Tight control of blood pressure in pregnant women with nonsevere hypertension: expectations for decreasing adverse maternal and fetal pregnancy outcomes

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It has been controversial regarding blood pressure (BP) levels at which antihypertensive drug therapy should be started in women with hypertensive disorders of pregnancy (HDP), which includes chronic hypertension (CH) as well as hypertension occurring at or after 20 weeks of gestation. In addition, the adequate BP level goal following antihypertensive drug therapy in those with HDP has also been controversial. The Japan Society for the Study of Hypertension in Pregnancy (JSSHP) committee previously recommended that antihypertensive drug therapy should be provided for pregnant women with severe hypertension (more than 160/110 mmHg), and BP should be maintained at 140–160/90–110 mmHg (Fig. 1) [1]. However, considering the recent recommendations of other guidelines [2, 3] and the results of the Control of Hypertension in Pregnancy Study (CHIPS) study [4], the JSSHP committee changed the recommendations for the initial BP levels at which to start antihypertensive drugs and the BP level goal following antihypertensive drug therapy in pregnant women with hypertension in the newest best practice guide (2021) [5]: (1) antihypertensive drug therapy should be used in pregnant women with severe hypertension, for whom BP levels equal to or more than 160/110 mmHg are repeatedly observed; however, it is possible to start antihypertensive drug therapy in pregnant women with BP levels that are $\geq 140/90$ mmHg at the discretion of attending physicians; and (2) the statement for the BP goal following

antihypertensive drug therapy in pregnant women with hypertension was retracted.

There have been concerns that tight control of BP in pregnancy might be associated with the occurrence of non-reassuring fetal status (NRFS) and/or fetal growth restriction (FGR). Regarding the association between tight BP control and the occurrence of NRFS, to the best of our knowledge, there have been no reports in English suggesting such an association, although it can be easily estimated that extreme control of BP levels in pregnant women with severe hypertension might lead to a significant reduction in uterine blood flow according to the decreasing BP levels, finally increasing the appearance of NRFS. Regarding the association between tight BP control and the occurrence of FGR, von Dadelszen et al. [6] reported an association between a fall in mean arterial pressure (MAP) and FGR in pregnant women with hypertension. In 45 randomized controlled trials (RCTs) including 3773 women with mild-to-moderate pregnancy hypertension, in which either placebo/no therapy or antihypertensive therapy was administered to controls, a greater mean difference in MAP with antihypertensive therapy was associated with higher incidence rates of small-for-gestational age (SGA) infants as well as lower mean birthweight [6]. However, in a recent meta-analysis assessing the effects of antihypertensive drug therapy for women with mild-to-moderate hypertension during pregnancy [7], including 63 trials with 5909 women, the use of antihypertensive drugs had no effect on the risk of SGA infants (adjusted relative risk: 0.96; 95% confidence interval: 0.78–1.18), suggesting that tight BP control might not have been performed in recent trials. Disappointingly, this meta-analysis did not include the CHIPS trial, where the effects of less-tight versus tight control of hypertension on pregnancy complications were assessed, and a target BP to prevent the outcome was not assessed [7].

Abe et al. [8], for the first time, estimated optimal BP levels for the prevention of severe hypertension in pregnant women with nonsevere hypertension by assessing the

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Fig. 1 Proposal of initial BP levels for starting antihypertensive drugs and adequate BP level goals in pregnant women with hypertension. Previously, the JSSHP committee recommended that antihypertensive drug therapy should be used in pregnant women with severe hypertension (more than 160/110 mmHg), and their BP should be kept at 140–160/90–110 mmHg. In this commentary, we proposed novel thresholds for initiating antihypertensive drug therapy and the adequate BP level goals in pregnant women with hypertension. BP blood pressure, JSSHP Japan Society for the Study of Hypertension in Pregnancy

effects of stratifying mean basal or achieved BP levels on adverse maternal and fetal pregnancy outcomes (APOs). They stratified systolic blood pressure (SBP) levels into 5 classes: 120–129, 130–139, 140–149, 150–159, and 160–169 mmHg, whereas they stratified diastolic blood pressure (DBP) levels into 3 classes: 80–89, 90–99, and 100–109 mmHg [8]. For basal BP levels, a significant interaction among basal SBP levels was found in the incidence rates of preeclampsia and placental abruption. For the achieved BP level, a significant interaction among women who achieved an SBP < 130 mmHg was found in the incidence rate of severe hypertension, whereas there was no reduction of severe hypertension in women who achieved an SBP of ≥140 mmHg; these results led to their conclusion that BP-lowering treatment aimed at achieving an SBP < 130 mmHg, accompanied by careful monitoring of fetal growth, might be recommended to prevent severe hypertension [8]. These results are consistent with the results of the recent CHIPS study, where less-tight control was associated with a significantly higher frequency of severe maternal hypertension [4]; however, in the most recent guideline of the International Society for the Study of Hypertension in Pregnancy (ISSHP), it is recommended that the target BP for antihypertensive therapy should be a DBP of 85 mmHg, regardless of the SBP [9]. Therefore, further study is needed to determine the appropriate target BP for antihypertensive therapy in women with HDP.

This meta-analysis also revealed that BP-lowering treatment in pregnant women with nonsevere hypertension may contribute to several APOs, including severe hypertension, preeclampsia, severe preeclampsia, placental abruption, and preterm birth [8]. In a previous meta-analysis by Abalos et al. [7], the use of antihypertensive drugs was associated with decreased severe hypertension, but it was not associated with preeclampsia, placental abruption, or

preterm birth. As discussed by the authors in the present study, one plausible explanation for this discrepancy may have been the inclusion of several large RCTs in which low-dose aspirin (LDA) was prescribed during the study period [4, 10, 11]. Furthermore, the authors pointed out that the intake of antihypertensive drugs prior to enrollment might have influenced the results. A recent report on the effects of BP levels in early pregnancy on pregnancy outcomes by Ueda et al. [12] suggested that an SBP < 130 mmHg within 14 weeks of gestation reduced the risk of developing early-onset superimposed preeclampsia in women with CH, although these effects have not been evaluated in a prospective cohort study or RCT.

Recently, it was revealed that the early administration of LDA in women with a high probability score for the occurrence rate of preterm preeclampsia may reduce its incidence rate by almost 60% (ASPRE trial) [13]; however, surprisingly, administering LDA for pregnant women with CH was not effective in the subanalysis of the ASPRE trial [14]. In contrast, a preventive effect of LDA on the occurrence of preeclampsia was reported in women with BP levels of 130–139 mmHg/80–89 mmHg at or before 16 weeks of gestation [15]. Therefore, an RCT to evaluate the effect of LDA on pregnant women with CH is strongly needed in the future.

Based on the current study and recent evidence from the CHIPS trial, we propose novel thresholds for initiating antihypertensive drug therapy and the adequate BP level goal in pregnant women with hypertension (Fig. 1). The use of antihypertensive drugs in pregnant women should be started at BP levels at or more than 140/90 mmHg at any gestational week, and an adequate BP level goal might be an SBP/DBP < 130/85 mmHg.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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