



Temporary hypertension and white coat hypertension in the first trimester as risk factors for preeclampsia

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Abstract

We compared the risk of preeclampsia (PE) among women with normal blood pressure (BP), high-normal BP, high BP, temporary hypertension (THT), white coat hypertension (WCH), and chronic hypertension (CH) in the first trimester. This was a retrospective cohort study involving 2858 pregnant women, who received regular maternal checkups at <12 weeks. BP levels were evaluated using the average of the second and third BP readings. When patients showed HT in the first trimester that later normalized during 14–19 weeks, we called this condition THT. BP levels were classified as normal BP, high-normal BP, high BP, THT, WCH, and CH. PE was defined as a new onset of HT after 20 weeks accompanied by either proteinuria or other organ dysfunctions. Gestational hypertension (GH) was defined as the new onset of HT after 20 weeks. The proportion of WCH in women with newly diagnosed HT was 47%. PE occurred in 1.3, 4.3, 8.1, 8.2, 14.3, and 25.0% of women with normal BP, high-normal BP, high BP, THT, WCH, and CH, respectively. GH occurred in 0.3, 1.8, 9.9, 2.0, and 28.6% of women with normal BP, high-normal BP, high BP, THT, and WCH, respectively. After adjusting for possible confounding variables, high-normal BP, high BP, THT, WCH, and CH were independent risk factors for PE vs. normal BP; in addition, high-normal BP, high BP/THT, and WCH were independent risk factors for GH vs. normal BP. In conclusion, THT and WCH in the first trimester were risk factors for PE, and WCH was a risk factor for GH.

Keywords White coat hypertension · Chronic hypertension · Gestational hypertension · Preeclampsia · Prognosis

Introduction

Hypertension (HT) is a major risk factor for cardiovascular diseases (CVD) [1]; similarly, hypertensive disorders of pregnancy (HDPs) are also known to be a major risk factor for CVD [2, 3]. Recently, Mito et al. [4] reported that HDP is a strong risk factor for subsequent HT 5 years after delivery and that the occurrence age of HT following HDP was relatively young: the average age was 39.0 years old. This

evidence suggests that long-term postpartum management for women with HDPs might be necessary for preventing the occurrence of CVD.

The number of elderly pregnant women are rapidly increasing in Japan. For example, in 1995, 2005, and 2016, deliveries involving women ≥ 35 years old accounted for 9.5, 16.4, and 28.5%, respectively, of all deliveries, and those involving women ≥ 40 years old accounted for 1.1, 1.9, and 5.6%, respectively [5]. Accordingly, the number of pregnant women with HT or diabetes mellitus is also gradually increasing. Recently, for the diagnosis of HT in pregnancy, home blood pressure (HBP) monitoring (HBPM) and ambulatory blood pressure monitoring (ABPM) have been used [6], although diagnoses of gestational hypertension (GH) and preeclampsia (PE) have been made according to the criteria for clinic blood pressure (BP) measurement in Japan [7, 8]. Correct measurement of BP is mandatory for the diagnosis of HT. Because BP levels in individuals show fluctuation [9, 10], the Japan Society for the Study of Hypertension in Pregnancy recommended that a diagnosis of HT should be made based on BP levels

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measured during at least two different opportunities [11]. In addition, it is usually difficult for outpatients to accurately measure BP in a clinical setting, although the BP in strict accordance with the procedure to measure the clinic BP shows a value comparable to that of HBPM and ABPM [12, 13]. Moreover, in patients showing HT based on the clinic BP, it is estimated that $\geq 15\%$ of them actually show white coat hypertension (WCH): WCH is a condition wherein the BP level measured in a clinical setting is at a hypertensive level but the BP level measured in a non-clinical setting is within the normal range [6]. WCH is diagnosed using only HBPM or ABPM.

To the best of our knowledge, only two studies have attempted to answer the following clinical questions: (1) how frequently women with WCH and chronic hypertension (CH) develop PE and (2) how frequently women with WCH develop GH [14, 15]. It is not also known whether pregnant women with CH develop PE more frequently than those with WCH [16, 17].

Relatively high BP levels (SBP/DBP $\geq 130/80$ mmHg) and CH at the first medical examination are risk factors for PE [18]. We previously reported that BP levels of 120–129/80–84 as well as 130–139/85–89 mmHg in the first and second trimesters were risk factors for the occurrence of both GH and PE [19, 20]. Recently, the American College of Cardiology/American Heart Association Task Force changed the definition of HT from SBP/DBP of $\geq 140/90$ mmHg to $\geq 130/80$ mmHg, based on several sources of evidence on the association between SBP/DBP and cardiovascular diseases, suggesting that BP levels of 130–139/80–89 mmHg are not normal, considering the high later occurrence of adverse vascular events [21]. In addition, the Japan Society of Hypertension (JSH) changed the nomination and definition of the classification of normal-range BP in The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019): in the JSH 2014, normal-range BP was classified as optimal BP (clinic SBP < 120 and DBP < 80 mmHg), normal BP (clinic SBP: 120–129 and/or DBP: 80–84 mmHg), high-normal BP (clinic SBP: 130–139 and/or DBP: 85–89 mmHg); however, in the JSH 2019, normal-range BP was reclassified and renamed as follows: normal BP (clinic SBP < 120 and DBP < 80 mmHg), high-normal BP (clinic SBP: 120–129 and DBP < 80 mmHg), high BP (clinic SBP: 130–139 and/or DBP: 80–89 mmHg) [22]. The reasons for such changes in the nomination and definition of classification of normal-range BP were mainly two: first, adults with BP levels of 120–129/80–84 mmHg showed a higher incidence of cerebral cardiovascular disease than those with BP levels of $< 120/80$ mmHg [23–25]; second, adults with BP levels of 120–139/80–89 mmHg frequently progressed to HT in their lifetime [26]. Interestingly, in our previous study, the adjusted odds ratio (aOR) of PE in women with a BP level of 120–129/80–84 or 130–139/

