Original Article

Normal and High-Normal Blood Pressures, but Not Body Mass Index, Are Risk Factors for the Subsequent Occurrence of Both Preeclampsia and Gestational Hypertension: A Retrospective Cohort Study

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Blood pressure (BP) levels and body mass index (BMI) are known as risk factors for preeclampsia and gestational hypertension. However, there have been few investigations regarding the effects of BP and BMI levels on preeclampsia and gestational hypertension in the same cohort. In the present study, we conducted a retrospective cohort study using multiple logistic regression analysis. The cohort included 1,518 patients without nephritis. The unadjusted odds ratios (ORs) of preeclampsia and gestational hypertension were increased in pregnant women with normal BP (120–129 mmHg systolic or 80–84 mmHg diastolic), high-normal BP and hypertension in the second trimester compared to those with optimal BP. The unadjusted ORs of preeclampsia and gestational hypertension were also increased in obese women in the pre-pregnancy period compared to women with normal range BMI. When adjustment was made for both the BP levels and pre-pregnancy BMI levels, the ORs (95% confidence intervals) of normal BP, high-normal BP, hypertension and obesity for the subsequent occurrence of preeclampsia were 5.1 (2.2–12), 8.3 (3.1–22), 16 (5.0–50) and 2.0 (0.67–5.9), and those for the subsequent occurrence of gestational hypertension were 7.0 (2.6–19), 7.4 (2.1–25), 22 (6.1–83) and 1.3 (0.33–4.8), respectively. For the subsequent occurrence of preeclampsia or gestational hypertension, normal BP, high-normal BP and hypertension in the second trimester may be independent risk factors. Obesity in the pre-pregnancy period, however, may not be an independent risk factor. (*Hypertens Res* 2006; 29: 161–167)

***Key Words*: gestational hypertension, high-normal blood pressure, hypertension, obesity, preeclampsia**

Introduction

Recent studies indicated that high-normal blood pressure (BP) (130–139 mmHg systolic or 85–89 mmHg diastolic) was associated with the development of hypertension and target organ damage (*1–6*). In fact, the early identification of high-normal BP was emphasized as clinically important by both the sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood

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Table 1. Characteristics and Maternal Outcomes in 4 Groups of Women Divided by the Initial Blood Pressure during the First Half of Pregnancy

	All women (n=1,518)	Blood pressure levels in the second trimester				p value	Significant pairs among 4 groups
		Optimal (group 1) (n=1,054)	Normal (group 2) (n=304)	High-normal (group 3) (n=119)	Hypertension (group 4) (n=41)		
Age (years)	30.9±6.4	30.7±6.5	30.8±6.5	31.7±6.0	31.5±5.3	n.s.	
Nulliparous women (%)	50.1 (n=760)	49.5 (n=522)	48.0 (n=146)	53.8 (n=64)	68.3 (n=28)	n.s.	
Pre-pregnancy BMI (kg/m^2)	21.8±3.6	21.0±2.6	22.9±4.3	24.0±4.0	26.2±6.6	<0.001	1 *vs*. 2, 1 *vs*. 3, 1 *vs*. 4, 2 *vs*. 4
Blood pressure in the second trimester							
Date of examination (weeks)	19.8±1.4	19.9±1.4	19.8±1.4	19.9±1.4	19.3±1.5	n.s.	
Systolic blood pressure (mmHg)	113±13	106±8	124±3	133±3	145±5	<0.001	all pairs
Diastolic blood pressure (mmHg)	66±9	62±7	73±5	78±6	82±7	<0.001	all pairs
Mean arterial pressure (mmHg)	82±10	77±7	90±4	96±4	103±6	<0.001	all pairs
Maternal outcomes							
Preeclampsia (%)	2.5 (n=38)	0.9 (n=9)	4.6 (n=14)	7.6 (n=9)	14.6 (n=6)	<0.001	1 *vs*. 2, 1 *vs*. 3, 1 *vs*. 4, 2 *vs*. 4
Gestational hypertension (%)	1.8 (n=28)	0.6 (n=6)	3.9 (n=12)	4.2 (n=5)	12.2 (n=5)	<0.001	1 *vs*. 2, 1 *vs*. 3, 1 *vs*. 4, 2 *vs*. 4

n.s., not significant. BMI, body mass index.

Table 2. Characteristics and Maternal Outcomes in 3 Groups of Women Divided by Pre-Pregnancy Body Mass Index

	Pre-pregnancy BMI levels (kg/m^2)				p value	Significant pairs among 4 groups
	<18.5 (group 1) (n=184)	18.5–24.9 (group 2) (n=1,128)	25.0–29.9 (group 3) (n=155)	≥30.0 (group 4) (n=51)		
Age (years)	29.5±6.6	30.8±6.5	32.2±5.1	30.8±7.0	0.002	1 *vs*. 2, 1 *vs*. 3, 2 *vs*. 3
Nulliparous women (%)	57.6 (n=106)	49.7 (n=561)	41.3 (n=64)	56.9 (n=29)	0.019	1 *vs*. 3, 2 *vs*. 3
Pre-pregnancy BMI (kg/m^2)	17.7±0.7	21.2±1.6	26.9±1.3	34.0±3.4	<0.001	all pairs
Blood pressure in the second trimester						
Systolic blood pressure (mmHg)	108±12	111±12	123±11	128±12	<0.001	all pairs
Diastolic blood pressure (mmHg)	63±9	66±8	72±8	76±8	<0.001	all pairs
Mean arterial pressure (mmHg)	78±9	81±9	89±8	93±9	<0.001	all pairs
Maternal outcomes						
Preeclampsia (%)	1.6 (n=3)	2.0 (n=22)	5.1 (n=8)	9.8 (n=5)	<0.001	1 *vs*. 4, 2 *vs*. 3, 2 *vs*. 4
Gestational hypertension (%)	1.1 (n=2)	1.6 (n=18)	3.2 (n=5)	5.9 (n=3)	n.s.	

n.s., not significant. BMI, body mass index.

