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SMFM Statement

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Society for Maternal-Fetal Medicine Statement: Antihypertensive therapy for mild chronic hypertension in pregnancy The Chronic Hypertension and Pregnancy trial

Society for Maternal-Fetal Medicine; Publications Committee

The recently published Chronic Hypertension and Pregnancy study provides important data to inform the management of mild chronic hypertension in pregnancy. The purpose of this statement is to review the results of this trial and provide guidance for the implementation of the study findings. Based on the available evidence, SMFM recommends treatment with antihypertensive therapy for mild chronic hypertension in pregnancy to a goal blood pressure of <140/90 mm Hg. Patients with treated chronic hypertension should continue established antihypertensive therapy during pregnancy or change to a regimen compatible with pregnancy to achieve this treatment goal.

Key words: antihypertensive therapy, Chronic Hypertension and Pregnancy (CHAP) trial

Chronic hypertension occurs in approximately 2% of pregnancies in the United States and remains a major cause of maternal and perinatal morbidity and mortality.[1] Specifically, chronic hypertension is associated with an increased risk for preeclampsia, pulmonary edema, acute kidney injury, cardiomyopathy, stroke, medically indicated preterm birth, placental abruption, small-for-gestational-age (SGA) newborns, maternal mortality, and perinatal deaths.[1 3] Although there is a consensus supporting the treatment of severe chronic hypertension in pregnancy to mitigate these risks, significant variation in international guidelines exists regarding the treatment of mild chronic hypertension (defined as systolic blood pressure [BP] of ≥140 mm Hg and <160 mm Hg or diastolic BP of ≥90 mm Hg and <110 mm Hg or both).[2 6] The purpose of this statement is to review the results of the recently published Chronic Hypertension and Pregnancy (CHAP) randomized controlled trial and to provide guidance for the implementation of the study findings.[7]

The most updated guidelines from the American College of Obstetricians and Gynecologists, which have been supported by the Society for Maternal-Fetal Medicine (SMFM), do not recommend treatment for mild chronic hypertension during pregnancy.[2,3] Historically, these recommendations were based on a lack of data confirming maternal or perinatal benefit with treatment and concerns that antihypertensive therapy may impair fetal growth. A Cochrane systematic review and meta-analysis of 58 trials (including 5909 patients) concluded that the treatment of mild chronic hypertension during pregnancy reduced the incidence of severe hypertension by approximately 50% but did not reduce the frequency of preeclampsia, preterm birth, fetal growth restriction, fetal death, or other pertinent maternal or perinatal outcomes.[8] In addition, other meta-analyses have suggested that antihypertensive therapy is associated with a 2-fold increase in the risk for SGA newborns.[9,10] The 2015 Control of Hypertension in Pregnancy Study (CHIPS), an international randomized trial comparing tight control (target diastolic BP <85 mm Hg) with less tight control (target diastolic BP <100 mm Hg) of BP in 987 pregnant patients of whom 75% had chronic hypertension, demonstrated similar findings.[11] The primary outcome of pregnancy loss or the need for high-level neonatal care for ≥48 hours did not differ between the study groups (31.4% vs 30.7%; adjusted odds ratio [aOR], 1.02; 95% confidence interval [CI], 0.77 1.35). The frequency of severe hypertension was higher in the less tightly controlled group (40.6% vs 27.5%; aOR, 1.8; 95% CI, 1.3 2.4), although the overall risk for SGA newborns and serious maternal complications did not differ between the groups. Important limitations of the CHIPS trial included that >56% of participants in each group were maintained on antihypertensive therapy at randomization, only 35% were enrolled before 21 weeks of gestation, and there was limited power to evaluate other pertinent perinatal outcomes potentially influenced by

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treatment. These limitations precluded generalization of the results to direct management decisions regarding the treatment of mild chronic hypertension during pregnancy. SMFM recommended that clinicians continue to follow the existing guidelines regarding the management of mild chronic hypertension in pregnancy until additional data regarding the benefits and safety of pharmacologic therapy during pregnancy were available.[12]

