg was the threshold for diagnosing chronic hypertension in pregnancy,

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.<sup>6</sup> Furthermore, women with stage 1 hypertension would benefit from low-dose aspirin, based on a secondary analysis of a larger trial.<sup>7</sup>

### 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%).<sup>8</sup> 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.<sup>9,10</sup> Chronic hypertension is a singular clinical risk factor for preeclampsia,<sup>11</sup> which itself accentuates risk for adverse pregnancy outcomes<sup>12–15</sup>; 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.<sup>16–20</sup>

### 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,<sup>21</sup> 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,  $\approx$ 1 mm Hg) that contribute to our understanding of the pathogenesis of hypertension but not to the care of individuals.<sup>22</sup> 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.<sup>23</sup> 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%).<sup>24</sup>

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.<sup>25</sup>

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.<sup>26–28</sup> 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 ( $\approx$ 20%),<sup>29,30</sup> 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 <sup>a</sup>
Electrocardiogram <sup>b</sup>
Establish results of baseline blood work critical to evaluation of superimposed preeclampsia
Complete blood count (particularly for platelet count)
Serum creatinine <sup>c</sup>
Liver enzymes (AST or ALT)

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

<sup>a</sup> Not performed in pregnancy as the normal range is higher and management would not be changed; <sup>b</sup> Not routinely performed in pregnancy but may be useful as part of a hemodynamically guided antihypertensive therapy; <sup>c</sup> 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.<sup>31</sup> 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.<sup>32</sup> 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).<sup>33</sup> The UK clinical practice guideline suggests that thiazides are teratogenic,<sup>34</sup> but this statement is not supported by animal or limited human studies.<sup>35</sup> 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.<sup>36</sup> Therefore, women with chronic hypertension may have used

HBPM preconceptionally; the coronavirus disease 2019 pandemic has broadened pregnancy HBPM implementation.<sup>37</sup>

In pregnancy, women using HBPM report greater awareness of risks and empowerment.<sup>38,39</sup> 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).<sup>40</sup> Another study suggested possible cost reductions.<sup>41</sup> In trials outside pregnancy and 1 postpartum (91 women), self-monitoring and self-titration of antihypertensives improved BP control<sup>42–44</sup>; ongoing trials have not raised safety concerns.<sup>37</sup>

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.<sup>45–47</sup> Used to monitor the BP of unselected and pregnant women with hypertension,<sup>48</sup> HBPM reduces false-positive diagnoses of severe hypertension and unnecessary interventions.<sup>49</sup>

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<sup>50</sup>; regularly updated lists of acceptable devices are available.<sup>51,52</sup> 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.<sup>48</sup> 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.<sup>53</sup> User involvement in development and evaluation, easy-to-use formats, portability, and multifunctionality support clinical decision support.<sup>54</sup> 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.<sup>41,49</sup>

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.<sup>55–57</sup>

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

### Aspirin

Chronic hypertension is a uniform indication for low-dose aspirin in practice guidelines,<sup>4</sup> 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,<sup>72</sup> and the cost-effectiveness of early pregnancy multivariable screening is disputed.<sup>73–75</sup> 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,<sup>76</sup> but women with chronic hypertension were the only subgroup not to benefit.<sup>76</sup> This observation is consistent with subgroup analyses in the relevant individual participant data meta-analysis<sup>77</sup> and 2 randomized trials, although aspirin was used in low dose<sup>78,79</sup> and/or often started after 20 weeks' gestation<sup>78</sup>; a trial is planned (NCT04356326). No practice guideline currently recommends against administering aspirin to these women.<sup>4</sup> These issues are discussed in detail elsewhere.<sup>80</sup>

### Calcium

Increasing calcium intake to  $\geq 1$  g/d reduces the likelihood of preeclampsia in women with low intake<sup>81–83</sup>; most women in more developed countries have adequate intake.<sup>84</sup> Unresolved controversies include whether calcium adds benefit to aspirin, whether high-dose ( $\geq 1.0$  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.<sup>80,85–87</sup>

## 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  $< 10$ th percentile and lower mean birthweight.<sup>88,89</sup> Such concerns must be balanced by oral antihypertensive therapy halving the risk of severe hypertension (systematic review, 31 trials, 3485 women),<sup>90</sup> 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.<sup>91</sup>

