Hypertension Research
In Pregnancy

ORIGINAL ARTICLE

Tight systolic blood pressure control early in pregnancy improves pregnancy outcomes in women with chronic hypertension

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Key words:
chronic hypertension, early pregnancy, foetal growth restriction, nifedipine, tight systolic blood pressure control

Received: September 9, 2019
Revised: October 25, 2019
Accepted: October 25, 2019
J-STAGE Advance published date: November 15, 2019

DOI:10.14390/jsshp.HRP2019-014

Objectives: To clarify the effects of tight blood pressure control on pregnancy outcomes.
Methods: This retrospective study included 38 cases of singleton pregnancies which were diagnosed with essential hypertension either before pregnancy or during the first trimester of pregnancy. Patients were subdivided according to systolic blood pressure (< 130 mmHg, 130–139 mmHg, ≥ 140 mmHg) between 8–11, 12–15, and 16–19 weeks' gestation, respectively. The influence of systolic blood pressure in each gestational period was assessed with regard to the risk of preterm birth, foetal growth restriction, and superimposed preeclampsia.
Results: At 16–19 weeks' gestation, systolic blood pressure ≥ 140 mmHg and in the range of 130–139 mmHg was strongly linked to a shorter gestational period and lower z-scores for birth weight. The incidence of early onset superimposed preeclampsia was lower in women who had systolic blood pressure < 130 mmHg at 16–19 weeks' gestation (11%) compared with those with a systolic blood pressure of 130–139 mmHg (27%) and ≥ 140 mmHg (75%).
Conclusions: Tight control of blood pressure, with a target systolic blood pressure < 130 mmHg early in pregnancy improves pregnancy outcomes in patients with chronic hypertension.

Introduction

Chronic hypertension in pregnancy, defined as hypertension diagnosed before pregnancy or before 20 weeks' gestation, is estimated to be present in 1–5% of pregnancies.[1,2] Chronic hypertension increases the risk for development of superimposed preeclampsia, small-for-gestational-age neonates, and indicated preterm birth.[1–5] In nonpregnant women, antihypertensive therapy is universally recommended for those with a blood pressure (BP) ≥ 140/90 mmHg, and most guidelines now recommend that the target systolic BP be lowered to 130 mmHg.[6] In pregnant women, however, there is no agreement on BP thresholds for initiating antihypertensive medication and the target BP. The International Society for the Study of Hypertension in Pregnancy (ISSHP) states that chronic hypertension in pregnancy should be managed such that the target BP is in the range of 110–140/80–85 mmHg, using antihypertensives.[1] The National Institute for Health and Care Excellence also recommends that antihypertensives should be initiated if pregnant women with chronic hypertension have BP ≥ 140/90 mmHg, aiming for a target BP of 135/85 mmHg.[3] In contrast, the American College of Obstetricians and Gynaecologists (ACOG) advocates for looser BP control due to the absence of clear evidence demonstrating improvement in maternal and perinatal outcomes by tight BP control. ACOG recommends that antihypertensive therapy for chronic hypertension be started when pregnant women have a BP ≥ 160/110 mmHg and aims for a BP of 120–159/80–109 mmHg.[2] Thus, much controversy exists over both the BP threshold at which antihypertensive therapy begins and the optimum BP target range. Therefore, we designed a pilot study to investigate whether tight BP control aiming for a systolic BP below 130 mmHg

in pregnant women with chronic hypertension was associated with a decreased risk of adverse maternal and perinatal outcomes.

Materials and methods

A retrospective study was conducted using the electronic medical records and delivery records of women with singleton pregnancies who delivered at Kyoto University Hospital between April 2008 and March 2019. The study included pregnant women with essential hypertension either before pregnancy or within the first 14 weeks' gestation. Hypertension was defined as BP ≥ 140/90 mmHg. Exclusion criteria were secondary hypertension, pre-existing renal or liver disease, major foetal abnormalities and planned termination of pregnancy before 22 weeks' gestation. The study was approved by the institutional ethical review board (R2053).

