Hypertension Research
https://doi.org/10.1038/s41440-022-00992-3

ARTICLE

Special Issue: Current evidence and perspectives for hypertension management in Asia

A multicenter prospective study of home blood pressure measurement (HBPM) during pregnancy in Japanese women

Yoshikatsu Suzuki[1] · Keiichi Matsubara[2] · Kazushi Watanabe[3] · Kanji Tanaka[4] · Tamao Yamamoto[1] · Tomoyoshi Nohira[5] · Kazuya Mimura[6] · Hirotada Suzuki[7] · Fumiaki Hamada[8] · Shintarou Makino[9] · Keiko Koide[10] · Haruki Nishizawa[11] · Katsuhiko Naruse[12] · Yukiko Mikami[13] · Ikuno Kawabata[14] · Jun Yoshimatsu[15] · Kohta Suzuki[16] · Shigeru Saito[17]

Received: 12 January 2022 / Revised: 3 June 2022 / Accepted: 23 June 2022
© The Author(s), under exclusive licence to The Japanese Society of Hypertension 2022

Abstract

In the near future, hypertensive disorders of pregnancy (HDP) have been diagnosed by home blood pressure monitoring (HBPM) instead of clinic BP monitoring. A multicenter study of HBPM was performed in pregnant Japanese women in the non-high risk group for HDP. Participants were women ($n = 218$), uncomplicated pregnancy who self-measured and recorded their HBP daily. Twelve women developed HDP. HBP was appropriate (100 mmHg in systole and 63 mmHg in diastole), bottoming out at 17 to 21 weeks of gestation. It increased after 24 weeks of gestation and returned to non-pregnant levels by 4 weeks of postpartum. The upper limit of normal HBP was defined as the mean value +3 SD for systolic and mean +2 SD for diastolic with reference to the criteria for non-pregnant women. Using the polynomial equation, the hypertensive cut-off of systolic HBP was 125 mmHg at 15 weeks and 132 mmHg at 30 weeks of gestation, while it for diastolic HBP was 79 mmHg at 15 weeks and 81 mmHg at 30 weeks of gestation. Systolic HBP in women who developed HDP was higher after 24 weeks of gestation, and diastolic HBP was higher during most of the pregnancy compared to normal pregnancy. When the variability of individual HBP in women developed HDP compared to normal pregnant women was examined using the coefficient of variation (CV), the CV was lower in HDP before the onset of HDP. HBPM can be used not only for HDP determination, but also for early detection of HDP.

Keywords Home Blood Pressure · Hypertensive Disorders Of Pregnancy · Individual Variability

Introduction

To date, hypertension has been diagnosed based on blood pressure (BP) in the clinical setting, and hypertensive disorders of pregnancy (HDP) have naturally been diagnosed using clinic BP (CBP). However, home BP (HBP) is lower than CBP. There is also diurnal variation in BP, and it changes with various stimuli in life. It is also possible to differentiate between white coat hypertension (WCH) and masked hypertension (MH) using HBP. WCH is known to be more frequent in pregnant women than in non-pregnant women. Women with WCH are at a marginally increased cardiovascular risk and could also develop sustained hypertension [1]. Therefore, they should be regularly followed using HBP and CBP. In addition, MH is increased more with HBP than CBP, and it also increases the risk of cardiovascular events [2] Parati et al. reported that management of WCH and MH should be decided on the basis of both HBP monitoring (HBPM) and CBPM [3].

Therefore, HBPM is strongly recommended by hypertension guidelines to confirm the diagnosis of hypertension and evaluate the efficacy of medications [4]. HBPM is a valuable tool in the daily management of hypertension with medical supervision. In the near future, HBPM will be necessary along with CBPM for the diagnosis and treatment of HDP. However, there is insufficient evidence in pregnant women in Japan or anywhere else in the world.

Thus, we conducted a multicenter study of HBPM in pregnant Japanese women to describe the trajectories of HBPM and to explore the characteristics of HBPM among normal pregnant women and HDP patients.

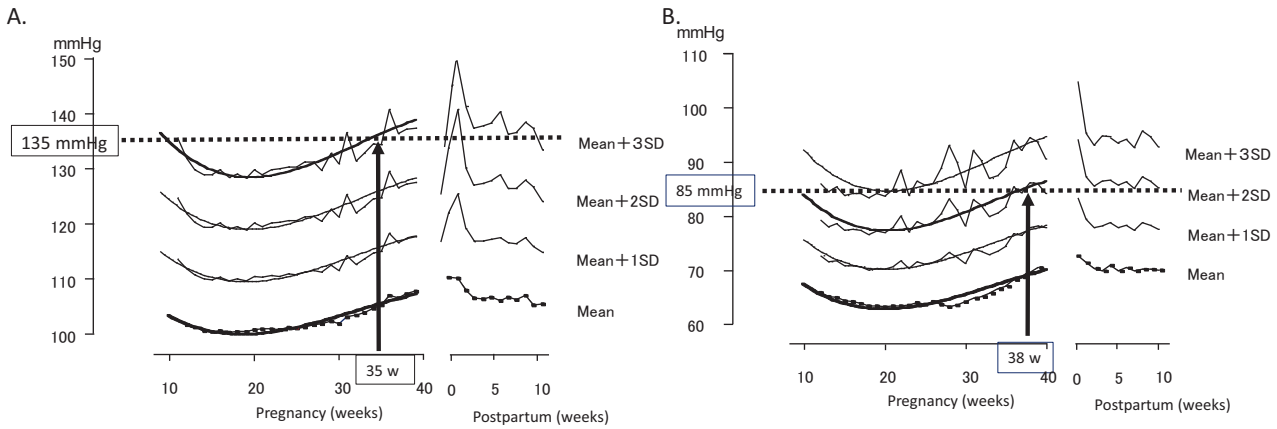
✉ Yoshikatsu Suzuki
ogyo_537@hotmail.com

Extended author information available on the last page of the article

Published online: 16 August 2022

Graphical Abstract

The hypertensive cut-off in HBP by HBPM was determined in Japanese pregnant women. (A) Optimizing the polynomial of systolic HBP that induces the hypertensive boundary value by HBPM. By the polynomial equation of mean +3 SD, systolic HBP at 35 weeks gestation equal to non-pregnant was 135 mmHg, the current reference value for non-pregnant hypertension of HBPM. Polynomial of mean +3 SD was considered optimal. (B) Optimization of polynomial of diastolic HBP that induces the hypertensive boundary value by HBPM. By polynomial of mean +2SD, diastolic HBP at 38 weeks gestation equal to non-pregnant was 85 mmHg, the current standard for non-pregnant hypertension by HBPM. Thus, polynomial of mean +2 SD was considered optimal.



Point of view

Clinical relevance

The multicenter study in Japanese pregnant women was able to establish hypertension criteria for each gestational week using a polynomial equation.

Future direction

The criteria for hypertension at each week of gestation established in this study are expected to be applied to (1) the development of hypertension criteria by HBPM at a global level, as in non-pregnant women, and (2) HDP management and prediction.

Consideration for the Asian population

This study will contribute to the development of HDP criteria for HBPM in the JSSHP guidelines, and the new criteria will play an important role in the management of HDP in Asian women, including Japanese.

Subjects and methods

A total of 268 pregnant women with uncomplicated pregnancies were enrolled with their consent in this study. Excluded were pregnant women who met the exclusion criteria: essential hypertension, diabetes mellitus, gestational diabetes, thyroid dysfunction, renal dysfunction, and psychiatric disorders. The enrolled period was from January 1, 2016 to March 31, 2018.