85–89 mmHg in the second trimester was 5.1 and 8.3, respectively, compared with a BP level of $< 120/80$ mmHg, which yielded almost 1/3- to 1/2-fold the aOR of PE in women with CH [20], suggesting that the higher BP of $\geq 120/80$ mmHg during pregnancy may not be a normal condition. Therefore, BP levels during pregnancy should also be subdivided. In addition, pregnancy itself has a specific effect on BP levels in the second trimester; some pregnant women show a mid-trimester BP drop [27–29]. We recently noticed that some women with HT in the first trimester show a normal BP in the second trimester; thus, we designated this tentative HT (SBP/DBP $\geq 140/90$ mmHg) in the first trimester with mid-trimester BP-level reductions to SBP/DBP $< 140/90$ mmHg as temporary HT (THT).

Our first aim was to compare the risk of PE among women with normal BP, high-normal BP, and high BP, THT, WCH, and CH in the first trimester. The second aim was to investigate whether high-normal BP, high BP, THT, and WCH were risk factors for the occurrence of GH. The third aim was to evaluate whether high BP levels are independent risk factors for the occurrence of PE or GH after adjusting for other relevant risk factors.

Methods

Design

This was a retrospective cohort study conducted after approval by our Institutional Ethics Committee (Rin-Dai15-167). The data on clinic BP in all pregnant women were collected using Omron HEM-906[®] (OMRON Healthcare, Co. Ltd., Japan), whose algorithm for calculating SBP/DBP was already validated for measuring BP in adults (information not open to the public). The data on HBP in some women with suspected HT, WCH, and CH were collected using HBPM (Omron HEM-5001[®] [OMRON Healthcare, Co. Ltd., Japan] and Omron HEM-7080IC[®] [OMRON Healthcare, Co. Ltd., Japan]), whose algorithms for calculating SBP/DBP were demonstrated to be accurate for use predominantly in an outpatient antenatal clinical setting [30].

Protocol and diagnosis of HT and classification of BP levels

During the current pregnancy, we measured clinic BP using an automated digital oscillometric sphygmomanometer. BP was measured three times consecutively at 15-s intervals after 1–2 min of rest in the waiting room. We suspected HT based on clinic BP in the following cases: (1) SBP ≥ 140 mmHg by clinic BP measurement on the second and/or third measurements during pregnancy and the puerperal period, (2) DBP ≥ 90 mmHg by clinic BP measurement on the second and/or

third measurements during pregnancy and the puerperal period. When a pregnant woman did not show HT in the first half of the pregnancy period, we considered her as not having HT. THT was diagnosed when pregnant women showed tentative HT (SBP/DBP \geq 140/90 mmHg) in the first trimester, but showed mid-trimester BP level reductions to SBP/DBP $<$ 140/90 mmHg.

WCH and CH were diagnosed if SBP \geq 140 mmHg and/or DBP \geq 90 mmHg were observed upon averaging the second and third BP readings using a clinic or an office BP device, at least two times on different consecutive occasions. HT criteria for either WCH or CH by HBPM or ABPM during pregnancy and the puerperal period were as follows: (1) for HBPM, HT was defined when mean SBP \geq 135 mmHg and/or mean DBP \geq 85 mmHg using BP measured in the morning and at bedtime for 5–7 days (JSH 2014, JSH 2019) [6, 22], (2) for ABPM, HT was defined when (a) 24-h SBP \geq 130 mmHg and/or 24-h DBP \geq 80 mmHg, (b) daytime SBP \geq 135 mmHg and/or daytime DBP \geq 85 mmHg, and (c) nighttime SBP \geq 120 mmHg and/or nighttime DBP \geq 70 mmHg (JSH 2014, JSH 2019) [6, 22]. To discriminate WCH from CH in pregnant and puerperal women with HT, we defined WCH as HT observed by clinic BP but not by HBPM and/or ABPM, and we defined CH as HT observed by clinic BP as well as by HBP and/or ABPM [6, 22]. If pregnant women in the first half of pregnancy showed HT by clinic BP but were not evaluated by HBPM and/or ABPM, we did not classify them as having either WCH or CH and only observed them for suspected HT. In a woman with a past history of either CH or WCH diagnosed before the current pregnancy, we adopted the same diagnosis for the current pregnancy.

In this study, clinic BP levels of SBP/DBP $<$ 140/90 mmHg were classified as SBP/DBP $<$ 120/80 mmHg (normal BP), SBP: 120–129 mmHg and DBP $<$ 80 mmHg (high-normal BP), and SBP: 130–139 mmHg and/or DBP: 80–89 mmHg (high BP); clinic BP levels of SBP \geq 140/90 mmHg were considered HT, according to JSH 2019 [22].