Patient electronic medical records and delivery records were reviewed, and clinical data on the pregnant women and their neonates were obtained, including maternal age, body mass index (BMI), pregnancy history, history of hypertension, maternal BP, proteinuria, blood tests, gestational age at delivery, pregnancy complications (e.g., superimposed preeclampsia, foetal growth restriction, placental abruption), obstetric indications for earlier delivery, mode of delivery, birth weight, and neonatal death. Chronic hypertension and superimposed preeclampsia in the study were defined according to the revised ISSHP classification (2018) for hypertensive disorders in pregnancy.[1] Partial HELLP (haemolysis, elevated liver enzymes, and low platelet count) syndrome was defined by the presence of one or two features of HELLP syndrome[2] but not the complete syndrome. Uncontrolled hypertension was determined based on the presence of BP resistant to concurrent use of three antihypertensive drugs of different classes.

All patients had outpatient visits to hospitals or small-scale obstetric facilities, such as clinics, between 8–11 weeks' gestation. BP thresholds to initiate antihypertensive drug treatment, the treatment target, the choice of initial antihypertensive medication, as well as the intervals for prenatal visits, were determined according to the discretion of the doctors. Women were subdivided according to systolic BP (< 130 mmHg, 130–139 mmHg, ≥ 140 mmHg) between 8–11 weeks' gestation, 12–15 weeks' gestation, and 16–19 weeks' gestation, respectively. The influence of systolic BP at each gestational period was assessed for the risk of preterm birth, foetal growth restriction and superimposed preeclampsia. A subset analysis was also performed in women who were diagnosed with essential hypertension before pregnancy.

The potential impact of the selected antihypertensive treatment on pregnancy outcomes was analysed in a subset of women treated with antihypertensive drugs at the end of early pregnancy (15 weeks' gestation). Patients were divided into two subgroups; women treated with methyldopa alone and those treated with nifedipine ± methyldopa/hydralazine. Differences between the two groups were investigated in terms of pregnancy duration, birth weight, and frequency of superimposed preeclampsia. Because nifedipine has been used off-label in the past for hypertension in pregnant women 20 weeks of gestation in Japan, the administration of long-acting oral nifedipine in our institution has been performed after the approval of the evaluation committee on off-label drug use and obtaining informed consent.

Statistical analyses were performed using GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA). Z-scores for birth weight were determined using mean newborn gestational age based on data derived from a reference population in Japan.[7] Between-group differences of categorical variables and continuous variables were conducted using the chi-square test and nonparametric one-way ANOVA with the Kruskal-Wallis test followed by Dunn's multiple comparisons test, respectively. Comparisons of categorical variables between two groups were performed using Fisher's exact test.

Results

We identified a total of 42 pregnancies with essential hypertension either before pregnancy or in the first trimester of pregnancy during the study period. Among them, four cases were excluded from the analyses due to secondary hypertension. Thus, 38 pregnancies were included in the current analysis. The mean age of the study population was 36.0 ± 0.7 years, BMI was 26.7 ± 0.8, and 24 (63.1%) women were primiparous. All women were Japanese and seven (18.4%) had a previous history of hypertensive disorders of pregnancy. Low-dose aspirin was used for three women. There were 17 women who had been diagnosed with essential hypertension before pregnancy. Of these 17, eight (47%) received antihypertensive medications before conception, and two of them discontinued soon after pregnancy. Antihypertensive treatments were started during early pregnancy for 13 women. Thus, a total of 19 women (50.0%) had used antihypertensive medications early in the pregnancy. Of the 38 women, 9 (24%) started prenatal care at our hospital soon after conception. The others were referred to our hospital at < 12 ($n = 10$), 12–15 ($n = 10$), or > 16 ($n = 9$) weeks' gestation. Mean gestational age at delivery was 35.7 ± 0.8 weeks, and mean z-scores for birth weight were −0.7 ± 0.2. Early onset superimposed preeclampsia developed in 11 cases (28.9%). There were 23 caesarean deliveries (60.5%). Indicated preterm