Participating and cooperating institutions were: Hokkaido University, Hirosaki University, Tohoku University, Jichi Medical University, Saitama Medical University Medical Center, Tokyo Medical University, Nippon Medical School, Juntendo University, Showa University, Toyama University, Aichi Medical University, Fujita Health University, Osaka University, National Cerebral and Cardiovascular Center, Ehime University Hospital, Sano Kosei General Hospital, Kochi Prefectural Hata Kenmin Hospital, Kochi Prefectural Health Science Center as higher tertiary hospitals, and Fukui Women's Clinic, Kanda Maternity Clinic, Mommy Rose Clinic as general practitioners and Suzuki Hospital, St. Barnabas Hospital, Daiyu Kai Hospital, Gamagori Municipal Hospital as non- higher tertiary hospitals.

In this study, we targeted non-high risk of pregnant women of HDP to participate. Thus, we also invited participants from general practitioners and non-higher tertiary hospital in addition of higher tertiary hospital. Of 268, 100 participants were entered (80 women at general practitioners and 20 women at non- tertiary hospitals).

HBPM was performed daily using an automatic sphygmomanometer (HEM-8712, Omron Corporation, Kyoto, Japan) from early pregnancy to one month postpartum. According to guidelines for the management of hypertension 2014 [5] by Guidelines Subcommittees of the Japanese Society of Hypertension, measurement environments were (1) a quiet, appropriate environment at room temperature, (2) after resting for 1–2 min in a seated position with the legs not crossed, (3) no conversation, (4) smoking and alcohol/caffeine consumption should be avoided before measurement, and (5) the cuff position can be maintained at the heart level.

Measurement conditions were essential conditions; (a) morning: within 1 h after waking up, after urination, before dosing in the morning, before breakfast, and after 1–2 min resting in a sitting position, (b) evening (at the bedtime): after

1-2 min resting in a sitting position and additional conditions; (a) according to instructions: before dinner, before dosing in the evening, before bathing, or before alcohol consumption.

As a rule, measurement should be performed twice per occasion, and the mean value of two measurements should be adopted. When measurement is performed only once per occasion, the BP value is used. Values to be evaluated both mean of morning and evening values obtained for 7 days (at least 5 days).

BP was measured in the outpatient clinic and at home using the same type of sphygmomanometer.

HDP was finally diagnosed 3 months after delivery based on the Japan society of study for hypertension in pregnancy (JSSHP) criteria [6]. HDP was defined as hypertension (systolic BP ≥ 140 and/or diastolic BP ≥ 90 mmHg) during pregnancy. Gestational hypertension (GH) was defined as hypertension without proteinuria, maternal organ failure (liver damage, progressive kidney damage), stroke, neurological complications (clonus, eclampsia, visual field disturbances, severe headache other than primary headache, etc.), hematological complications, or uteroplacental insufficiency. Preeclampsia (PE) was defined as hypertension with proteinuria, maternal organ damage, or uteroplacental insufficiency (fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or stillbirth) after 20 weeks of gestation.

Data were collected at the end of the study period and analyzed at Aichi Medical University. Age, height, pre-pregnancy weight, parity, gestational weeks at delivery, and baby's birth weight were also evaluated. Small for gestational age (SGA) was determined according to Glossary of Obstetrics and Gynecology, 4th edition [7]. Family history was essential hypertension and diabetes in father and or mother and HDP in mother.

The protocol of this study was approved by the Clinical Research Ethics Committee of Aichi Medical University and the ethics committees of the participating and cooperating institutions. Written, informed consent was obtained from each patient prior to enrollment.

Statistical analysis

First, we described the means and standard deviations of background characteristics (age, pre-pregnancy BMI, gestational age of birth and baby weight) and compared with normal pregnancy and HDP patients by student *t*-test.

We described percentage of SGA, family history and cesarean section and compared with normal pregnancy and HDP patients by Fisher's extract test.

Second, we described the means and standard deviations of HBPs in the morning and at night per week. Then, the comparisons between the lowest HBP which might be measured during 2nd trimester and other weeks were conducted by using Turkey-Kramer HSD because, usually, the BPs among population were normally distributed in each period during pregnancy and was used to adjust the effect of multiple comparisons.

Next, we used the difference in diastolic HBP and CBP to examine the white coat effect during pregnancy. The definition of the difference was determined by the formula as follows: δBP at each week = CBP-HBP. Then, the means and standard deviations of CBP at each week were calculated. The mean δBP at xx to yy weeks was compared with the mean at XX to YY weeks by Student's *t*-test.

Polynomial formulae of HBP in the morning for mean, mean +1 SD, mean +2 SD, and mean +3 SD were expressed by KaleidaGraph ver 3.01 (Synergy Software, Reading, PA).

The mean systolic and diastolic BP formulas were used to determine which gestational week BP values were equal to the BP values after 4 weeks postpartum, which is considered the standard BP for non-pregnant women.

At the determined gestational weeks, we determined what BP formula was optimal to indicate more than135 mmHg in systolic and 85 mmHg in diastolic, the current HBPM reference values for hypertension in non-pregnant women.

Finally, the differences in BP between HDP and normal pregnancy were examined by Student's *t*-test if equal variances and by Welch's *t*–test if not equal variances.

P values of <0.05 were considered statistically significant. All statistical analyses were performed using JMP13 (SAS Institute Inc., Cary, NC).

The polynomial representation of BP was analyzed using KaleidaGraph.

Results

Of the 268 pregnant women, 218 were included in the analysis. There were 50 dropouts included 26 withdrawals of consent, 10 BPMs were no longer, 8 with insufficient number of BPMs (less than 5 days weekly), one abortion and 5 untraceable due to transfer hospital.

The background characteristics of the participants were not different between normal pregnancy and HDP. (Table 1) Furthermore, they were not different between in non-higher tertiary hospital ($n = 80$) and in higher tertiary hospital ($n = 138$).

Twelve participants developed HDP after 34 weeks of gestation, including 11 with GH and 1 with PE (Table 1). The incidence rate of HDP was 5.5%.

There were no differences between normal pregnancy and HDP patients in all survey items.

Changes in HBP during pregnancy

The mean HBP in the morning and at night per week is shown in Fig. 1A, B. Systolic HBP was not different between morning and night.

Table 1 Background characteristics of the participants

	Total	Normal pregnancy	HDP
Number (*n*)	218	206	12
Age (y)	31.8 ± 4.5	31.6 ± 4.5	33.9 ± 4.2
Primipara (%)	57	57	56
Prepregnacy BMI (kg/m^2)	21.4 ± 2.8	21.3 ± 2.7	22.0 ± 4.5
Gestational age of birth (days)	273 ± 13	273 ± 13	273 ± 9
Baby weight (g)	2955 ± 425	2939 ± 432	2883 ± 313
Small for gestational age (%)	4	4	8
Family history (%)	22	21	30
Cesarean section(%)	18	17	27

HDP hypertensive disorders of pregnancy, 11 gestational hypertension and one preeclampsia

Family history: Essential hypertension and diabetes in father and or mother and HDP in mother

Small for gestational age was determined according to Glossary of Obstetrics and Gynecology, 4th edition

From 16 to 21 weeks of gestation, morning systolic HBP was around 100 mmHg (lowest BP). After 21 weeks of gestation, it increased and was above 108 mmHg at 35 weeks of gestation. Immediately after delivery, it rose sharply. It decreased and remained appropriate at 108 mmHg by the fourth postpartum week. This is considered to represent non-pregnant levels of systolic HBP. Systolic HBP in non-pregnant women was equal to that at 35 weeks of gestation (Fig. 1C).

Diastolic HBP was also not different between morning and night. Diastolic HBP at 12 weeks of pregnancy was around 60 mmHg, but it decreased thereafter, reaching its lowest level at 20 weeks of gestation. It was elevated after 29 weeks of gestation and reached more than 70 mmHg at term (71 mmHg at 38 weeks of gestation). Immediately after delivery, it rose sharply. It decreased and remained appropriate at 71 mmHg by the fourth postpartum week. This is considered to possibly represent non-pregnant levels of diastolic HBP. Diastolic HBP in non-pregnant women was also equal to that at 38 weeks of gestation (Fig. 1C).