When pregnant and puerperal women were suspected of having or were diagnosed with HT by clinic BP, we selected one of the following: (1) referring them to the cardiovascular department, especially when they showed a clinic BP of \geq 160/110 mmHg or (2) lending them an HBP device to measure their HBP twice a day (every morning and at bedtime) for at least 7 days, mostly when they had suspected HT, followed by diagnosing whether the patients had CH or WCH. In all women with newly suspected and diagnosed HT at $<$ 20 weeks of gestation during 2009–2014, either HBPM and/or ABPM was used to discriminate WCH from CH during pregnancy.

Subjects

In 2009–2014, we collected data on clinic BP in the hospital, HBP, and ABPM and information on 2910 pregnant women

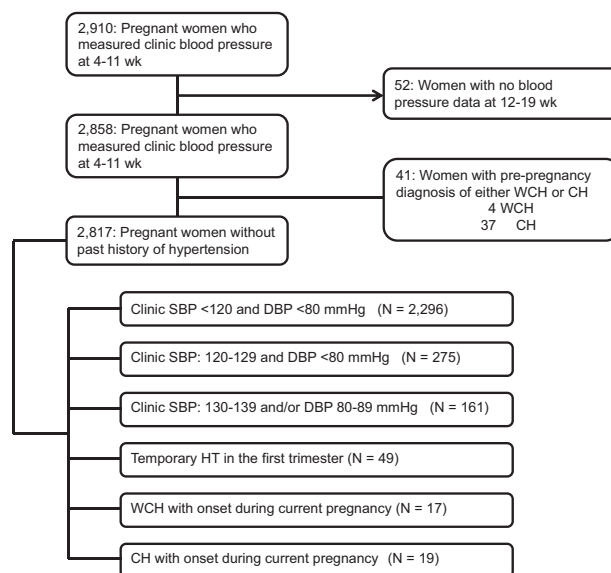


Fig. 1 Flow diagram for creating the normal BP group (clinic SBP $<$ 120 mmHg and DBP $<$ 80 mmHg), high-normal BP group (clinic BP: 120–129 mmHg and DBP $<$ 80 mmHg), high BP group (clinic SBP: 130–139 mmHg and/or DBP: 80–89 mmHg), temporary HT (THT) group (clinic BP \geq 140/90 mmHg, with clinic BP $<$ 140/90 mmHg in mid-trimester), WCH group, and CH group, using clinic BP levels in the first trimester. BP, blood pressure; HT, hypertension; WCH, white coat hypertension; CH, chronic hypertension

who sought a maternal checkup at $<$ 12 weeks of gestation and delivered babies at our tertiary center. All women had their clinic BP measured three times on all days of the maternal checkup during their pregnancy and the puerperal period.

Of the 2910 subjects, 52 women did not seek a maternal checkup between 12 and 19 weeks of gestation because they had a maternal checkup in other clinics/hospitals after 11 weeks of gestation but were referred to our hospital after 28 weeks of gestation to deliver their babies in our hospital. Of the remaining 2858 women, 41 had a past history of pre-pregnancy diagnosis of either WCH or CH (Fig. 1); there were 4 women with a past history of WCH and 37 women with a past history of CH. Thus, 2817 women had no past history of HT.

Definitions of PE, superimposed PE (SPE), and GH

PE was defined as persistent de novo HT with one or more of the following new-onset conditions occurring at or after 20⁺⁰ weeks of gestation, but all symptoms were normalized by 12 weeks postpartum: (1) proteinuria, (2) liver involvement without any underlying diseases, (3) progressive kidney injury, (4) stroke, neurological complications, (5) hematological complications, and (6) uteroplacental dysfunction [8]. GH was defined as persistent de novo HT in the absence of features of PE, but HT was normalized by 12 weeks postpartum [8]. SPE was defined as follows: (1) HT, which is diagnosed pre-pregnancy or before 20 weeks of gestation, followed by new-onset proteinuria, liver or renal involvement without any

underlying diseases, stroke, neurological complications, hematological complications, or uteroplacental dysfunction at or after 20 weeks of gestation; (2) HT and proteinuria, diagnosed pre-pregnancy or before 20 weeks of gestation, followed by the exacerbation of one or both of the symptoms after 20 weeks of gestation; and (3) renal disease with only proteinuria without HT, diagnosed pre-pregnancy or before 20 weeks of gestation, followed by new-onset persistent HT after 20 weeks of gestation [8]. In this study, we defined a new disease concept of “exacerbation of HT”, which was defined as an obvious increase in BP, start of antihypertensive drugs, or increase in the dosage of antihypertensive drugs to control HT during pregnancy and/or the puerperal period. Proteinuria was defined as ≥ 300 mg/day from 24-h urine collection and/or ≥ 0.27 mg/mg CRE by spot urine testing [8]. If only test tape was available, semiquantitative test results of $\geq 2+$ at least once just before delivery, which represented almost 100 mg/dL protein, were considered to be positive [31]. Early onset PE was defined as features of PE emerging at < 34 weeks, and early-onset GH was defined as HT emerging at < 34 weeks. A small-for-gestational-age (SGA) infant was defined as an infant with a birth weight of the 10th percentile of the Japanese population [32].

Statistics

The results are presented as the mean \pm SD. Fisher’s exact test followed by the Bonferroni test was used for categorical data. One-way analysis of variance (ANOVA) followed by the Turkey test was used for comparison of differences among ≥ 3 groups based on continuous data. The paired *t*-test was used for comparisons between paired continuous data. The Cochran–Armitage test for trends in proportions was used to assess the association between dichotomous variables and ordinal variables with three or more categories. Multiple logistic regression was performed to determine independent risk factors for the occurrence of PE and GH. All analyses were performed using IBM SPSS Statistics (version 25 for Windows) and R commander (EZR ver. 1.37) [33]. We considered $P < 0.05$ with two-sided tests as significant.

