Hypertension in pregnancy remains a significant cause of maternal and neonatal morbidity and mortality. The structure of prenatal care with increasing frequency of visits near term is designed to identify generally asymptomatic women with hypertension or proteinuria and deliver them before the development of life-threatening hypertension. In the developed world, this strategy has been generally successful with marked reductions in the rates of maternal mortality and eclampsia. In low- and middle-income countries, where access and use of prenatal care are limited, maternal mortality and eclampsia remain commonplace.

Treatment of severe hypertension (systolic blood pressure [DBP] ≥160 mmHg; or diastolic BP ≥110 mmHg) is broadly recommended.1,2 The California Maternal Quality Care Collaborative mandates initiation of treatment of severe hypertension within 1 hour of confirmation as minimal requirement for standard process.3 In contrast, the American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin on Hypertension in Pregnancy recommends withholding antihypertensive therapy for BPs <160/110 mmHg (or 160/105 mmHg for chronic hypertension).1 Current recommendations are largely based on committee opinions with particular concern on the effect of treatment on the fetus. Recommendations to manage BP expectantly at >160/110 mmHg and then emergently at >160/110 mmHg seem logically inconsistent.

The Control of Hypertension in Pregnancy Study (CHIPS) was a multicenter randomized, controlled trial of BP management in pregnancy.4 The trial was designed to evaluate what the authors described as tight control compared with less tight control. The trial was pragmatic in that pregnant women between 14 and 34 weeks of gestation with a diastolic BP of ≥90 mm Hg (≥85 mm Hg if on antihypertensive medication) were eligible without regard to classification of gestational or chronic hypertension; randomization was stratified to achieve a balance between groups. Seventy-five percent had chronic hypertension. Women with proteinuria, severe, uncontrolled hypertension, and comorbidities were excluded. Thus, the trial investigates a cohort of pregnant women commonly encountered in clinical practice. Implicit in the design is an approach that considers hypertension a potentially modifiable risk independent of a more specific classification. The trial has clear relevance to a population of pregnant women largely in the care of general obstetric providers.

In the tight control arm, the goal was a target diastolic BP of 85 mmHg with a target of 100 mm Hg in the less tight control arm. On the basis of a pilot study, the investigators expected to achieve an average difference of 5 mmHg. The trial specifically did not test the ACOG recommendation for initiating treatment for BP in excess of 160/110 mmHg. Labetalol was recommend but not required as a first-line agent. The study was powered for a composite perinatal outcome of pregnancy loss or prolonged high-level neonatal care and for a composite maternal outcome of serious complications. Notably, the composite did not include maternal thrombocytopenia.

The trial enrolled women in 95 sites from 16 countries with 987 randomized subjects available for analysis. Completion of the trial is a notable accomplishment. In the tight control and less tight control arms, 93% and 73%, respectively, of women received antihypertensive medications before delivery. The mean diastolic BP achieved in the tight control arm was 85.2±0.3 mm Hg compared with 89.9±0.3 mm Hg in the less tight control arm as anticipated. Given the small difference, we might have reasonably expected the effect of tight control to be limited.

No differences were found between groups in the incidence of primary composite perinatal outcome: 31.4% versus 30.7%: adjusted odds ratio [aOR], 1.02 (0.77–1.35). The incidence of pregnancy loss was low in each group, and the incidence of high-level neonatal care was 29.4% and 29.0%. No particular advantage was associated with either strategy. Some trend was present toward an increased incidence of birth weight <10th percentile in the tight control arm, 19.7% versus 16.1%: aOR, 0.78 (0.56–1.08). The CHIPS trial was not powered to this outcome. On the basis of the results of the CHIPS trial, we can be generally reassured that more aggressive therapy is not detrimental to the neonate.

No differences were found in the incidence of secondary composite maternal outcome: 3.7% versus 2.0%: aOR, 1.74 (0.79–3.84). However, the incidence of severe maternal hypertension was substantially higher in the less tight control arm: 40.6% versus 27.5%: aOR, 1.80 (1.34–2.38); P=0.001. This difference represents a substantial number of women requiring urgent therapy and at risk for stroke. Thrombocytopenia, a significant adverse outcome, was more common in the less tight control arm: 4.4% versus 1.6%: aOR, 2.63 (1.15–6.05) as was elevated aspartate transaminase or alanine transaminase: 4.3% versus 1.8%: aOR, 2.33 (1.05–5.16). These results should be interpreted with caution because they were neither primary nor secondary outcomes although they were both comparison specified a priori. If
one takes some editorial license, clearly not available to the investigators, and adds thrombocytopenia to the definition of adverse maternal outcome, a different result is obtained. If the women with thrombocytopenia are unique to the cohort of adverse outcomes, the incidence is now 7.9% versus 3.7% with significance. If only half of the women with thrombocytopenia are unique, the change in result remains significant. Clearly, this interpretation must be taken with caution, but in the context of limited information, it probably should not be entirely ignored. At a minimum, it should be used in the design of subsequent trials.