White coat effect

CBP was measured in outpatients using an automatic sphygmomanometer (HEM-8712). The difference in systole between CBP and HBP in the morning (δBPs = CBPs -HBPs) increased by 10% from 12 to 19 weeks, gradually decreased with gestational week, and decreased significantly at 34 to 36 weeks (4.5 ± 9.0 mmHg at 34 weeks, $p < 0.05$) compared with at 12 to 23 weeks (10.2 ± 9.2 mmHg at 12 to 15 weeks, $p < 0.05$).

On the other hand, diastolic δBP was slightly increased by 2.5% from 12 to 33 weeks of gestation, and by 1-2% after 34 weeks of gestation. However, there was no significant difference (Fig. 2).

Determination of hypertension criteria during pregnancy by HBPM

Polynomial formulae of HBP in the morning for mean, mean +1 SD, mean +2 SD, and mean +3 SD were expressed by Kaleida Graphs (Fig. 3A, B).

For systolic BP, the polynomial formulae were $y = 118–2.30x + 0.0874x^2–0.000919x^3$ ($r^2 = 0.916$) for the mean, $y = 133–2.82x + 0.106x^2–0.00110x^3$ ($r^2 = 0.853$) for the mean + 1 SD, $y = 147–3.35x + 0.124x^2–0.00129x^3$ ($r^2 = 0.751$) for the mean +2 SD, and $y = 161–3.87x + 0.142x^2–0.00147x^3$ ($r^2 = 0.658$) for the mean +3 SD.

The mean systolic HBP at 35 weeks gestation was 108 mmHg, estimated to be the mean standard value for non-pregnant women (Fig. 1C). The polynomial formulae of mean+3 SD was considered optimal at 35 weeks gestation, showing 135 mmHg, the current standard value for non-pregnant HBP by HBPM (Fig. 3A).

The hypertensive borderline of diastolic BP at every gestational week is shown in Table 2.

For diastolic HBP, the polynomial formulae were $y = 84 – 2.47x + 0.0882x^2–0.000881x^3$ ($r^2 = 0.875$) for the mean, $y = 107–3.45x + 0.122x^2–0.00122x^3$ ($r^2 = 0.784$) for the mean +2 SD, and $y = 119–3.95x + 0.140x^2–0.00140x^3$ ($r^2 = 0.684$) for the mean +3 SD.

The mean diastolic HBP at 38 weeks gestation is 72 mmHg, which was estimated to be the mean standard for non-pregnant women (Fig. 1C). The diastolic HBP at 38 weeks gestation was 85 mmHg, which is the current standard for non-pregnant hypertension by HBPM, so a polynomial formula of mean+2 SD was considered optimal (Fig. 3B).

The determined hypertensive boundaries of BP in both systolic and diastolic for each gestational week determined are shown in Fig. 3C.

Characteristic changes in BP before the onset of HDP

The morning systolic and diastolic HBPs for each week of pregnancy for the 12 women who developed HDP are shown in Fig. 4A, B.

The HBP of women who would develop HDP remained at the bottom between 15 and 24 weeks of gestation and increased after 25 weeks of gestation, as in normal pregnant women, but it was higher than that of normal pregnant women at almost all gestational periods (Fig. 4C, D).

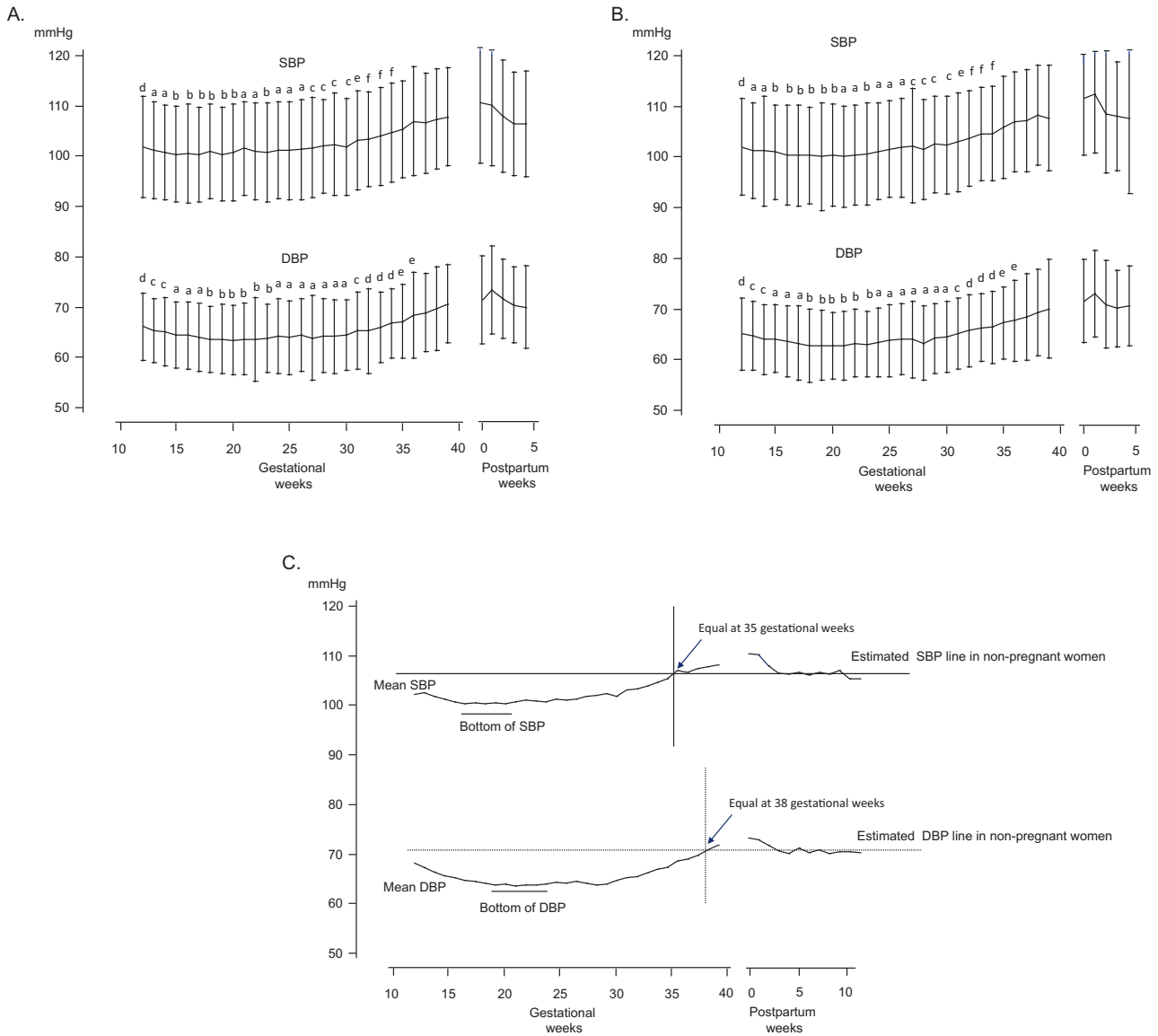


Fig. 1 HBP in every week during pregnancy. HBPM showing average daily BP data for every day in the morning (**A**) and at night (**B**). Data are expressed as means ± SD, $p < 0.05$ by Turky-Krammer HSD test, a: vs. each week at 35–39 gestational week (gw) and at 0–4 postpartum week (pw), b vs. each week at 34–39 gw and at 0–4 pw, c: vs. each week at 36–39 gw and at 0–4 pw, d: vs each week at 37–39 gw and at 0–4 pw, e: vs. each week at postpartum 0–2 pw, f: vs. each week at 0-1 pw. **C** The estimated HBP line in non-pregnant women using HBPM in the morning. The bottom of HBP is appropriate at 100 mmHg in systole and 63 mmHg in diastole at 17 to 21 weeks of gestation. The non-pregnant level of HBP is considered after 4 weeks postpartum. The mean systolic HBP at 35 weeks gestation was 108 mmHg, and estimated to be the mean standard value for non-pregnant women. The mean diastolic HBP at 38 weeks gestation is 72 mmHg, which was estimated to be the mean standard for non-pregnant women

The mean systolic and diastolic HBPs of women with HDP were higher than those of normal pregnant women from early pregnancy to 5 weeks postpartum.