Table 1. Characteristics and pregnancy outcomes in women categorised by systolic blood pressure at 16–20 weeks of pregnancy

	sBP < 130	130 ≤ sBP < 140	sBP ≥ 140	*p*-value[‡]
Case, *n*	19	11	8	
Age, years (median, IQR)	35 (31.5–37)	37 (35–39)	38 (36–40)	0.16
BMI[†] (median, IQR)	26.8 (22.9–30.7)	27.3 (24.4–31.2)	23.6 (20.9–28.7)	0.64
Nulliparity, *n* (%)	13 (68%)	7 (64%)	4 (50%)	0.22
Pre-pregnancy hypertension, *n* (%)	9 (47%)	4 (36%)	4 (50%)	0.80
History of HDP with severe features, *n* (%)	4 (21%)	2 (18%)	1 (13%)	0.87
Usage of low-dose aspirin	2 (11%)	1 (9%)	0 (0%)	0.64
Usage of antihypertensive drugs at 15 weeks of pregnancy, *n* (%)	14 (73%)[§]	5 (45%)	0 (0%)	0.002
— Methyldopa alone	6 (32%)	5 (45%)	0 (0%)	0.09
— Nifedipine alone	3 (16%)	0 (0%)	0 (0%)	0.20
— More than 2 drugs	5 (26%)	0 (0%)	0 (0%)	0.06
Gestational age at delivery, weeks (median, IQR)	38.7 (37.4–40.5)	36.3 (31.4–38.5)	30.3 (29.5–30.8)	< 0.001
Z-scores for birth weight (median, IQR)	0.18 (−0.43–0.67)	−1.08 (−1.45–−0.39)	−2.02 (−3.16–−1.65)	< 0.001
Superimposed preeclampsia, *n* (%)				
Total	6 (32%)	6 (55%)	6 (75%)	0.10
Onset < 34 weeks	2 (11%)[§]	3 (27%)	6 (75%)	0.003
Indicated preterm delivery, *n* (%)	2 (11%)[¶]	7 (64%)	8 (100%)	< 0.001
Non-reassuring foetal status	1 (5.3%)[¶]	4 (36%)	5 (63%)	0.006
Partial HELLP syndrome	0 (0%)	1 (9%)	2 (25%)	0.09
Uncontrolled hypertension	1 (5.3%)	2 (18%)	0 (0%)	0.29
Renal impairment	0 (0%)	0 (0%)	1 (13%)	0.15
Mode of delivery				
Caesarean section	8 (42%)	8 (73%)	7 (88%)	0.10

[‡] *p*-value < 0.05 represents a statistically significant difference among the three subgroups in the Kruskal-Wallis (continuous variable) or chi-square for trend (categorical variable).
[§] Statistically significant difference between group 1 and group 3 using Fisher's exact test.
[¶] Statistically significant difference between group 1 and groups 2 and 3 using Fisher's exact test.
sBP, systolic blood pressure; HDP, hypertensive disorders of pregnancy; IQR, interquartile range; BMI, body mass index.

delivery was needed due to obstetric indication, such as a non-reassuring foetal status ($n = 10$), partial HELLP syndrome ($n = 3$), uncontrolled hypertension ($n = 3$), and renal impairment ($n = 1$) (Table 1).

Systolic BP between 8–11 weeks' gestation was not associated with gestational age at delivery or z-scores for birth weight (Figure 1A). At 12–15 weeks' gestation, systolic BP ≥ 140 mmHg was associated with a significantly shorter pregnancy duration compared with systolic BP < 130 mmHg (Figure 1B, 33.5 ± 1.0 versus 39.1 ± 1.0 weeks, $p = 0.009$). Z-scores for birth weight were also significantly lower in pregnancies with a systolic BP ≥ 140 mmHg compared with a systolic BP < 130 mmHg (Figure 1B, −1.4 ± 0.3 vs 0.3 ± 0.3, $p = 0.007$). There was no significant difference in the incidence of superimposed preeclampsia between the levels of systolic BP (< 130, 130–139, ≥ 140 mmHg) within the first 15 weeks' gestation (data not shown). At 16–19 weeks' gestation, no significant difference was observed in patient characteristics, except the usage of antihypertensive drugs between the three groups with respect to systolic BP levels (Table 1). Pregnancy duration differed much between three groups (Figure 1C, < 130 mmHg: 38.9 ± 0.5 weeks, 130–139 mmHg: 34.5 ± 1.4 weeks, ≥ 140 mmHg: 30.0 ± 0.9 weeks). Systolic BP ≥ 140 mmHg and in the range of 130–139 mmHg were linked to a shorter gestational period compared with systolic BP < 130 mmHg ($p < 0.001$ and $p < 0.05$, respectively). Mildly elevated BP (130–139 mmHg, ≥ 140 mmHg) also distinguished z-scores for birth weight (Figure 1C, < 130 mmHg: 0.2 ± 0.2, 130–139 mmHg: −1.1 ± 0.3, ≥ 140 mmHg: −2.2 ± 0.4). A systolic BP ≥ 140 mmHg and in the range of 130–139 mmHg were related to lower z-scores for birth weight compared to a systolic BP < 130 mmHg ($p < 0.001$ and $p < 0.05$, respectively). Additionally, a subset