Post-CHIPS, is there an optimal strategy to manage hypertension during pregnancy? Abalos et al5 have summarized the results of as many as 23 trials and a total of 2851 randomized subjects. Treatment of mild to moderate hypertension was found to decrease the risk for severe hypertension: relative risk (RR), 0.49 (0.40–0.60). When the analysis was limited to β-blockers and methyldopa, the effect size was somewhat larger: RR, 0.38 (0.26–0.57) and RR, 0.32 (0.17–0.58). When limited to calcium-channel blockers, the effect was lost: RR, 0.81 (0.60–1.11). The analysis did not find a reduction in the rate of preeclampsia when all drugs were analyzed together: RR, 0.93 (0.80–1.08). β-blockers, when analyzed separately, did reduce the incidence of preeclampsia: RR, 0.73 (0.57–0.94), whereas calcium-channel blockers significantly increased the risk: RR, 1.40 (1.06–1.86). The CHIPS trial confirms what has been suggested by meta-analysis. Treatment of mild to moderate hypertension reduces the incidence of severe maternal hypertension. The suggestions from meta-analysis that positive effect may be specific to class of drug is an important observation that deserves further investigation.

The meta-analysis by Abalos et al5 did not suggest an increased incidence of fetuses small for gestational age: RR, 0.97 (0.80–1.92) when all drugs were evaluated together.5 When β-blockers were analyzed alone, a strong trend was observed: RR, 1.38 (0.99–1.92). The possible risk of small for gestational age with β-blockers is balanced by a decreased risk for respiratory distress syndrome in the fetus: 0.28 (0.11–0.71), an effect as favorable of that associated with antenatal steroids. In a meta-regression analysis, von Dadelszen et al8 reported an increased risk of small for gestational age with treatment independent of duration of therapy and antihypertensive agent. The absolute magnitude of effect was small, 140 g per 10-mm Hg BP reduction.

In summary, the CHIPS trial was large international trial of BP control in pregnancy.3 The study design did not address the level of control advocated by ACOG—withholding therapy until >160/110 mm Hg. The results are consistent with what we might have expected from extensive meta-analysis: a clear reduction in severe maternal hypertension without an adverse neonatal effect. A modest effect on fetal growth cannot be excluded. Importantly, these outcomes (including a possible reduction in the incidence of thrombocytopenia and elevated aspartate transaminase/alanine transaminase) are associated with a small reduction in diastolic BP: 90 to 85 mm Hg—far less than the diastolic of 110 mm Hg advocated by ACOG. We can only speculate as to what the results might have been if the ACOG standard had been tested.

How should an obstetric provider or consultant use this information? First, treatment of mild to moderate hypertension in pregnancy will clearly reduce the incidence of severe maternal hypertension, even at the small incremental difference of 5 mm Hg achieved in the CHIPS trial. Larger increments in reduction would seem likely to have a greater effect. The question remains: is a reduction in the incidence of severe hypertension an important outcome? Some have argued that it is not.7 In contrast, the failure to control severe hypertension has been cited by the Joint Commission as a major preventable cause of maternal mortality in the United States.4 Consensus protocols have classified severe maternal hypertension as a medical emergency requiring initiation of treatment within an hour.1–3 Recommendations to manage BP expectantly at <160/110 mm Hg and then emergently at ≥160/110 mm Hg seem logically inconsistent—especially when a medical emergency can be prevented. Preventing severe maternal hypertension may be particularly important in lower volume facilities and under-resourced settings where emergently treating hypertension, often with intravenous medications, is challenging.

Second, treatment of mild to moderate hypertension in pregnancy has been suggested to have an effect on fetal growth. That said, the CHIPS trial did not confirm this possibility;4 and meta-analysis has not clearly supported a risk.5 A modest reduction in fetal growth (140 g per 10-mm Hg reduction in BP) must be considered possible.6 Does then a clear reduction in maternal risk balance a possible modest reduction in fetal growth? Different providers will, in consultation with their patients, answer this question differently. Comorbidities and previous pregnancy outcomes will influence the decision as will the environment of care and provider experience level. The CHIPS trial offers clear support for the management of BP in pregnancy more consistent with standards outside pregnancy where tight control is associated with improved outcomes.2 Prevention of severe hypertension should be a clear maternal imperative consistent with our duty to the women who are our patients.

Questions do remain to be answered.10 Is a diastolic BP target of 85 mm Hg used in CHIPS the optimal target? Should systolic BP, as suggested by some studies outside pregnancy, be used to guide care? Given suggestions from meta-analysis that classes of drug may differentially affect outcomes, do we know the best pharmacological approach?

Disclosures
None.

References


Post–Control of Hypertension in Pregnancy Study (CHIPS): What Is the Optimal Strategy to Manage Hypertension During Pregnancy?
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