In addition, the lowest BP of women with HDP was higher than that of normal pregnant women (systolic: HDP 101.8 ± 10.0 mmHg, normal pregnancy 95.4 ± 7.9 mmHg; diastolic: HDP 63.9 ± 9.1 mmHg, normal pregnancy 59.7 ± 5.7 mmHg) (Table 2).

In the sub-analysis of HBP change on HDP, individual variability was evaluated by the coefficient of variation (CV). The percent (%) CV was calculated as mean/standard deviation (SD). Furthermore, the δCV, a novel indicator of individual variation, was calculated as follows: 1. the lowest HBP at 16–19 gestational weeks for each woman was determined; 2. δBP = (HBP in each week of pregnancy 16–27) – lowest HBP; 3. the mean and standard deviation (SD) were calculated using the absolute value of δBP; and 4. CV of δBP (δCV) = SD/δ mean value of BP.

First, the %CV of HBP in women who developed HDP (both systolic and diastolic) was equal to that of normal

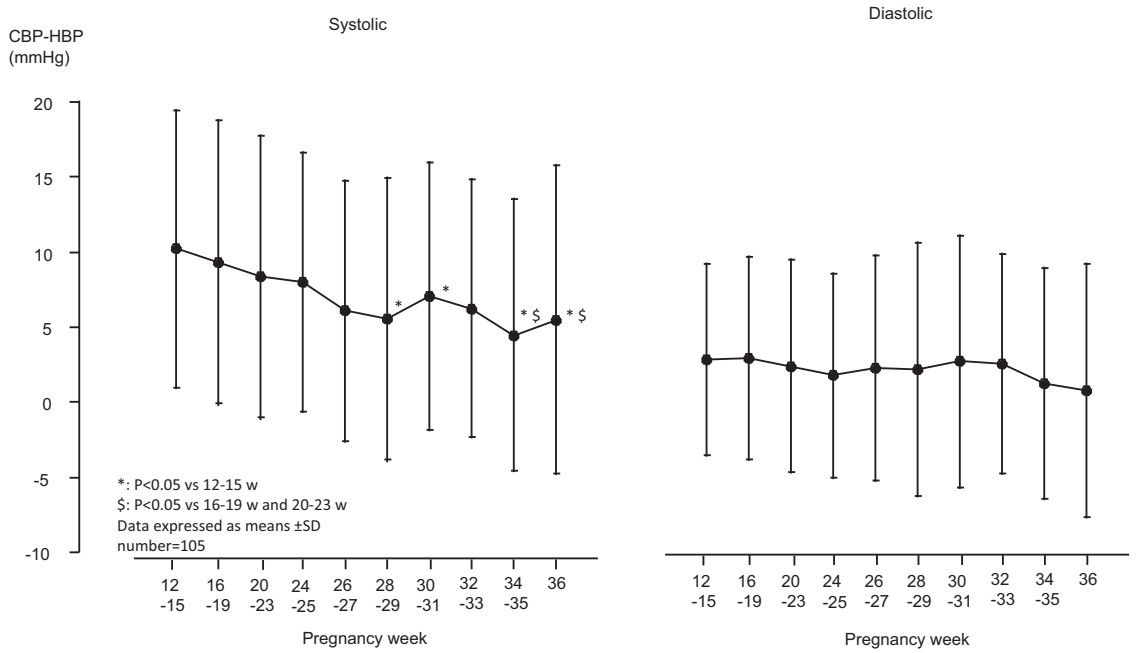
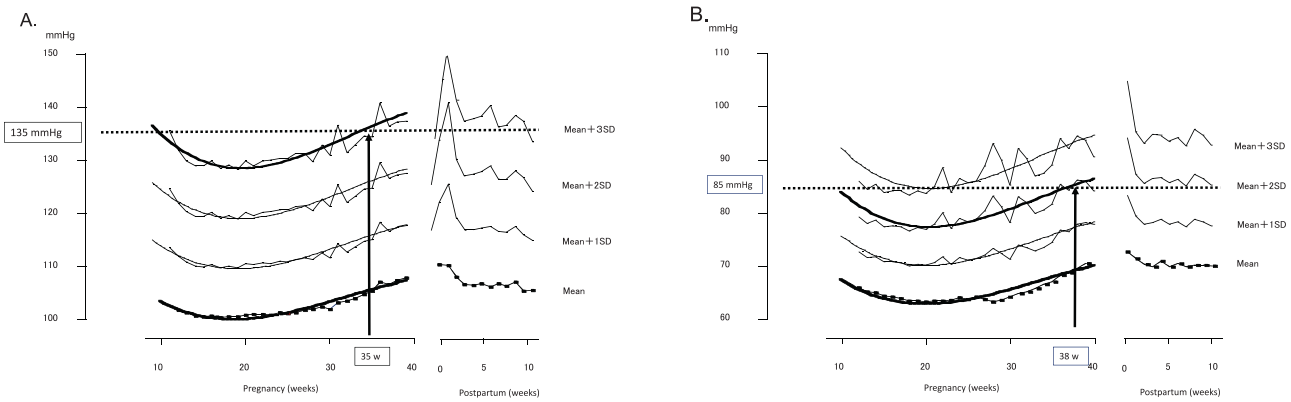


Fig. 2 The white coat effect during pregnancy. The differences of BPs (δBPs) between CBPs and HBPs in the morning are calculated as follows: δBPs = CBPs − HBPs (mmHg). *$p < 0.05$ vs 12–15 weeks of gestation. Data are expressed as means ± SD, Number = 105



C.

Gestational weeks	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38
hypertensive borderline (mmHg)																											
Systolic	132	131	130	129	129	128	128	128	128	128	128	128	128	129	129	130	130	131	132	132	133	134	134	135	136	136	137	138
Diastolic	82	81	80	79	78	78	78	78	78	78	78	78	78	78	78	79	79	80	80	81	81	82	83	83	84	84	85	86

Fig. 3 Determination of the hypertensive cut-off in HBP. **A** Optimizing the polynomial of systolic HBP that induces the hypertensive boundary value by HBPM. By the polynomial equation of mean +3 SD, systolic HBP at 35 weeks gestation equal to non-pregnant was 135 mmHg, the current reference value for non-pregnant hypertension of HBPM. Polynomial of mean +3 SD was considered optimal. **B** Optimization of polynomial of diastolic HBP that induces the hypertensive boundary value by HBPM. By polynomial of mean +2 SD, diastolic HBP at 38 weeks gestation equal to non-pregnant was 85 mmHg, the current standard for non-pregnant hypertension by HBPM. Thus, polynomial of mean +2 SD was considered optimal. **C** Hypertensive borderline BP values at each gestational week. The cut-off values for hypertension at each gestational week could be gained by the polynomial equation mean +3 SD for systolic and mean +2 SD for diastolic

pregnancy at 16–19 gestational weeks, 20-23 gestational weeks, and 24–27 gestational weeks. On the other hand, women who developed HDP at 16–19 and 20–23 weeks of gestation had lower systolic δCV (HDP 2.25 ± 3.21, normal pregnancy 3.50 ± 7.49 at 16–19 gestational weeks; HDP 2.19 ± 3.71, normal pregnancy 3.10 ± 7.10). Patients who developed HDP at 16–19, 20–23 and 24–27 gestational weeks had lower diastolic δCV (HDP 1.36 ± 2.96, normal pregnancy 3.66 ± 8.87 at 16–19 gestational weeks; HDP 1.56 ± 2.57, normal pregnancy 3.50 ± 6.64 at 20–23