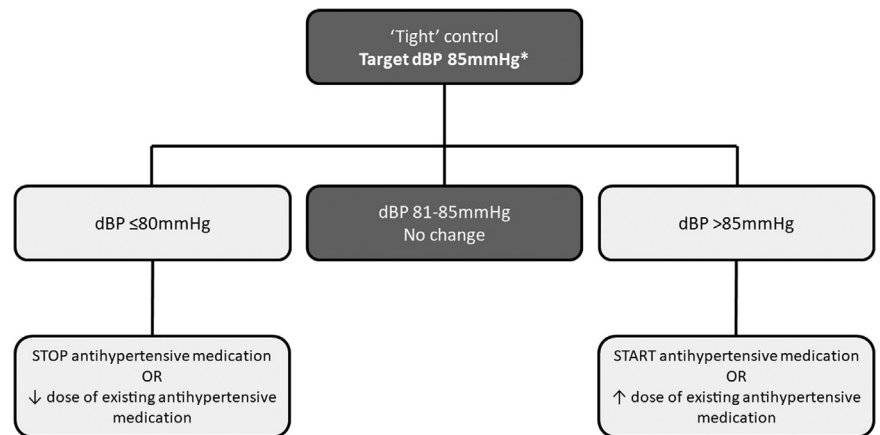
The international Control of Hypertension In Pregnancy Study (CHIPS) trial aimed to evaluate the impact of BP control on pregnancy outcomes. Overall, 987 women with chronic (75%) or



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,  $<100 \times 10^9/L$ ; 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).<sup>92</sup> Women with comorbidities (eg, kidney disease, preeclampsia, pregestational diabetes) were excluded, as "tight" control was an established practice to reduce the progression of underlying kidney or cardiovascular disease, as outside pregnancy.<sup>5</sup> 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,<sup>93</sup> 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.<sup>94</sup> 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  $<10$ th 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)<sup>95</sup>; the effects of "tight" vs "less tight" control on perinatal outcome were balanced across the gestational ages at which women were recruited.<sup>96</sup> Women in "tight" (vs "less tight") control were equally satisfied with their care.<sup>97</sup> "Tight" control was probably cheaper (average \$6000 [Canadian dollars]), based on lower NICU costs ( $P=.07$ ).<sup>98</sup>

"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  $\geq 160$  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.<sup>92</sup>

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  $\geq 160$  mm Hg, regardless of dBP, for safety. The mean BP achieved in the "tight" control group, 133/85 mm Hg,<sup>92</sup> was in the lower half of the ACC and AHA "stage 1 hypertension" range,<sup>5</sup> and increasing antihypertensive medication when BP is "high normal" concurs with guidance from the Royal College of Obstetricians and Gynaecologists.<sup>37</sup> 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  $\pm 5$  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.<sup>92</sup> 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.<sup>4</sup> 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,  $\geq 160/110$  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.<sup>25</sup>

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.<sup>99</sup> 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.<sup>96</sup> 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.<sup>92</sup> 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.<sup>100</sup>

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.<sup>25</sup> 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.<sup>101</sup>

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.<sup>90</sup>

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.<sup>102</sup>

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.<sup>103</sup> In a 2020 network meta-analysis (14 trials, 1956 women with chronic hypertension, usually without comorbidities) of numerous agents (including placebo or no therapy),<sup>104</sup> 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.<sup>105,106</sup> However, the results suggest that nifedipine and methyldopa are most beneficial. Vitamin D may enhance the effectiveness of nifedipine.<sup>107</sup>

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.<sup>90</sup> 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.<sup>108</sup>

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<sup>109</sup>; 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.<sup>110</sup> 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<sup>4,90,111</sup>; all were used in the CHIPS trial, with <15% of women overall taking another antihypertensive.<sup>92</sup>

Additional antihypertensive drugs, required in 8% to 40% of women,<sup>90,92</sup> should be used if target BP levels are not achieved with midrange dose monotherapy.<sup>94</sup> Based on nonpregnancy care, add-on drugs should be from a different drug class.<sup>94</sup> 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.<sup>112</sup> This may prove useful as oral antihypertensives effectively resolve episodes of severe hypertension.<sup>113</sup> 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.<sup>4</sup> 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.<sup>101</sup> 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.<sup>114</sup>

Oral labetalol and oral methyldopa compared favorably with oral nifedipine in a recent Indian trial for severe pregnancy hypertension<sup>113</sup>; an in-target BP (ie, 120–150/70–100 mm Hg) was achieved without fetal compromise at 6 hours in  $\geq 75\%$  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.<sup>25,113,115</sup> 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.<sup>25</sup>

#### 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.<sup>56,104,116–119</sup> Many practitioners are uncomfortable using thiazides and thiazide-like diuretics owing to theoretical concerns about reducing gestational plasma volume expansion<sup>102</sup>; 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)		If BP not controlled on medium dosage	High <sup>b</sup>	Maximum
	Low <sup>a</sup>	If BP not controlled			
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.