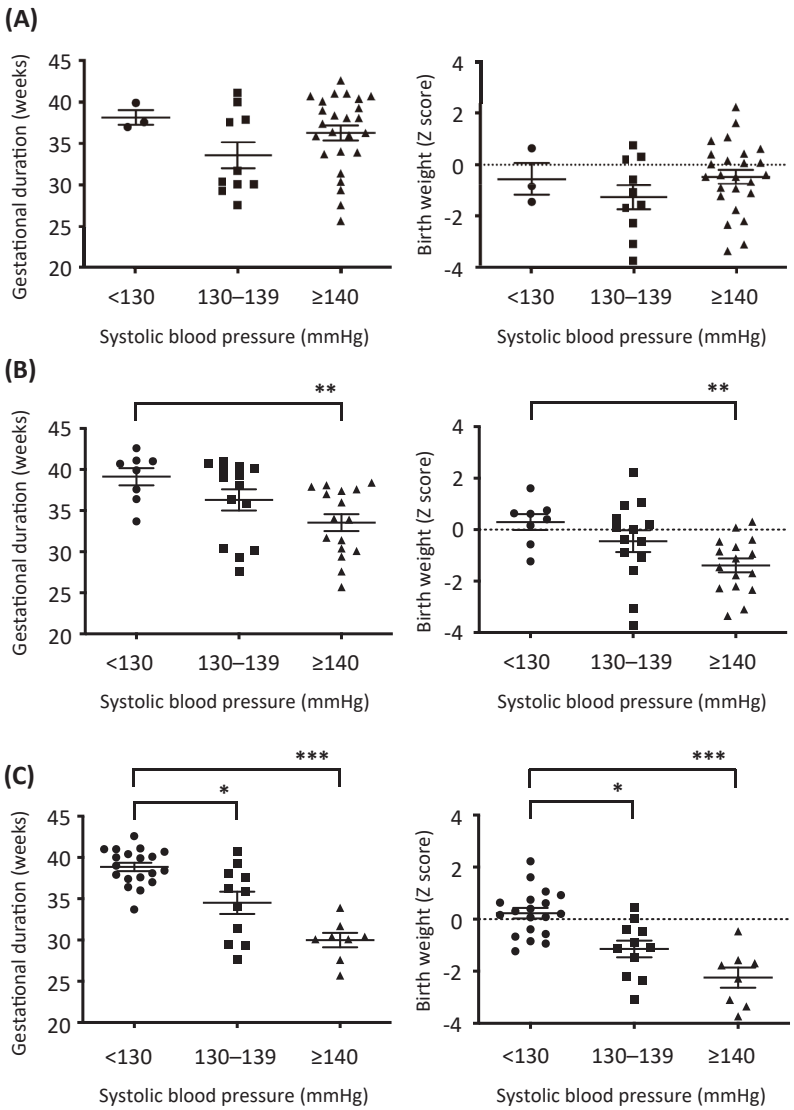