Table 2 Differences in the HNP changes between normal pregnancy and HDP

	Normal $n = 206$	HDP $n = 12$	
Systolic BP (mmHg)			
Mean BP			
16–19w	98.5 ± 8.0	104.4 ± 11.3	*
20–23w	98.5 ± 8.2	106.1 ± 10.4	*
24–27w	99.1 ± 7.8	108.2 ± 10.0	*
Minimum BP	95.4 ± 7.9	101.8 ± 10.7	*
%CV			
16–19 weeks	4.1 ± 4.4	4.0 ± 2.0	
20–23 weeks	3.7 ± 1.8	3.6 ± 1.6	
24–27 weeks	4.0 ± 4.0	4.1 ± 1.9	
δCV			
16–19 weeks	3.50 ± 7.49	2.25 ± 3.21	*
20–23 weeks	3.10 ± 7.10	2.19 ± 3.71	*
24–27 weeks	2.67 ± 7.36	2.55 ± 5.24	
Diastolic BP (mmHg)			
Mean BP			
16–19 weeks	62.3 ± 5.7	67.8 ± 8.5	*
20–23 weeks	61.8 ± 5.9	68.2 ± 8.1	*
24–27 weeks	62.1 ± 5.2	71.1 ± 8.6	*
Minimum BP	59.7 ± 5.7	63.9 ± 9.1	*
%CV			
16–19 weeks	5.3 ± 5.1	5.0 ± 2.8	
20–23 weeks	5.0 ± 2.4	4.6 ± 2.9	
24–27 weeks	6.1 ± 7.7	5.8 ± 4.6	
δCV			
16–19 weeks	3.66 ± 8.87	1.36 ± 2.96	*
20–23 weeks	3.50 ± 6.64	1.56 ± 2.57	*
24–27 weeks	2.44 ± 2.90	0.86 ± 0.77	*

*$P < 0.05$ vs normal pregnancy

gestational weeks; HDP 0.86 ± 0.77, normal pregnancy 2.44 ± 2.90 at 24–27 gestational weeks (Table 2).

Discussion

This multicenter study of HBPM of Japanese pregnant women targeted pregnant women belonging to the non-high risk HDP group.

We took care of selecting the low risk pregnant women by excluding women complicated with essential hypertension, diabetes mellitus, gestational diabetes, thyroid dysfunction, renal dysfunction, and psychiatric disorders. Furthermore, we invited participants from general practitioners and non-higher tertiary hospital. Of 218 participants analyzed, 57 were at general practitioners and 14 were at non- higher tertiary hospitals. Thus, we are confident that the participants were "non-high risk" groups of HDP because we were able to take into account the decrease in bias in this study.

In this study, the incidence of HDP was 5.5% (12/218), while its preeclampsia was 0.5%.

The incidence of HDP in the Japan Society of Obstetrics and Gynecology perinatal registry database (JSOG database) in 2015 [8] was 4.1% and about half of them were preeclampsia.

The usual incidence of HDP is estimated to be about 10% incidence. The JSOG database is from higher tertiary institutions, which often pick up severe HDP, but not non-severe HDP, which may explain the lower incidence rate. On the other hand, this study was conducted at a facility affiliated with JSSHP, and therefore, it is likely that the number of non-severe GH cases was well represented in the data. Based on those results, the HDP incidence rate is lower in JSOG database, and this study well reflects non-severe HDP, resulting in similar numbers.

The JSOG database on preeclampsia was collected from higher tertiary institutions, and therefore, early-onset preeclampsia was well represented in the data. In this study, we excluded chronic hypertension and complicated pregnancies, and included participants from non-higher tertiary institutions to include as many non-high risk pregnant women. As a result, the incidence of preeclampsia was low, with only one case (0.5%) of late-onset, non-severe preeclampsia from a non-higher tertiary institution.

There have been large-scale studies of HBPM in Japanese pregnant women [9–11].

Pregnant women's HBP was lowest in both systole and diastole between 17 and 21 weeks of gestation, and CBP was lowest around 20 weeks. Both BPs increased thereafter, and by the end of pregnancy, they were similar to pre-pregnancy levels [12, 13]. HBP was generally lower than CBP, and the trend of morning and evening HBP was similar, consistent with previous reports. [10, 11] Systolic BP was significantly higher in mid-pregnancy than in late pregnancy. Furthermore, it was not different between morning and night HBPs.

The criteria for hypertension on HBPM in non-pregnant women is a systolic BP of 135 mmHg or higher and/or a diastolic BP of 85 mmHg or higher. However, there is insufficient evidence to say whether the same criteria should be applied to HBPM in pregnant women.

Using the correlation between HBP and CBP, Mikami et al. reported that the borderline for hypertension of pregnant women in HBP was 121 mmHg systolic and 82 mmHg diastolic in the first trimester, 124 mmHg systolic and 85 mmHg diastolic in the first half of the second trimester, 126 mmHg systolic and 85 mmHg diastolic in the second half of the second trimester, and 135 mmHg systolic and 89 mmHg diastolic in the third trimester [11].