<sup>a</sup> Starting doses are higher than generally recommended for adults given more rapid clearance in pregnancy; <sup>b</sup> 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.<sup>55</sup>

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)<sup>94</sup>; although they do not seem to be teratogenic,<sup>33,120,121</sup> 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.<sup>122</sup> However, such associations have been based on low-quality data (eg, case reports and series), inconsistently observed, and may relate to underlying hypertension.<sup>27,123,124</sup>

### Individualized antihypertensive therapy

Outside pregnancy, age and race reflect different hemodynamic profiles in hypertension and response to antihypertensive therapy<sup>125,126</sup>; high renin hypertension is associated with young age and higher HR or volume expansion, and low renin hypertension is associated with the black race.<sup>125</sup> 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,<sup>127</sup> and is recommended outside pregnancy for adult hypertension.<sup>128</sup>

In observational work, demographic and hemodynamic parameters identify individual pregnant women less likely to achieve BP control with oral labetalol.<sup>129</sup> 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  $\geq 140/90$  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.<sup>130</sup>

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).<sup>131</sup> Most

**TABLE 3**  
**Suggested dose titration of antihypertensive therapy for urgent control of hypertension in pregnancy<sup>a</sup>**

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

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

<sup>a</sup> When severe hypertension has been resolved, switch to routine oral medication; <sup>b</sup> Do not exceed the maximum dose of IV labetalol, which is 300 mg total in a treatment course; <sup>c</sup> If nifedipine or hydralazine were the initial drug used, choose oral labetalol or oral methyldopa as the alternative drug; <sup>d</sup> Double the initial dose of IV labetalol; <sup>e</sup> To be swallowed whole, not bitten; <sup>f</sup> 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.<sup>132,133</sup>

## Superimposed Preeclampsia

### Definition

Superimposed preeclampsia is defined by most guidelines as the "development of preeclampsia."<sup>4</sup> Three guidelines specifically exclude deteriorating BP control from the definition because of subjectivity,<sup>134–136</sup> 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 PIGF (<5th percentile or <100 pg/mL) or soluble fms-like tyrosine kinase-1 (sFlt-1) to PIGF 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.<sup>137–141</sup> Three studies using commercial assays (268 women with chronic hypertension; 114 with superimposed preeclampsia) identified that either low maternal plasma PIGF or elevated sFlt-1, endoglin, or sFlt-1/PIGF 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.<sup>142–144</sup> In addition, 1 study confirmed the observations in a cohort of 123 women with chronic hypertension and CKD.<sup>143</sup> 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.<sup>145–149</sup>

### Prediction of complications

Detecting progression to preeclampsia when it occurs is the reason why many professional organizations emphasize evaluating maternal symptoms.<sup>111</sup> 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<sup>150</sup> 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  $\geq 25\%$ , 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).<sup>151</sup>

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).<sup>152</sup> Using  $\geq 10\%$  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).<sup>153</sup> Determining the added value of angiogenic markers is warranted.<sup>154,155</sup>

### 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

### miniPIERS CALCULATOR

English ▾

Gestational age at admission:  
 weeks  days

Any previous deliveries >20weeks gestation?

Chest pain and/or dyspnoea?

Headache and/or visual changes?

Vaginal bleeding with abdominal pain?

Systolic BP\* (mmHg):

Dipstick proteinuria:

SpO<sub>2</sub> (Optional):  
 %

**CALCULATE**

---

Probability of adverse maternal outcomes\*:  
 %

\*Risk should be calculated only for women with hypertension.

### fullPIERS CALCULATOR [help](#)

English ▾

Gestational age (at delivery, if *de novo* postpartum pre-eclampsia) :  
 weeks  days

Did the patient have chest pain or dyspnoea?

SpO<sub>2</sub>\* (use 97% if unknown):  
 %

Platelets (x10<sup>9</sup>/L):

Creatinine (μmol/L):

**Switch To Imperial Units**

AST/SGOT (U/L):

**CALCULATE**

---

Probability of adverse maternal outcomes:  
 %

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.

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

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.<sup>9,156</sup> These observational data are complemented by limited trial data related to 50 Egyptian women with

chronic hypertension<sup>157</sup> 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.<sup>158</sup>

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  $\geq 40$  0/7 weeks' gestation (or as clinical need dictates). The copriary outcomes are maternal death or serious morbidity (fullPIERS outcome<sup>152</sup>; superiority) and NICU admission for  $\geq 4$  hours (non-inferiority); 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<sup>159</sup>). 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.<sup>34</sup> 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).<sup>159</sup> 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.<sup>160</sup>

### 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. ■

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