Results

Background of pregnant women with normal BP, high-normal BP, high BP, THT, WCH, and CH in the first trimester

The proportion of WCH and CH in women with newly diagnosed HT in the current pregnancy was 47% (17/36) and 53% (19/36), respectively (Fig. 1). The frequency of WCH relative to all HT diagnosed in the current pregnancy

was significantly higher than that relative to all HT diagnosed in the pre-pregnancy period ($P < 0.001$). The overall rates of WCH and CH in all pregnant women with HT were 27 and 73%, respectively, and the overall prevalences of WCH and CH in the total cohort were 0.7 and 2.0%, respectively.

The frequency of age ≥ 40 years old was significantly higher in women with THT than in those with normal BP (Table 1). The pre-pregnancy body mass index (BMI) was significantly higher in women with high-normal BP, high BP, THT, WCH, and CH than in those with normal BP; the frequency of being overweight or obese was also significantly higher in women with high-normal BP, high BP, THT, WCH, and CH than in those with normal BP. The average clinic SBP and DBP on the second and third measurements at 8–11 weeks were not different between women with WCH and CH; however, they were significantly lower in women with THT than in those with CH. In women with WCH, SBP by HBPM at < 13 weeks, DBP by HBPM at < 13 weeks, SBP by HBPM at 14–19 weeks, and DBP by HBPM at 14–19 weeks were all significantly lower than in those with CH. Women with normal BP, high-normal BP, high BP and THT delivered later than those with CH; however, the birth weeks were not significantly different between women with WCH and those with CH. Similarly, birthweights in women with normal BP, high-normal BP, high BP and THT were significantly larger than in women with CH; however, the birthweights were not significantly different between women with WCH and those with CH.

Significant mid-trimester BP level reductions were observed in the following pairs: for clinic BP, all SBP/DBP pairs; for HBP, SBP/DBP pairs for women with CH, but not for those with WCH.

Comparison of the incidence of PE/SPE among pregnant women with normal BP, high-normal BP, high BP, THT, WCH, and CH in the first trimester

PE/SPE occurred in 76 (2.7%) women and consisted of 27 early-onset PE (0.9%) and 49 late-onset PE (1.8%) cases. In women with normal BP, high-normal BP, high BP, THT, WCH, and CH in the first trimester, PE/SPE occurred in 1.3, 4.3, 8.1, 8.2, 14.3, and 25.0%, respectively (Fig. 2). The incidence of PE/SPE was significantly higher in women with high-normal BP, high BP, THT, WCH, and CH than in those with normal BP. The incidence of PE/SPE was also significantly higher in women with CH than in those with high-normal BP and in those with high BP. The incidence of PE/SPE was not significantly different between women with WCH and those with CH (14.3 and 25.0%, respectively; $p = 0.373$).

Table 1 Background of pregnant women with normal BP, high-normal BP, and high BP, THT, WCH, and CH in the first trimester

	Normal BP in the first trimester (A: n = 2296)	High-normal BP in the first trimester (B: n = 275)	High BP in the first trimester (C: n = 161)	THT ^a in the first trimester (D: n = 49)	WCH (E: n = 21)	CH (F: n = 56)	Missing value (A/B/C/D/E/F)	P value
Maternal characteristics								
Age at delivery (yr)	33.7 ± 5.1	34.4 ± 5.6	34.8 ± 4.7	36.2 ± 4.9	36.4 ± 5.2	36.1 ± 5.1	0	<0.001 ^d
Age at delivery ≥40 yr (%)	240 (10.5)	39 (14.2)	21 (13.0)	12 (24.5)	6 (28.6)	12 (21.4)	0	<0.001 ^e
Race: non-Japanese (%)	58 (2.5)	2 (0.7)	1 (0.6)	2 (4.1)	0 (0)	2 (3.6)	0	0.204
Nulliparous women (%)	1125 (49.0)	163 (59.3)	83 (51.6)	30 (61.2)	13 (61.9)	27 (48.2)	0	0.015 ^f
Pre-pregnancy BMI	21.5 ± 3.5	24.6 ± 5.4	25.4 ± 5.4	28.2 ± 6.2	29.1 ± 7.4	28.1 ± 6.5	0	<0.001 ^g
Overweight or obese (%)	279 (12.2)	103 (37.5)	70 (43.5)	33 (67.3)	15 (71.4)	35 (62.5)	0	<0.001 ^h
Multiple pregnancy (%)	146 (6.4)	18 (6.5)	7 (4.3)	5 (10.2)	1 (4.8)	2 (3.6)	0	0.677
Twin pregnancy (%)	144 (6.3)	18 (6.5)	7 (4.3)	5 (10.2)	1 (4.8)	2 (3.6)	0	0.963
Triplet pregnancy (%)	2 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0	<0.001 ⁱ
Past history of GH/PE (%)	44 (1.9)	9 (3.3)	17 (10.6)	4 (8.2)	1 (4.8)	14 (25.0)	0	<0.001 ⁱ
BP profiles								
Antihypertensive drugs just before pregnancy	(-)	(-)	(-)	(-)	(-)	23 (41.1)	0	(-)
Average clinic SBP on the second and third measurements at 8–11 wk	106 ± 8	124 ± 3	128 ± 7	136 ± 12	142 ± 8	142 ± 17	0	<0.001 ^j
Average clinic DBP on the second and third measurements at 8–11 wk	61 ± 8	71 ± 6	80 ± 6	84 ± 10	89 ± 10	89 ± 15	0	<0.001 ^j
Average clinic SBP on the second and third measurements at 16–19 wk	101 ± 22 ^b	112 ± 25 ^b	118 ± 20 ^b	118 ± 28 ^b	124 ± 32 ^b	130 ± 23 ^b	0	<0.001 ^k
Average clinic DBP on the second and third measurements at 16–19 wk	56 ± 14 ^b	63 ± 16 ^b	71 ± 13 ^b	70 ± 18 ^b	77 ± 21 ^b	79 ± 16 ^b	0	<0.001 ^l
SBP in HBP at < 13 wk	(-)	(-)	(-)	(-)	121 ± 7	134 ± 12	(E/F:7/20)	<0.001
DBP in HBP at < 13 wk	(-)	(-)	(-)	(-)	77 ± 7	84 ± 12	(E/F:10/23)	0.035
SBP in HBP at 14–19 wk	(-)	(-)	(-)	(-)	118 ± 8	130 ± 12 ^c	(E/F:1/3)	<0.001
DBP in HBP at 14–19 wk	(-)	(-)	(-)	(-)	73 ± 6	80 ± 11 ^c	(E/F:3/7)	0.003
Infant characteristics								
In singleton pregnancy (n = 2679)								