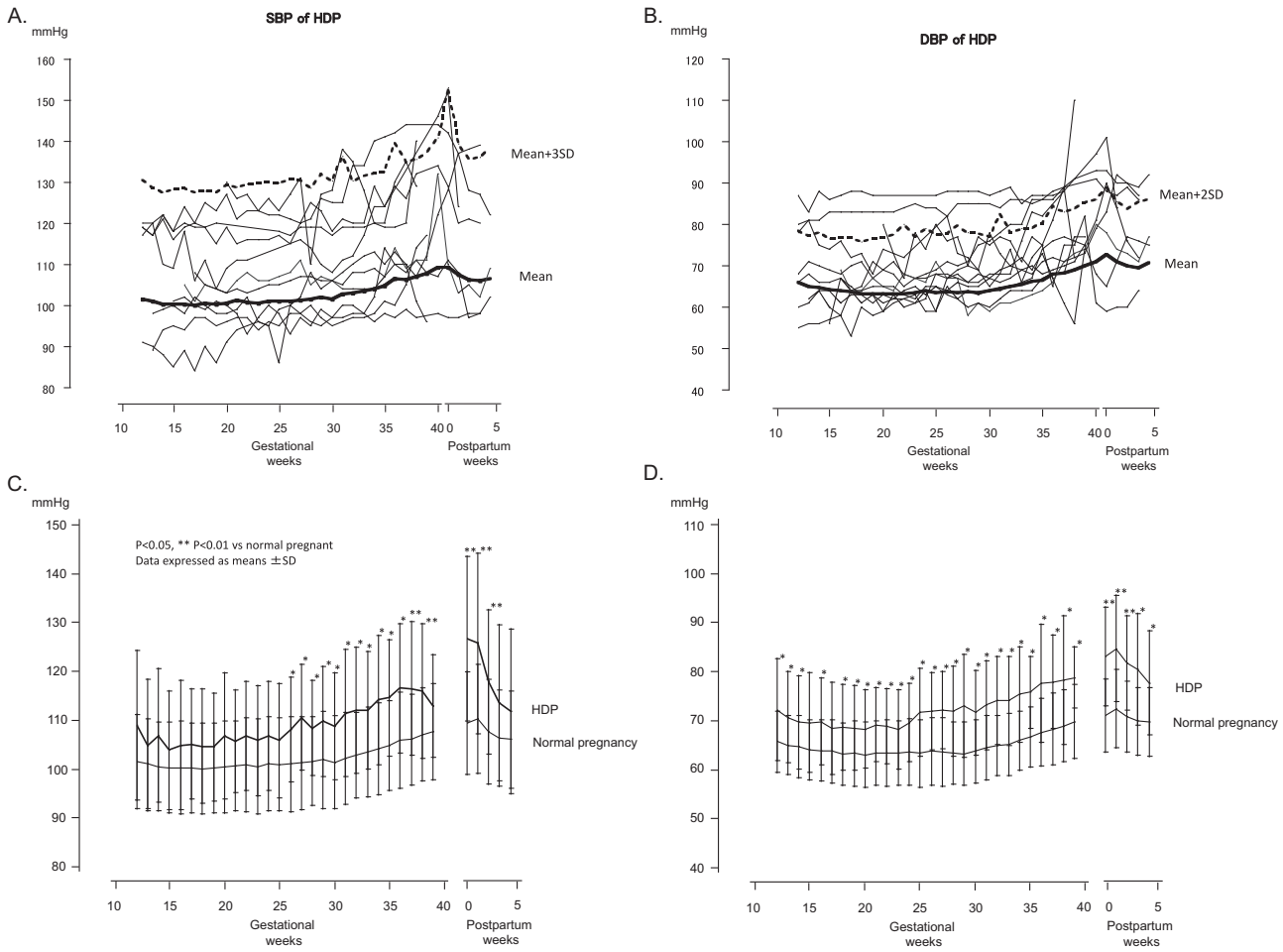


Fig. 4 HBPs in the morning in 12 women who developed HDP. The line graph shows systolic (**A**) and diastolic (**B**) HBPs in every HDP woman. The average HBP, systolic (**C**) and diastolic (**D**), of HDP compared with that in normal pregnancy. $P < 0.05$, $^{**}P < 0.01$ vs normal pregnancy. Data are expressed as means ± SD

If we focus on 135/85 mmHg, which is the criterion for hypertension in HBPM in non-pregnant women, we can analyze the results of Fig. 3 and find that the mean+3 SD for systolic HBP and the mean+2 SD for diastolic HBP are appropriate, since 135/85 mmHg is reached in late pregnancy. In non-pregnant women, hypertension is defined as a CBP of 140/90 mmHg or higher, whereas for HBP it is 135/85 mmHg or higher. Similarly in late pregnancy, an HBP of 135/85 mmHg or higher might be sufficient for a diagnosis of HDP.

Using the polynomial equation of the mean +3 SD for systolic HBP and the mean +2 SD for diastolic HBP, the hypertension cut-off for each week could be determined for the hypertension criteria for HDP in HBPM during pregnancy. Therefore, the threshold of hypertension diagnosis was calculated for systolic HBP to be 129 mmHg at 15 weeks of pregnancy, 128 mmHg at 20 weeks of pregnancy, 129 mmHg at 25 weeks of pregnancy, and 132 mmHg at 30 weeks of pregnancy. The threshold of hypertension diagnosis for diastolic HBP was calculated to be 79 mmHg at 15 weeks of gestation, 78 mmHg at 20 weeks of gestation, 78 mmHg at 25 weeks of gestation, and 81 mmHg at 30 weeks of pregnancy. In that case, the reference value for hypertension would be less than 135/85 mmHg in non-pregnant women due to gestational changes.

These results suggest that although the diagnostic criterion for HDP has been a BP of 140/90 mmHg or higher at all stages of pregnancy, it may be necessary to set the reference BP according to the stage of pregnancy.

However, in order to determine the standard for hypertension in pregnant women, it is necessary to consider the perinatal outcome of each pregnant woman.

In pregnant women, increased systolic BP in the clinic due to the white coat phenomenon decreased significantly in late pregnancy. These changes are consistent with the commonly reported changes in WCH. This change is most likely due to familiarity with the clinic. On the other hand, it has been demonstrated that pregnant women with WCH are more likely to develop HDP than those without WCH [14],

but the relationship between the white coat phenomenon and the development of HDP was not clear, because the number of cases of HDP in the present study was small.

As shown in Fig. 4, pregnant women with HDP showed the same HBP variation during the course of pregnancy as normal pregnant women. However, both systolic and diastolic HBPs were higher from the beginning of pregnancy than in normal subjects. These results suggest that HBP in early pregnancy may be able to predict the onset of HDP after 20 weeks of pregnancy. Compared to normal pregnant women at around 20 weeks of gestation, the HBPs of women who would develop HDP were all significantly higher, and the BPs of women who would develop HDP did not exceed the threshold of hypertension diagnosis. However, these differences are so small that it would be difficult to predict hypertension.

Measuring BP variability is useful to evaluate cardiovascular disease. Several studies found that the increases in office [15–17], ambulatory [17–21], and home [22–25] BP variability were correlated with adverse cardiovascular outcomes independent of the BP level. Although the first studies that showed the potential dangers of high BP variability used office and ambulatory BP measurements to quantify BP variability, HNPM could offer a more widely available and feasible option for assessing BP variability.

HBP variability has been assessed with different indices, such as SD, coefficient of variation (CV), and variation independent of the mean (VIM). SD is the simplest statistical measure for describing variation, but it is problematic, because it is highly dependent on the individual's BP level. CV is derived from the SD by dividing it by the mean. Consequently, CV is less affected by the BP level and is therefore considered an appropriate index in BP variability studies [26].

HBP variability using CV therefore might be a stronger indicator as a risk factor for cardiovascular disease in nearly all populations [24]; however, in the present study, there was no difference in CV between the HDP-onset group and the normal pregnancy group.

Therefore, we wondered why there was no difference in CV in this study. It is known that CV is strongly dependent on the mean value. Rothwell et al. [15, 27] therefore proposed BP variability independent of the mean (VIM), which might be a better predictor of cardiovascular outcomes over and beyond the BP level.

VIM is a transformation of SD that is defined to be not correlated with mean BP [15]. VIM is calculated as the SD divided by the mean to the power x and multiplied by the population mean to the power x. The power x is obtained by fitting a curve through a plot of SD against the mean using the model $SD = a \times \text{mean}\ x$, where x was derived by nonlinear regression analysis.

In the present study, the diurnal variation of HBP was evaluated using δCV as a novel index independent of the mean value. Since δCV is determined by the difference between the lowest HBP (bottom value of HBP during pregnancy) of each individual from 12 to 25 weeks of gestation and the difference at each week (δBP = HBP - lowest HBP), using δBP reduces the effect of the mean on CV.

The systolic and diastolic δCVs at 16-23 weeks of gestation were significantly lower in women with HDP than in normal pregnancies. This suggests that the δCV in early pregnancy may be useful for predicting HDP.

BP variability is regulated by the baroreflex. When BP rises, the sympathetic nervous system is inhibited, and conversely, the parasympathetic nervous system is stimulated, which decreases vascular resistance and heart rate, resulting in an immediate decrease in BP, and vice versa when BP decreases [28]. The baroreceptor reflex serves as a "buffering" mechanism to control sudden fluctuations in BP, and BP variability has been reported to be increased in patients with hypertension and CHD due to abnormalities in the baroreflex, by office BP [17], ambulatory BP [18], and home BP [24, 25].

This is the first report to examine the day-by-day variation of BP in women who developed HDP using HBP. Initially, we expected that the variability of HBP would be smaller in pregnant women who develop HDP than in normotensive women. However, the present study showed that, on the contrary, δCV was lower in pregnant women who developed HDP than in normotensive women.