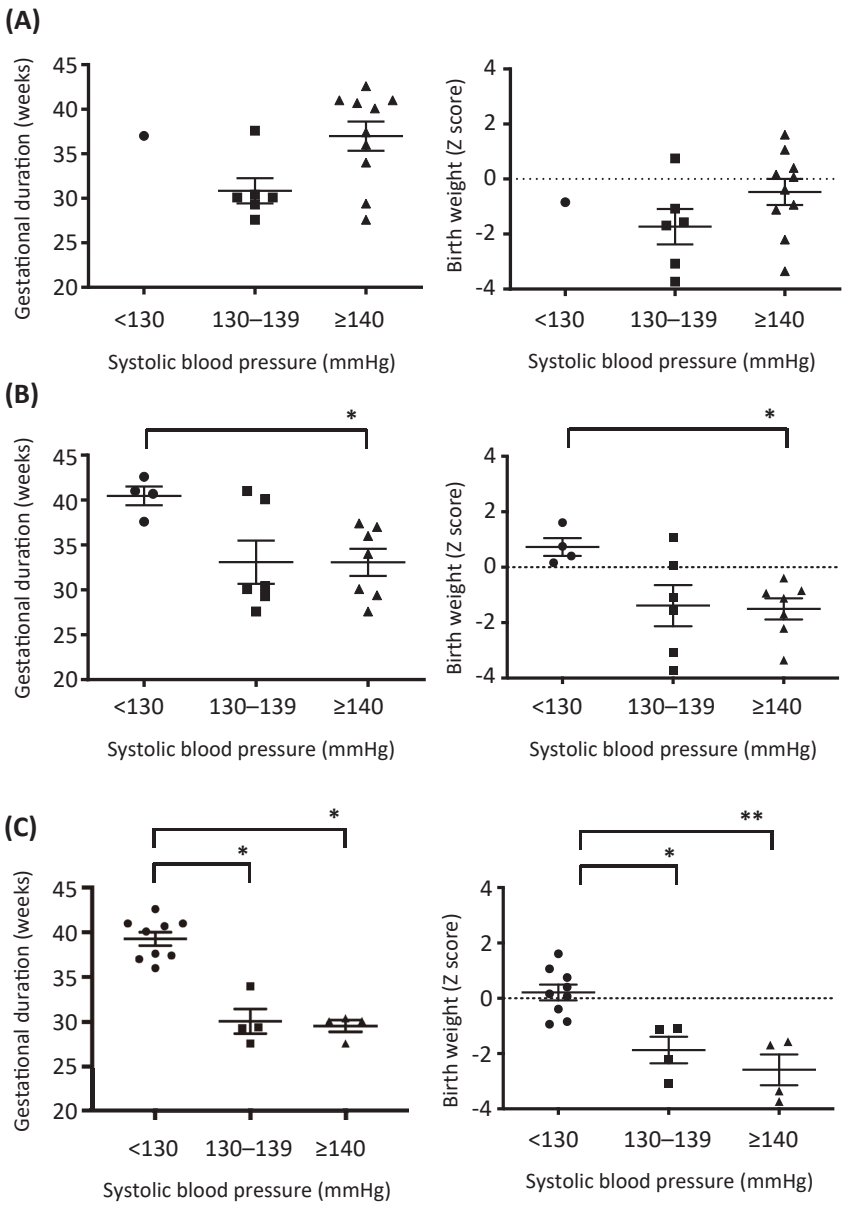