Table 1 (continued)

	Normal BP in the first trimester (A: n = 2296)	High-normal BP in the first trimester (B: n = 275)	High BP in the first trimester (C: n = 161)	THT ^a in the first trimester (D: n = 49)	WCH (E: n = 21)	CH (F: n = 56)	Missing value (A/B/C/D/E/F)	P value
Birth weeks (wk)	38.7 ± 2.1	38.5 ± 2.3	38.4 ± 2.6	38.6 ± 1.7	37.4 ± 3.2	36.9 ± 3.8	0	<0.001 ^m
Preterm delivery (%)	203/2150 (9.4)	28/257 (9.6)	14/154 (9.1)	4/44 (9.1)	5/20 (25.0)	16/54 (29.6)	0	<0.001 ⁿ
Birth weight (g)	2933 ± 487	2929 ± 545	2896 ± 580	2915 ± 511	2791 ± 855	2600 ± 114	0	<0.001 ^m
SGA infants (%)	191/2150 (8.9)	18/257 (7.0)	18/154 (11.7)	2/44 (4.5)	5/20 (25.0)	7/54 (13.0)	0	0.051

BP blood pressure, THT temporary hypertension, WCH white coat hypertension, CH chronic hypertension, yr years old, BMI body mass index, GH gestational hypertension, PE preeclampsia, SBP systolic blood pressure, DBP diastolic blood pressure, wk weeks of gestation, SGA small for gestational age

^aTHT was diagnosed when pregnant women showed temporary HT (SBP/DBP ≥ 140/90 mmHg) in the first trimester, but they showed mid-trimester BP drops to BP levels of SBP/DBP < 140/90 mmHg

^bSignificant between women at 8–11 wk and those at 16–19 wk

^cSignificant between women at <13 wk and those at 14–19 wk

^dSignificant pairs: A vs. D, and F

^eSignificant pair: A vs. D

^fSignificant pair: A vs. B

^gSignificant pairs: A vs. B, C, D, E, and F; B vs. D, E, and F; C vs. D, E, and F

^hSignificant pairs: A vs. B, C, D, E, and F; B vs. D, E, and F

ⁱSignificant pairs: A vs. C, D, and F; B vs. F

^jSignificant pairs: All except for D vs. E and E vs. F

^kSignificant pairs: A vs. B, C, D, E, and F; B vs. F; C vs. F

^lSignificant pairs: A vs. B, C, D, E, and F; B vs. C, D, E, and F; C vs. F; D vs. F

^mSignificant pairs: A, B, C, and D vs. F

ⁿSignificant pairs: A, B, and C vs. F

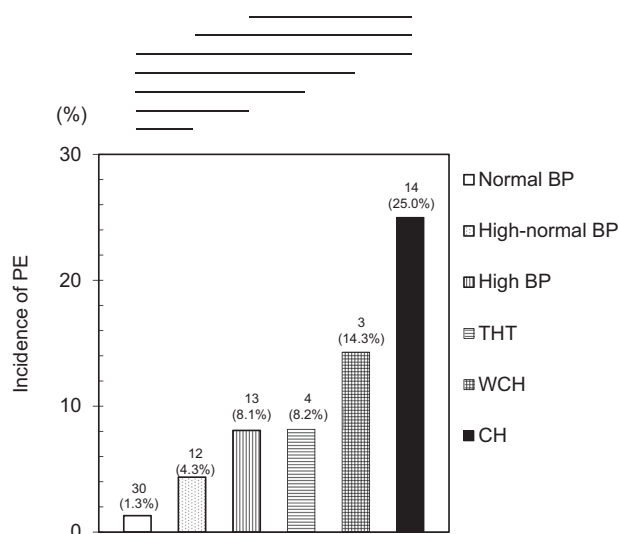


Fig. 2 Incidence of PE in women with normal BP, high-normal BP, high BP, THT, WCH, and CH. Significantly different pairs are shown above the bar chart using a thick horizontal line ($p < 0.05$). PE, pre-eclampsia; BP, blood pressure; THT, temporary hypertension; WCH, white coat hypertension; CH, chronic hypertension