There might be a few reasons, as follows:

1. Pregnancy is associated with a marked decrease in peripheral vascular resistance due to activation of endothelial-derived relaxing factors, especially nitric oxide (NO) [29, 30]. One possible mechanism by which the baroreflex, which modulates vascular constriction, is suppressed during pregnancy [31–34] is through increased NO [30, 35, 36]. Indirect evidence in support of this possibility is that NO reduces the baroreflex systemically [37] or centrally [38] and improves the baroreflex by blocking NO synthase (NOS). Thus, BP variability might be increased due to baroreflex reduction by NO during pregnancy.

   HDP, especially preeclampsia, was found to have reduced production of [39] or responsiveness [40] to NO. There might be decreased BP variability by a suppressed baroreflex due to NO dysfunction in women who develop HDP.
2. In this study, most of the women who developed HDP were classified as GH (one preeclampsia and 11 GH). Since most of the studies conducted so far on HDP and BP have been on baroreflex and autonomic nervous system (ANS) involvement in preeclampsia, this may have led to different results from the present study [41].

There is no report of BP variability in HBPM for GH. BP variability is associated with a higher incidence of CVD when it is large [25, 26]. GH was defined as hypertension without proteinuria, maternal organ failure, stroke, neurological complications, hematological complications, or uteroplacental insufficiency. If GH developed organ damage, it is classified with preeclampsia. Thus, we expected BP variability to be less variable in GH than in preeclampsia.

However, since this study was conducted in a non-high risk group, we could not examine BP variability of preeclampsia, especially late-onset preeclampsia, because it was not observed. Further comparative studies between GH and preeclampsia are needed.

GH has a high rate of postpartum conversion to chronic hypertension, suggesting the presence of some organ damage. We had assumed that BP variability would increase due to organ damage compared to normal pregnant women, although not as much as in preeclampsia at least. However, the results were the opposite, BP variability was more decreased in GH. It is known that in pregnancy, the sympathetic nervous system is suppressed by estrogen and other factors [42], and BP variability is increased. The changes in BP variability during pregnancy are not simple. Further study should be investigated in GH.

In one large cross-sectional study comparing the increase in heart rate variability, BP variability, and the baroreflex in HDP classified as PE or GH showed that, although there was a significant increase in BP variability in preeclampsia, this increase did not lead to a spontaneous increase in the baroreflex [42] by the sequence method to estimate the baroreflex. However, Weber et al. also used the same method, but the results obtained were contradictory [43]. Further examination of the baroreflex and ANS alteration in HDP, including GH, is needed.

Perspectives in Asia

The criteria for hypertension in HBP in pregnant women have not been established. A single-center prospective study in Japan showed that the criteria for hypertension were lower than those for non-pregnant women and differed according to the time of pregnancy [11].

In this study, new hypertension criteria by HBPM will be useful for the management of HDP in Asia, including Japan. Furthermore, it will be used as one of the representative study in Asia to develop world-class hypertension criteria for pregnant women similar to that in non-pregnant women [44].

Conclusions

This multicenter study evaluated HBPM in Japanese pregnant women in the non-high risk HDP group. To determine hypertension by HBPM, systolic HBP of approximately 130 mmHg from 15 to 25 weeks of gestation and 135 mmHg from 35 weeks of gestation onward, and diastolic HBP of approximately 80 mmHg from 15 to 25 weeks of gestation and 85 mmHg from 38 weeks of gestation onward are considered appropriate. Furthermore, it is thought that δCV might be useful for early detection of HDP.

References

1. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion J, Mancia G, et al. on behalf of the European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. J Hypertens. 2003;21:821–48.
2. Bobrie G, Chatellier G, Genes N, Clerson P, Vaur L, Vaisse B, et al. Cardiovascular prognosis of 'masked hypertension' detected by blood pressure self-measurement in elderly treated hypertensive patients. JAMA. 2004;291:1342–9.
3. Parati G, Stergiou G, O'Brien E, Asmar R, Beilin L, Bilo G, et al. European Society of Hypertension guidelines for blood pressure monitoring at home: a summary report of the Second International Consensus Conference on Home Blood Pressure Monitoring. J Hypertens. 2008;26:1505–26.
4. Liyanage-Don N, Fung D, Phillips E, Kronish IM. Implementing Home Blood Pressure Monitoring into Clinical Practice. Curr Hypertens Rep. 2019;21:14.
5. The Japanese Society of Hypertension. Guidelines Subcommittees of the Japanese Society of Hypertension. Guidelines for the Management of Hypertension 2014. The Japanese Society of Hypertension, Life Science Publishing Co, Ltd. 2014.
6. Watanabe K, Matsubara K, Nakamoto O, Ushijima J, Ohkuchi A, Koide K, et al. Outline of the new definition and classification of "Hypertensive Disorders of Pregnancy (HDP)"; a revised JSSHP statement of 2005. Hypertens Res Pregnancy. 2018;6:33–37.
7. Glossary of Obstetrics and Gynecology, 4th edition, ed. Japan Society of Obstetrics and Gynecology, 2018, p255-6.
8. Best practice guide 2021 for care and treatment of hypertension in pregnancy. ed. Japan society for the study of hypertension in pregnancy, Medical View. 2021. p52-4.
9. Inoue M, Tsuchihashi T, Hasuo Y, Ogawa M, Tominaga M, Arakawa K, et al. Salt Intake, Home Blood Pressure, and Perinatal Outcome in Pregnant Women. Circ J. 2016;80:2165–72.
10. Metoki H, Ohkubo T, Obara T, Akutsu K, Yamamoto M, Ishikuro M, et al. Daily Serial Hemodynamic Data During Pregnancy and Seasonal Variation: The BOSHI Study. Clin Exp Hypertension. 2012;34:290–6.
11. Mikami Y, Takai Y, Era S, Ono Y, Saitoh M, Baba K, et al. Provisional criteria for the diagnosis of hypertension in pregnancy using home blood pressure measurements. Hypertens Res. 2017;40:679–84.
12. Hibbard J, Shroff S, Cunningham F. Cardiovascular alterations in normal and preeclamptic pregnancy.: Elsevier-Academic Press, San Diego, CA; 2015.
13. Umemura S, Arima H, Arima S, Asayama K, Dohi Y, Hirooka Y, et al. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019). Hypertens Res. 2019;42:1235–481.
14. Ohkuchi A, Hirashima C, Arai R, Takahashi K, Suzuki H, Ogoyama M, et al. Temporary hypertension and white coat hypertension in the first trimester as risk factors for preeclampsia. Hypertens Res. 2019;42:2002–12.

15. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet. 2010;375:895–905.
16. Hata Y, Kimura Y, Muratani H, Fukiyama K, Kawano Y, Ashida T, et al. Office blood pressure variability as a predictor of brain infarction in elderly hypertensive patients. Hypertens Res. 2000;23:553–60.
17. Eguchi K, Hoshide S, Schwartz JE, Shimada K, Kario K. Visit-to-visit and ambulatory blood pressure variability as predictors of incident cardiovascular events in patients with hypertension. Am J Hypertens. 2012;25:962–8.
18. Stolarz-Skrzypek K, Thijs L, Richart T, Li Y, Hansen TW, Boggia J, et al. Blood pressure variability in relation to outcome in the International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome. Hypertens Res. 2010;33:757–66.
19. Kario K, Pickering TG, Umeda Y, Hoshide S, Hoshide Y, Morinari M, et al. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. Circulation. 2003;107:1401–6.
20. Mancia G, Bombelli M, Facchetti R, Madotto F, Corrao G, Trevano FQ, et al. Long-term prognostic value of blood pressure variability in the general population: results of the Pressioni Arteriose Monitorate Loro Associazioni Study. Hypertension. 2007;49:1265–70.
21. Hansen TW, Thijs L, Li Y, Boggia J, Kikuya M, Björklund-Bodegård K, et al. International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes Investigators. Prognostic value of reading-to-reading blood pressure variability over 24 hours in 8938 subjects from 11 populations. Hypertension. 2010;55:1049–57.
22. Johansson JK, Niiranen TJ, Puukka PJ, Jula AM. Prognostic value of the variability in home-measured blood pressure and heart rate: the Finn-Home Study. Hypertension. 2012;59:212–8.
23. Kikuya M, Ohkubo T, Metoki H, Asayama K, Hara A, Obara T, et al. Day-by-day variability of blood pressure and heart rate at home as a novel predictor of prognosis: the Ohasama study. Hypertension. 2008;52:1045–50.
24. Asayama K, Ohkubo T, Kikuya M, Obara T, Metoki H, Inoue R, et al. Prediction of stroke by home "morning" versus "evening" blood pressure values: the Ohasama study. Hypertension. 2006;48:737–43.
25. Kato T, Kikuya M, Ohkubo T, Satoh M, Hara A, Obara T, et al. Factors associated with day-by-day variability of self-measured blood pressure at home: the Ohasama study. Am J Hypertens. 2010;23:980–6.
26. Mena L, Pintos S, Queipo NV, Aizpurua JA, Maestre G, Sulbaran T. A reliable index for the prognostic significance of blood pressure variability. J Hypertens. 2005;23:505–11.
27. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, et al. Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. Lancet Neurol. 2010;9:469–80.
28. PaolaA A, Lanfranch, Virend KS. Arterial baroreflex function and cardiovascular variability: interactions and implications. Am J Physiol Regul Integr Comp Physiol. 2002;283:R815–R826.
29. McLaughlin MK, Conrad KP. Nitric oxide biosynthesis during pregnancy: Implications freduction or circulatory changes. Clin Exp Pharm Physiol. 1994;22:164–71.
30. Sladek SM, Magness RR, Conrad KP. Nitric oxide and pregnancy. Am J Physiol Regul Integr Comp Physiol. 1997;272:R441–R463.
31. Brooks VL, Dampney RA, Heesch CM. Pregnancy and the endocrine regulation of the baroreceptor reflex. Am J Physiol Regul Integr Comp Physiol. 2010;299:R439–R451.
32. Heesch CM, Foley CM. CNS effects of ovarian hormones and metabolites on neural control of circulation. Ann N. Y Acad Sci. 2001;940:348–60.
33. Fu Q, Levine BD. Autonomic circulatory control during pregnancy in humans. Semin Reprod Med. 2009;27:330–7.
34. Rang S, Wolf H, Montfrans GA, Karemaker JM. Non-invasive assessment of autonomic cardiovascular control in normal human pregnancy and pregnancy- associated hypertensive disorders: a review. J Hypertens. 2002;20:2111–9.
35. McLaughlin MK, Conrad KP. Nitric oxide biosynthesis during pregnancy: implications for circulatory changes. Clin Exp Pharm Physiol. 1995;22:164–71.
36. Weiner CP, Thompson LP. Nitric oxide and pregnancy. Semin Perinatol. 1997;21:367–80.
37. Liu JL, Murakami H, Zucker IH. Effects of NO on baroreflex control of heart rate and renal nerve activity in conscious rabbits. Am J Physiol Regul Integr Comp Physiol. 1996;270:R1361–R1370.
38. Matsumura K, Abe I, Tsuchihashi T, Fujishima M. Central nitric oxide attenuates the baroreceptor reflex in conscious rabbits. Am J Physiol Regul Integr Comp Physiol. 1998;274:R1142–R1149.
39. Poston L, McCarthy AL, Ritter JM. Control of vascular resistance in the maternal and fetoplacental arterial beds. Pharmacol Therapeutics. 1995;65:215–39.
40. Suzuki Y, Kajikuri J, Suzumori K, Itoh T. Mechanisms underlying the reduced endothelium-dependent relaxation in human omental resistance artery in pre-eclampsia. J Physiol. 2000;527:163–74.
41. Yousif D, Bellos I, Penzlin AI, Hijazi MM, Illigens BM, Pinter A, et al. Autonomic dysfunction in preeclampsia: A systematic Review. Front Neurol. www.frontiersin.org.
42. Weber TM, Lackner HK, Roessler A, Papousek I, Kolovetsiou-Kreiner V, Lucovnik M, et al. Heart rate variability and baroreceptor reflex sensitivity in early- versus late-onset preeclampsia. PLoS ONE. 2017;12:e0186521.
43. Faber R, Baumert M, Stepan H, Wessel N, Voss A, Walther T. Baroreflex sensitivity, heart rate, and blood pressure variability in hypertensive pregnancy disorders. J Hum Hypertens. 2004;18:707–12.
44. Niiranen TJ, Asayama K, Thijs L, Johansson JK, Ohkubo T, Kikuya M, et al. Outcome-driven thresholds for home blood pressure measurement: international database of home blood pressure in relation to cardiovascular outcome. Hypertension. 2013;61:27–34.

Acknowledgements The authors would like to thank the following collaborators: Gen Ishikawa, Masahiro Ohashi, Mitsumasa Shimazu, Takuya Saitoh, Chiharu Fukue, Ai Iwasaki, Kenji Yamaguchi, Koji Kanda, Keisuke Fukui, and Hiroki Suzuki.

Funding This work was supported by Intramural Research Fund (28-4-2) for Cardiovascular Disease of the National Cerebral and Cardiovascular Center and by the 2015 JSSHP Foundation.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.

Affiliations

Yoshikatsu Suzuki[1] · Keiichi Matsubara[2] · Kazushi Watanabe[3] · Kanji Tanaka[4] · Tamao Yamamoto[1] · Tomoyoshi Nohira[5] · Kazuya Mimura[6] · Hirotada Suzuki[7] · Fumiaki Hamada[8] · Shintarou Makino[9] · Keiko Koide[10] · Haruki Nishizawa[11] · Katsuhiko Naruse[12] · Yukiko Mikami[13] · Ikuno Kawabata[14] · Jun Yoshimatsu[15] · Kohta Suzuki[16] · Shigeru Saito[17]

[1] Department of Obstetrics and Gynecology, Fukiage Maternity Clinic, Nagoya, Japan

[2] Department of Obstetrics and Gynecology, Ehime University School of Medicine, Toon, Japan

[3] Department of Obstetrics and Gynecology, Perinatal and Neonatal Medical Center, Aichi Medical University School of Medicine, Nagakute, Japan

[4] Perinatal Medical Center, Hirosaki University Hospital, Hirosaki, Japan

[5] Department of Obstetrics and Gynecology, Tokyo Medical University, Tokyo, Japan

[6] Department of Obstetrics and Gynecology, Osaka University Graduate School of Medicine, Suita, Japan

[7] Department of Obstetrics and Gynecology, Jichi Medical University School of Medicine, Shimotuke, Japan

[8] Department of Perinatology and Gynecology, Kochi Prefectural Hata Kenmin Hospital, Sukumo, Japan

[9] Department of Obstetrics and Gynecology, Juntendo University Faculty of Medicine, Tokyo, Japan

[10] Department of Obstetrics and Gynecology, Showa University School of Medicine, Tokyo, Japan

[11] Department of Obstetrics and Gynecology, Fujita Health University, Toyoake, Japan

[12] Department of Obstetrics and Gynecology, Nara Medical University, Kashihara, Japan

[13] Department of Obstetrics and Gynecology, Saitama Medical University, Kawagoe, Japan

[14] Department of Obstetrics and Gynecology, Nippon Medical School, Tokyo, Japan

[15] Department of Obstetrics and Gynecology, National Cerebral and Cardiovascular Center, Suita, Japan

[16] Department of Health and Psychosocial Medicine, Aichi Medical University School of Medicine, Nagakute, Japan

[17] Department of Obstetrics and Gynecology, University of Toyama, Toyama, Japan