Figure 1. Influence of systolic blood pressure on pregnancy outcomes.
Pregnancy outcomes based on systolic blood pressure between (A) 8–11, (B) 12–15 and (C) 16–19 weeks' gestation, respectively. (A) Systolic blood pressure (< 130 mmHg; $n = 3$, 130–139 mmHg; $n = 10$, ≥ 140 mmHg; $n = 25$) between 8–11 week' gestation was not associated with gestational age at delivery or z-score for birth weight. (B) At 12–15 weeks' gestation, systolic blood pressure ≥ 140 mmHg ($n = 16$) was associated with a significantly shorter pregnancy duration and lower z-score for birth weight, compared with systolic blood pressure < 130 mmHg ($n = 8$). (C) At 16–19 weeks' gestation, adverse pregnancy outcomes were observed in women with systolic blood pressure in the range of 130–139 mmHg ($n = 11$) and ≥ 140 mmHg ($n = 8$) compared to a systolic blood pressure < 130 mmHg ($n = 19$). (*$p <$ 0.05; **$p <$ 0.01; ***$p <$ 0.001)

analysis of women who were diagnosed with essential hypertension before pregnancy (a total of 17 cases) showed the same findings regarding pregnancy duration and z-scores for birth weight with respect to systolic BP levels (Supplementary Figure 1). The incidence of early onset superimposed preeclampsia and indicated preterm deliveries differed significantly between the three groups of systolic BP levels (Table 1). The incidence of early onset superimposed preeclampsia was lower in women whose systolic BP was < 130 mmHg ($n = 2$, 11%) compared with women whose systolic BP was 130–139 mmHg ($n = 3$, 27%) and ≥ 140 mmHg ($n = 6$, 75%). The incidences of indicated preterm deliveries were 11% (systolic BP < 130 mmHg), 64% (systolic BP 130–140 mmHg), and 100% (systolic BP > 140 mmHg). Among obstetric indications for indicated preterm delivery, the incidence of non-reassuring foetal status was lower in women with a systolic BP of < 130



Supplementary Figure 1. Influence of systolic blood pressure on pregnancy outcomes in women with hypertension before pregnancy.

Pregnancy outcomes based on systolic blood pressure between (A) 8–11, (B) 12–15, and (C) 16–19 weeks' gestation. (A) Systolic blood pressure (< 130 mmHg; $n = 1$, 130–139 mmHg; $n = 6$, ≥ 140 mmHg; $n = 10$) between 8–11 weeks' gestation was not associated with gestational age at delivery or z-scores for birth weight. (B) At 12–15 weeks' gestation, systolic blood pressure ≥ 140 mmHg ($n = 7$) was associated with a significantly shorter pregnancy duration (40.5 ± 1.0 vs 33.1 ± 1.5, $p = 0.047$) and lower z-scores for birth weight (0.7 ± 0.3 vs − 1.5 ± 0.4, $p = 0.04$) compared with systolic blood pressure < 130 mmHg ($n = 4$). (C) At 16–19 weeks' gestation, adverse pregnancy outcomes (gestational period; 39.3 ± 0.8 vs 30.1 ± 1.4 vs 29.6 ± 0.7, z-scores for birth weight; 0.2 ± 0.3 vs − 1.9 ± 0.5 vs − 2.6 ± 0.6) were observed in women with systolic blood pressure in the ranges of 130–139 mmHg ($n = 4$) and ≥ 140 mmHg ($n = 4$) compared to those with systolic blood pressure < 130 mmHg ($n = 9$). (*p < 0.05; **p < 0.01)

mmHg (5.3%) compared to women with a systolic BP of 130–139 mmHg (36%) and ≥ 140 mmHg (63%). Rates of caesarean delivery were high in women with a systolic BP of 130–139 mmHg (73%) and ≥ 140 mmHg (88%), compared to those with a systolic BP of < 130mmHg (42%), but did not reach statistical significance (chi-square, $p = 0.1$) (Table 1).

The choice of antihypertensive drugs was not

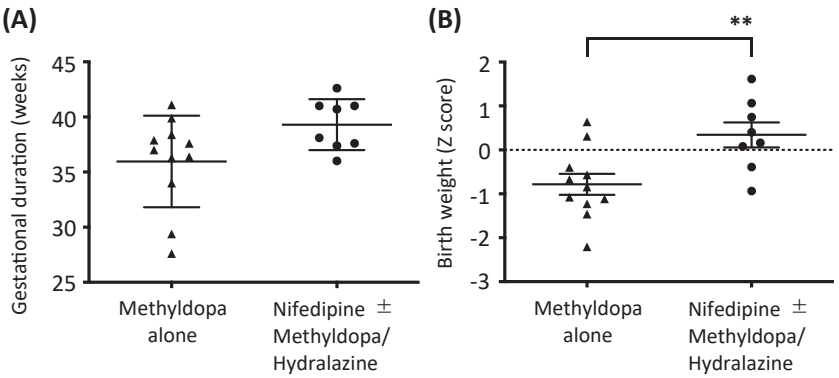


Figure 2. The potential impact of the selected antihypertensive medication on pregnancy outcomes.
(A) Gestational duration and (B) z-scores for birth weight in two subgroups: women treated with methyldopa alone ($n = 11$) and those treated with nifedipine ± methyldopa / hydralazine ($n = 8$). (**$p < 0.01$)

associated with gestational age at delivery (Figure 2A). Meanwhile, the investigation between the choice of antihypertensive drugs and pregnancy outcomes revealed that use of methyldopa alone was strongly linked to lower z-scores for birth weight (-0.8 ± 0.2 vs 0.3 ± 0.3, $p = 0.009$) compared with nifedipine ± methyldopa / hydralazine (Figure 2B).