Comparison of the incidence of GH among pregnant women with normal BP, high-normal BP, high BP, THT, and WCH in the first trimester; the incidence of exacerbation of HT in pregnant women with CH

GH occurred in 36 (1.3%) cases, which consisted of 4 early-onset GH (0.14%) and 32 late-onset GH (1.1%) cases. Of women with normal BP, high-normal BP, high BP, THT, and WCH in the first trimester, GH occurred in 0.3, 1.8, 9.9, 2.0, and 28.6%, respectively (Fig. 3). In women with high-normal and high BP, the incidence of GH was significantly higher than in those with normal BP, and the incidence of GH in women with high BP was also significantly higher than in those with high-normal BP. In addition, in women with WCH, the incidence of GH was also significantly higher than in those with normal BP, those with high-normal BP, and those with THT. Exacerbation of HT without PE occurred in 19 (33.9%) women with CH.

Odds ratio of BP levels at 8–11 weeks, pre-pregnancy BMI, primiparity, age, past history of GH/PE, and multiple pregnancy for the occurrence of PE/SPE and GH

Regarding the occurrence of PE/SPE, high-normal BP, high BP, THT, WCH, and CH were independent risk factors vs. normal BP (Table 2). Although pre-pregnancy overweight/obesity and age ≥ 40 were associated with the occurrence of PE/SPE, they were not independent risk factors. A past

history of GH/PH was an independent risk factor for the occurrence of PE/SPE. Multiple pregnancies involving twins/triplets were an independent risk factor for the occurrence of PE/SPE, whereas a significant association was not observed in the univariate logistic regression analysis, indicating that some factors might suppress the occurrence of PE/SPE in women with multiple pregnancies.

As for the occurrence of GH, high-normal BP, high BP/THT, and WCH were independent risk factors vs. normal BP, but other factors were not independent risk factors (Table 3). Thus, a higher BP of $\geq 120/80$ mmHg was the only independent risk factor for the occurrence of GH.

Discussion

We obtained three novel findings in this research. First, almost half of the newly diagnosed HT in the current pregnancy was WCH. Second, the incidences of PE between women with WCH and those with CH were not significantly different. Third, THT as well as WCH in the first trimester was an independent risk factor for the occurrence of PE. We also confirmed evidence generated by previous studies: first, higher BP levels (SBP: 120–139 and/or DBP: 80–89 mmHg) in the first trimester were independent risk factors for PE and GH; second, pre-pregnancy BMI was not an independent risk factor for PE and GH after adjusting for other relevant risk factors; third, WCH was the strongest risk factor for the occurrence of GH, and women with WCH developed GH in almost 1/4 of the cases.

In this cohort study, almost half of the newly diagnosed HT in the current pregnancy was WCH. This cohort study was, to the best of our knowledge, the first study to elucidate the prevalence of WCH in pregnant women without a past history of HT. Of nonpregnant hypertensive patients, it is estimated that 15–56% have WCH [34–37]. Gorostidi et al. [34], Melgarejo et al. [35], de la Sierra et al. [36], and Tocci et al. [37], reported that the prevalences of WCH were 18.3–37.5%, 23.5–56.2%, 26.1–27.2%, and 15.9%, respectively. Therefore, the prevalence of WCH in pregnant women without a past history of HT might be relatively higher than the prevalence of WCH in the elderly population.

In our cohort study, the incidences of PE in women with WCH and CH were 14.3 and 25.0%, respectively. The incidences of PE between women with WCH and those with CH were not significantly different. Brown et al. [14], reported that PE occurred more frequently in women with CH than in those with WCH (22 vs. 8%, respectively). Rodrigues et al. [15], also reported that PE occurred more frequently in women with CH than in those with WCH (39.4 vs. 12.0%, respectively). These results indicate that the occurrence rate of PE in women with WCH may be lower than in those with CH. However, our results were not

Fig. 3 a Incidence of GH in women with normal BP, high-normal BP, high BP, THT, and WCH. Significantly different pairs are shown above the bar chart using a thick horizontal line ($p < 0.05$). **b** Incidence of exacerbated HT without PE. GH, gestational hypertension; BP, blood pressure; THT, transient hypertension; WCH, white coat hypertension; PE, preeclampsia

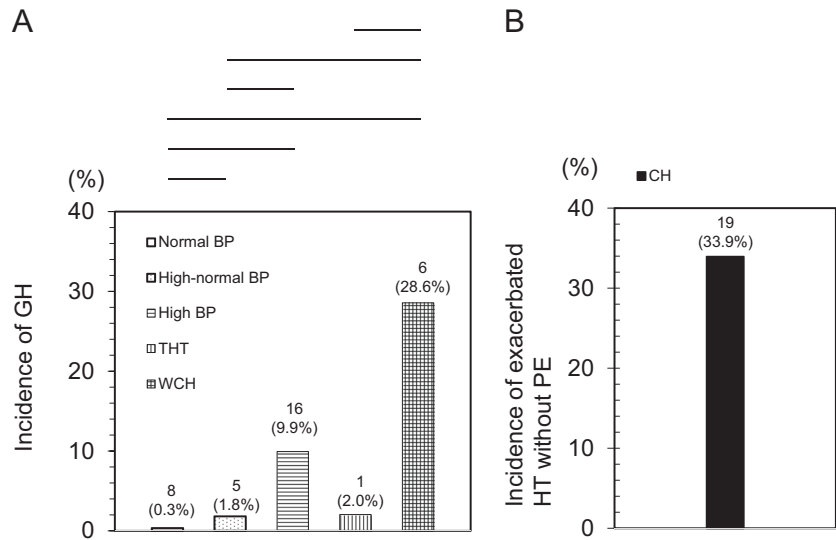


Table 2 Odds ratio of BP levels at 8–11 weeks of gestation, pre-pregnancy BMI, primiparity, age, past history of GH/PE, and multiple pregnancy for the occurrence of PE/SPE