The CHAP trial was a multicenter, pragmatic, open-label randomized controlled trial supported by the National Heart, Lung, and Blood Institute to test the hypothesis that treatment of pregnant patients with mild chronic hypertension to reach a BP goal of <140/90 mm Hg reduces the frequency of adverse pregnancy outcomes when compared with no treatment unless severe hypertension developed, without compromising fetal growth.[7] Pregnant patients with a known or new diagnosis of mild chronic hypertension (defined as systolic BP <160 mm Hg and diastolic BP <105 mm Hg) and a viable singleton gestation <23 weeks of gestation were eligible for recruitment. Those with severe hypertension (systolic BP ≥160 mm Hg or diastolic BP ≥105 mm Hg), secondary hypertension, multiple gestations, or other high-risk medical comorbidities were excluded. Enrolled participants were randomized to either the active treatment group (antihypertensive therapy with the goal of reaching a systolic BP <140 mm Hg and diastolic BP of <90 mm Hg) or the standard treatment group (antihypertensive therapy withheld or stopped at randomization and initiated if systolic BP increased to ≥160 mm Hg or if diastolic BP increased to ≥105 mm Hg). Per the trial protocol, when antihypertensive therapy was indicated based on group allocation, first-line drugs for pregnancy (labetalol, extended-release nifedipine, or other medications including amlodipine or methyldopa based on patient and provider discretion) were used with dose escalation to the maximum tolerated or recommended dose before initiation of a second agent. The primary outcome was a composite of preeclampsia with severe features occurring up to 2 weeks postpartum, medically indicated preterm birth at <35 weeks of gestation, placental abruption, fetal death, or neonatal death. A safety outcome of fetal growth was assessed by determining the incidence of SGA, defined as a birthweight <10th percentile for gestational age and infant sex. Major secondary outcomes included a composite of serious maternal cardiovascular outcomes and severe neonatal morbidities.

A total of 29,772 patients were screened at more than 70 recruiting centers in the United States. The final study sample included 2408 patients, of whom 1208 were randomly assigned to the active treatment group and 1200 were assigned to the standard treatment group. Most of the enrolled patients (56%) had known chronic hypertension on therapy, and >40% were randomized before 14 weeks of gestation. Compliance with antihypertensive therapy in the trial was high (86%). Mean postrandomization clinic BP values until delivery were significantly lower in the active treatment group (systolic BP, 129.5 vs 132.6 mm Hg; diastolic BP, 79.1 vs 81.5 mm Hg). Notably, the primary outcome was lower in the active treatment group than in the standard treatment group (30.2% vs 37.0%; adjusted relative risk [aRR], 0.82; 95% CI, 0.74 0.92), leading to a number needed to treat of 14.7. Active treatment was also associated with a reduction in the frequency of preeclampsia with severe features (23.3% vs 29.1%; aRR, 0.80; 95% CI, 0.70 0.92) and medically indicated preterm birth <35 weeks of gestation (12.2% vs 16.7%; aRR, 0.73; 95% CI, 0.60 0.89). The safety measure of SGA <10th percentile did not differ significantly between the groups (aRR, 1.04; 95% CI, 0.82 1.31). The active treatment group also had significant reductions in the incidence of severe hypertension (36.1% vs 44.3%; RR, 0.82; 95% CI, 0.74 0.90), preeclampsia with or without severe features (24.4% vs 31.1%; RR, 0.79; 95% CI, 0.69 0.89), preterm birth at <37 weeks of gestation (27.5% vs 31.4%; RR, 0.87; 95% CI, 0.77 0.99), and low birthweight neonates (19.2% vs 23.1%; RR, 0.83; 95% CI, 0.71 0.97). Otherwise, the maternal composite cardiovascular outcome and composite neonatal morbidity did not differ significantly between groups. Aspirin use was equal between the study groups with approximately 45% of patients on therapy at baseline and 77% being treated at delivery, and a post hoc analysis demonstrated that aspirin use did not influence the primary outcome measure. The CHAP study investigators concluded that the treatment of mild chronic hypertension in pregnancy to a target BP of <140/90 mm Hg improves maternal and perinatal outcomes without negatively impacting fetal growth.

The CHAP study provides important data to inform the management of mild chronic hypertension in pregnancy. This trial clarifies 2 previously unaddressed questions. First, what is an evidence-based, safe, and appropriate BP target in pregnant patients with mild chronic hypertension? And second, should antihypertensive therapy be continued or discontinued in patients entering pregnancy with chronic, nonsevere hypertension? The results of this trial support the approach of recommending pharmacologic treatment for mild chronic hypertension to a BP goal of <140/90 mm Hg, including continuing established antihypertensive therapy. Other notable study strengths include that the trial population demonstrated diversity in age, race, and ethnicity, and the results are generalizable to the US population of pregnant patients with chronic hypertension. Because patients were enrolled early in pregnancy, study results were not confounded by the inclusion of patients with both chronic and gestational hypertension. This large trial was adequately powered to detect differences in important maternal and neonatal outcomes, which was a limitation of previous trials. One potential study limitation was that the ratio of patients screened to those randomized was high; however, the characteristics of the screened and the enrolled populations were ultimately similar. The CHAP study did not incorporate home BP assessments into the study eligibility, which would likely occur in routine clinical practice. Although the average differences in BP between the groups were modest, they

were unadjusted for time after randomization and therefore did not reflect larger differences over the course of pregnancy that likely contributed to the study findings.