Discussion

The main finding of the present study was that it would be better to initiate tight control of BP, targeting a systolic BP < 130 mmHg for chronic hypertension in pregnancy, ideally before 12 weeks' gestation, but definitely before 16 weeks' gestation, using long-acting oral nifedipine.

Optimal clinical management of chronic hypertension in pregnancy remains unclear. Confusion remains particularly surrounding the target BP and when to initiate antihypertensive therapy for pregnant women, due to the lack of appropriate clinical trials and prospective studies. The 2015 CHIP trial, adjusting for the interventions of "less tight" (target diastolic BP of 100 mmHg) *versus* "tight" control (target diastolic BP of 85 mmHg), did not seem to benefit the foetus, and it did not decrease the frequency of preeclampsia; notably, tight control of hypertension reduced the occurrence of severe hypertension.[8] However, the study recruited women at 14–33 weeks' gestation with chronic hypertension (75%) and gestational hypertension (25%). Moreover, "tight" control targeting a diastolic BP of 85 mmHg is not laterally tight BP control in practice. Thus, the heterogeneity of the recruited pregnancies makes it hard to conclude that tight BP control is a worthwhile approach to improve pregnancy outcomes when chronic hypertension is involved. Several recent studies have reported that mildly elevated BP in early pregnancy in women without chronic hypertension increases the risk of preeclampsia.[9–12] Interestingly, our findings indicate potential benefits to both mother and baby with tight BP control (target systolic BP below 130 mmHg), ideally before 12 weeks, but definitely before 16 weeks. The tight BP control markedly prevented indicated preterm delivery and preserved foetal growth. Since placental disorders, including preeclampsia and foetal growth restriction, are mainly attributed to insufficient early placentation, and early placentation is almost completed by the end of the first trimester of pregnancy,[13] even mild elevation of maternal BP may be harmful to normal placentation. Collectively, medication to achieve a systolic BP below 130 mmHg would be important for the management of chronic hypertension at the beginning of pregnancy and even before conception.

The choice of antihypertensive agents may affect pregnancy outcomes in women with chronic hypertension. Methyldopa is one of the most widely used antihypertensive drugs in pregnancy. However, a recent prospective cohort study showed that methyldopa therapy for chronic hypertension in the first trimester is associated with lower birth weights adjusted for gestational age, compared to those in pregnancies without chronic hypertension.[14] This may be because methyldopa is less effective in lowering BP early in pregnancy, though the study has no information regarding BP. Moreover, uterine artery resistance to blood flow is improved by nifedipine, but not by methyldopa, in pregnancies with hypertensive disorders.[15,16] These data are limited, but may support the report of a recent Cochrane analysis that noted that methyldopa is less effective than calcium channel blockers and beta blockers for preventing severe hypertension in women with mild to moderate hypertension during pregnancy.[17] Taken together, the use of nifedipine, rather than methyldopa early in pregnancy, would be an ideal choice for antihypertensive therapy to normal placenta development, and nifedipine may help

reduce the incidence of indicated earlier deliveries, foetal growth restriction, and superimposed preeclampsia.

One strength of this study was that we obtained comprehensive maternal health data, including BP data from as early as 8–12 weeks' gestation, which were available in all cases because of the perinatal care system in Japan. Study limitations included a small sample size, referral filter bias, and retrospective data collection. In addition, the indication for the use and choice of antihypertensive drugs was up to the discretion of the doctors. An ongoing multicenter retrospective cohort study is currently working to assess the importance of tight systolic BP control in women with chronic hypertension.

In conclusion, tight control of BP aimed at a systolic BP < 130 mmHg early in pregnancy improves pregnancy outcomes in patients with chronic hypertension.

Acknowledgements

None.

Conflict of interest

The authors declare no interest to disclose.

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