	Number of risk factors	PE/SPE numbers (frequency)	Incidence of PE/SPE	
			cOR (95% CI)	aOR (95% CI)
BP levels at 8–11 weeks				
Normal BP	2288	30 (1.3)	1	1
High-normal BP	270	12 (4.4)	3.5 (1.8–6.9)	3.0 (1.5–6.2)
High BP	145	13 (9.0)	7.4 (3.8–14.5)	6.5 (3.2–13.3)
THT	48	4 (8.3)	6.8 (2.3–20.3)	4.9 (1.5–15.5)
WCH	15	3 (20.0)	18.8 (5.1–70.1)	13.8 (3.4–55.4)
CH	56	14 (25.0)	25.1 (12.4–50.7)	17.9 (7.9–40.7)
Pre-pregnancy BMI				
18.5–24.9	1930	39 (2.0)	1	1
<18.5	371	8 (2.2)	1.07 (0.50–2.3)	1.4 (0.64–3.1)
25.0–29.9	327	17 (5.2)	2.7 (1.5–4.8)	1.3 (0.70–2.5)
≥30.0	194	12 (6.2)	3.2 (1.6–6.2)	1.2 (0.54–2.5)
Parity				
Multiparity	1403	27 (1.9)	1	1
Primiparity	1419	49 (3.5)	1.8 (1.13–2.9)	2.3 (1.3–4.0)
Age				
Age < 40 yr	2499	59 (2.4)	1	1
Age ≥ 40 yr	323	17 (5.3)	2.3 (1.3–4.0)	1.8 (0.99–3.3)
Past history of GH/PE				
Absence	2736	66 (2.4)	1	1
Presence	86	10 (11.6)	5.3 (2.6–10.8)	3.7 (1.5–9.1)
Multiple pregnancy				
Singleton pregnancy	2645	68 (2.6)	1	1
Twins or Triplets	177	8 (4.5)	1.8 (0.85–3.8)	2.3 (1.07–5.2)

For this multivariate logistic regression analysis, women with GH were excluded. Therefore, 2822 women were used for this analysis

BP blood pressure, BMI body mass index, GH gestational hypertension, PE preeclampsia, SPE superimposed preeclampsia, cOR crude odds ratio, CI confidence interval, aOR adjusted odds ratio, THT temporary hypertension, WCH white coat hypertension, CH chronic hypertension, yr years old

Table 3 Odds ratio of BP levels at 8–11 weeks of gestation, pre-pregnancy BMI, primiparity, age, past history of GH/PE, and multiple pregnancy for the occurrence of GH

Risk factors	Number of risk factors	GH numbers (frequency)	Incidence of GH	
			cOR (95% CI)	aOR (95% CI)
BP levels at 8–11 weeks				
Normal BP	2258	8 (0.4)	1	1
High-normal BP	263	5 (1.9)	5.5 (1.8–16.8)	5.5 (1.8–17.4)
High BP or THT	193	17 (8.8)	27.3 (11.6–64.1)	27.6 (11.1–68.5)
WCH	18	6 (33.3)	141 (42.5–469)	160 (40.5–632)
Pre-pregnancy BMI				
<25.0	2259	22 (1.0)	1	1
25.0–29.9	306	7 (2.3)	2.4 (1.01–5.6)	0.79 (0.313–2.0)
≥30.0	175	7 (4.0)	4.2 (1.8–10.1)	0.71 (0.25–2.0)
Parity				
Multiparity	1366	14 (1.0)	1	1
Primiparity	1,374	22 (1.6)	1.6 (0.80–3.1)	1.5 (0.68–3.2)
Age				
Age <40 yr	2436	29 (1.2)	1	1
Age ≥40 yr	304	7 (2.3)	2.0 (0.85–4.5)	1.4 (0.55–3.5)
Past history of GH/PE				
Absence	2673	33 (1.2)	1	1
Presence	67	3 (4.5)	3.8 (1.12–12.5)	2 (0.49–8.1)
Multiple pregnancy				
Singleton pregnancy	2571	34 (1.3)	1	1
Twins or Triplets	169	2 (1.2)	0.89 (0.21–3.8)	0.93 (0.20–4.3)

For this multivariate logistic regression analysis, women with PE/SPE and those with CH were excluded. In addition, high BP and THT were combined because the incidence of GH in women with THT was only 1. Moreover, women with pre-pregnancy BMI of 18.5 and those with pre-pregnancy BMI of 18.5–24.9 were also combined because the incidence of GH in women with pre-pregnancy BMI of 18.5 was 0%. Therefore, 2740 women were used for this analysis