Other important considerations and questions remain unanswered by the CHAP study. In 2017, the American College of Cardiology/American Heart Association (ACC/AHA) Hypertension Clinical Practice Guidelines definition of chronic hypertension lowered the threshold for the diagnosis of stage 1 hypertension from 140/90 mm Hg to 130/80 mm Hg.[13] Observational and retrospective data in obstetrical populations have demonstrated an association between hypertension, as defined by the revised ACC/AHA criteria, and a risk for preeclampsia and other adverse pregnancy outcomes.[14–16] Future trials in pregnant patients with mild chronic hypertension should investigate if treatment until the target BP is reached, which is currently recommended for nonpregnant adult populations, would confer further maternal and perinatal benefits or increased risks. In the prespecified subgroup analyses, the primary outcome measure was not significant for patients with newly diagnosed chronic hypertension during pregnancy and for patients with a body mass index of $\geq$40 kg/m^2. However, the CHAP study was not powered to assess differences across these subgroups, and further evaluation of the impact of antihypertensive therapy in these commonly encountered patients is recommended. In addition, given that the CHAP study excluded patients with secondary hypertension or other significant comorbidities (eg, cardiac or renal disease), evidence-based BP targets in these high-risk pregnant patients remain undetermined. Last, the CHAP trial only provided data on short-term maternal and neonatal outcomes. Studies on the long-term impact of antihypertensive therapy on maternal cardiovascular risk and other pregnancy and future health risks for pregnant people and their children may inform the management approach to chronic hypertension in pregnancy.

In conclusion, the CHAP trial provides evidence that the treatment of mild chronic hypertension in pregnancy reduces the risk for maternal and perinatal morbidity without increasing the risk for SGA infants or other neonatal morbidities when compared with no treatment unless hypertension becomes severe. Based on the available evidence, **SMFM recommends treatment with antihypertensive therapy for mild chronic hypertension in pregnancy to a goal BP of <140/90 mm Hg.** Patients with treated chronic hypertension should continue established antihypertensive therapy during pregnancy or change to a regimen compatible with pregnancy to achieve this treatment goal.

REFERENCES

1. 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.
2. 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.
3. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122:1122–31.
4. National Guideline Alliance (UK). Evidence review for interventions for chronic hypertension: hypertension in pregnancy: diagnosis and management: evidence review A. London: National Institute for Health and Care Excellence (NICE). (NICE Guideline, No. 133.). 2019. Available at: https://www.ncbi.nlm.nih.gov/books/NBK577927/. Accessed May 3, 2022.
5. Sinkey RG, Battarbee AN, Bello NA, Ives CW, Oparil S, Tita ATN. Prevention, diagnosis, and management of hypertensive disorders of pregnancy: a comparison of international guidelines. Curr Hypertens Rep 2020;22:66.
6. Garovic VD, Dechend R, Easterling T, et al. Hypertension in pregnancy: diagnosis, blood pressure goals, and pharmacotherapy: a scientific statement from the American Heart Association. Hypertension 2022;79:e21–41.
7. Tita AT, Szychowski JM, Boggess K, et al. Treatment for mild chronic hypertension during pregnancy. N Engl J Med 2022 [Epub ahead of print].
8. 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.
9. Magee LA, Elran E, Bull SB, Logan A, Koren G. Risks and benefits of beta-receptor blockers for pregnancy hypertension: overview of the randomized trials. Eur J Obstet Gynecol Reprod Biol 2000;88:15–26.
10. 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.
11. 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.
12. SMFM Publications Committee. Electronic address: pubs@smfm.org. SMFM Statement: benefit of antihypertensive therapy for mild-to-moderate chronic hypertension during pregnancy remains uncertain. Am J Obstet Gynecol 2015;213:3–4.
13. 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.
14. 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.
15. Hauspurg A, Parry S, Mercer BM, et al. Blood pressure trajectory and category and risk of hypertensive disorders of pregnancy in nulliparous women. Am J Obstet Gynecol 2019;221:277.e1–8.
16. Norton E, Shofer F, Schwartz H, Dugoff L. Adverse perinatal outcomes associated with stage 1 hypertension in pregnancy: a retrospective cohort study. Am J Perinatol 2021 [Epub ahead of print].

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Review Committees and final approval by the SMFM Executive Committee. SMFM accepts sole responsibility for the document content. SMFM publications do not undergo editorial and peer review by the *American Journal of Obstetrics & Gynecology*. The SMFM Publications Committee reviews publications every 18 to 24 months and issues updates as needed. Further details regarding SMFM publications can be found at www.smfm.org/publications.

SMFM recognizes that obstetrical patients have diverse gender identities and is striving to use gender-inclusive language in all of its publications. SMFM will be using terms such as "pregnant person" or "pregnant individual" instead of "pregnant woman" and will use the singular pronoun "they." When describing study populations used in research, SMFM will use the gender terminology reported by the study investigators.

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