BP blood pressure; BMI body mass index; GH gestational hypertension; PE preeclampsia; cOR crude odds ratio, CI confidence interval; aOR adjusted odds ratio, THT temporary hypertension, WCH white coat hypertension, CH chronic hypertension, yr years old, SPE superimposed preeclampsia

consistent with these previous reports [14, 15]. Our results suggest that women with WCH in pregnancy may be at a high risk of PE. This may be supported by the fact that the higher the BP levels in the first and second trimesters, the more frequently PE occurs [19, 20]. In fact, pregnant women with WCH in a previous study showed a relatively higher BP level of 122 ± 7 mmHg for daytime BP measured during 24-h ABPM, although the BP levels were within normal ranges [14]. In contrast, normal pregnant women in the Japanese low-risk cohort showed SBP/DBP of $102 \pm 8/60 \pm 6.5$ mmHg, and the +2SD values of SBP/DBP were 118/73 [38]. Thus, the BP levels in most pregnant women with WCH may deviate from the normal ranges of HBP in the pregnancy period, suggesting that women with WCH in pregnancy may be at a high risk of PE. Our data support this suggestion because women with WCH showed a relatively high HBP level of 121 ± 7 mmHg in the first trimester and 118 ± 8 mmHg in the second trimester.

THT and WCH in the first trimester were independent risk factors for the occurrence of PE. The clinic BP levels in the first trimester were associated with the incidence of PE in parallel: the average clinic SBP levels at 8–11 weeks were 106, 124, 128, 136, and 142 mmHg in normal BP, high-normal BP, high BP, THT, and WCH, respectively; the incidences of PE were 1.3, 4.3, 8.1, 8.2, and 14.3%, respectively (Cochran–Armitage test for trend in proportions: $p < 0.001$). In this study, we, for the first time, defined a new concept of THT whereby pregnant women show tentative HT (SBP/DBP $\geq 140/90$ mmHg) in the first trimester but mid-trimester BP level reductions to SBP/DBP $< 140/90$ mmHg. Although the mid-trimester BP drop was a specific phenomenon in pregnancy [27–29], we recently noticed that some women with HT in the first trimester showed normal BP in the second trimester, suggesting that the mid-trimester BP drops are a phenomenon observed not only in women with normal-range BP but also in those with

HT. Interestingly, the difference between the SBP at 8–11 weeks and the SBP at 16–19 weeks was the largest in women with THT and those with WCH; the difference in women with normal BP, high-normal BP, high BP, THT, and WCH was -5 , -12 , -10 , -18 , and -18 , respectively. The large decrease in SBP in women with THT may reflect marked strain in the clinic in the first trimester, which may be reduced by gaining experience toward the mid-trimester.

In this study, high-normal BP and high BP in the first trimester were independent risk factors for the occurrence of PE. In addition, high-normal BP and high BP/THT were also independent risk factors for GH. These results are consistent with our previous results, whereby BP levels of 120–129/80–84 mmHg and BP levels of 130–139/85–89 mmHg in the second trimester were independent risk factors for the occurrence of either PE or GH [20]. Interestingly, in this study, pre-pregnancy overweightness and obesity were not independent risk factors for either PE or GH; such a disappearance of the risk associated with BMI after adjustment of BP levels for the occurrence of PE/GH was also observed in the second trimester in our previous study [20].

WCH was the strongest risk factor for the occurrence of GH; women with WCH developed GH in almost 1/4 of the cases. Two previous studies also showed that WCH is a risk factor for GH, although how frequently women with WCH develop GH differed in these two studies (42.1% according to Brown et al. [14] and 16.0% according to Rodrigues et al. [15]). This discrepancy may have been due to differences in the study population or study design. We confirmed that WCH is a strong risk factor for GH, but whether WCH is a risk factor for PE remains unknown.

Our research has two limitations. First, the mid-trimester BP drop might start from 9 weeks of gestation [39]. Therefore, some women with normal BP in the first trimester might have had previous hypertension. Although we used only pregnant women recruited at <12 weeks of gestation, some women with WCH and/or CH might have shown normal BP at the first visit to our hospital. Therefore, our estimation of the prevalence of WCH may not have been accurate. Second, in our study, the diagnoses of PE and GH were based on BP measured under clinical settings. Therefore, the incidences of PE and GH under clinical settings might be overdiagnosed.

In conclusion, almost half of the newly diagnosed HT in pregnancies observed in the current study was WCH, indicating that a precise diagnosis of WCH is essential to avoid unnecessary antihypertensive therapy in pregnant women. The current research did not reveal whether the risk of PE is higher in women with CH than in those with WCH. Currently, a prospective multicenter cohort study to solve this clinical question is ongoing (JP-WCH study, UMIN000032790) [17]. We proposed the novel disease

concept of “THT” in the first trimester and disclosed that THT and WCH were independent risk factors for PE. We also confirmed three previously reported findings: first, high-normal BP and high BP were independent risk factors for both PE and GH; second, the effects of BMI on the occurrence of PE/GH disappeared after adjusting for other risk factors; and third, WCH was a strong independent risk factor for GH.

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Compliance with ethical standards

Conflict of interest The measurements of clinic BP in all pregnant women who sought maternal checkups at our hospital were conducted using Omron HEM-906[®], and measurements of HBP were performed using HBPM devices (Omron HEM-5001[®] and Omron HEM-7080IC[®]) in some women with suspected HT, based on a research contract with OMRON Healthcare Co., Ltd. (RinA-Dai07-30 and RinA-Dai15-215).

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