Pressure (*7*) and the hypertension treatment guidelines of 2004 by the Japanese Society of Hypertension (JSH 2004) (*8*). Several reports have also suggested that there are strong associations between BP in the early pregnancy period and the later occurrence of preeclampsia (PE) and gestational hypertension (GH) (*9–11*). A mean BP of ≥90 mmHg in the second trimester predicted the future development of PE or GH (*9*). Our recent studies have also shown that the BP value in the second trimester of pregnancies was higher in women who later developed PE or GH than those who did not develop them (*10*, *11*). However, it is not known whether or not high BP levels in the second trimester are risk factors for the later occurrence of PE and GH.

Obesity is also a well known risk factor for PE and GH (*12–14*). Since obesity is associated with both hypertension and prehypertension (120–139 mmHg systolic or 80–89 mmHg

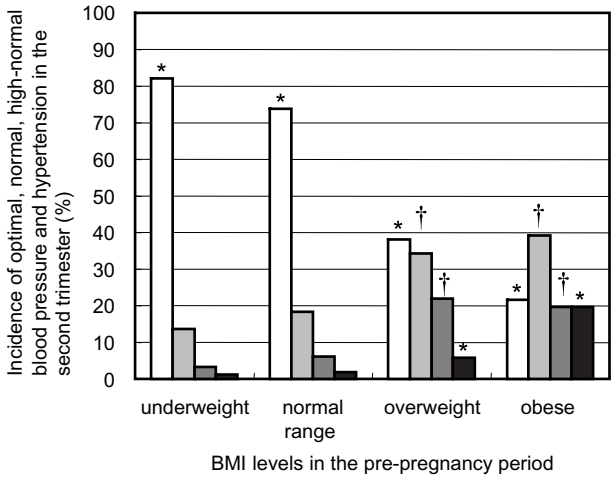

Fig. 1. *Percentage of women with optimal, normal, high-normal blood pressure and hypertension in the 4 subgroups of the pre-pregnancy body mass index (BMI). White bar, the percentage of pregnant women with optimal blood pressure; light-shaded bar, the percentage of those with normal blood pressure; dark-shaded bar, the percentage of those with high-normal blood pressure; black bar, the percentage of those with hypertension. The underweight subjects were defined as those with a BMI of < 18.5 kg/m^2 in the pre-pregnancy period; the normal range subjects as those with a BMI of 18.5–24.9 kg/m^2; the overweight subjects as those with a BMI of 25.0–29.9 kg/m^2; and the obese subjects as those with a BMI of ≥30.0 kg/m^2. *Significantly different among any groups; †significantly different* vs. *the underweight group and the normal range group.*

diastolic) (*15–17*), the effect of obesity on the subsequent development of PE or GH should be evaluated after removing the effect of BP levels. In the present study, we studied the effects of BP and BMI levels on PE and GH in the same cohort using multivariate logistic regression analysis.

Methods

Subjects

We reviewed the charts of 1,548 women who sought antenatal care at <14 weeks of gestation and gave birth to singleton infants at our hospital at ≥22 weeks of gestation from January 1996 to December 1999. The gestational ages were confirmed by ultrasonographic measurements in all women. Among them, a total of 1,518 women were analyzed in this study after excluding 27 women who had had proteinuria during the first trimester of pregnancies and 3 women whose pre-pregnancy weights were unclear. This study was approved by the institutional ethics committee.

Procedure

The BP levels were recorded twice at around 20 weeks. The BP was assessed using one noninvasive automated measurement machine (BP-203RV II; Nippon Colin Co., Tokyo, Japan) with patients in the sitting position and with the right arm held at heart level. The BP was usually measured once. If the BP was ≥140/90 mmHg, it was measured a second time after an at least 5 min rest. We adopted the lower value of the BP in such cases.

We categorized the BP levels into 4 groups according to JSH 2004 (*8*): optimal, normal, high-normal and hypertension. Using the pre-pregnancy weight and height, we calculated the pre-pregnancy BMI. We categorized the BMI levels into 4 groups: underweight (<18.5 kg/m^2), normal range (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2) and obese (≥30.0 kg/m^2).

Using an arbitrary mean BP (MBP) of 80 mmHg in the second trimester and an arbitrary pre-pregnancy BMI of 23.6 according to Tomoda *et al*. (*18*), we classified women with an MBP of ≥80 mmHg into the large MBP group, women with an MBP of <80 mmHg into the small MBP group, women with a pre-pregnancy BMI of ≥23.6 into the large pre-pregnancy BMI group, and women with a pre-pregnancy BMI of <23.6 into the small pre-pregnancy BMI group.

The net change in BMI from the pre-pregnancy period to the second trimester was represented by ΔBMI (BMI in the second trimester minus BMI in the pre-pregnancy period). Since the 90th percentile of the ΔBMI distribution was 3.0, women with a ΔBMI of ≥3.0 were classified into the large ΔBMI group, and women with a ΔBMI of <3.0 were classified into the small ΔBMI group.

We defined PE and GH according to the definition and classification of pregnancy-induced hypertension (PIH) (2004) of the Japan Society for the Study of Hypertension in Pregnancy (JSSHP) (*19*). In brief, PIH was defined as hypertension with or without proteinuria occurring after the 20th week of gestation, but resolving by the 12th week of postpartum. PIH was classified as either PE, GH or superimposed PE. PE was defined as hypertension with proteinuria occurring after the 20th week of gestation, and GH was defined as hypertension without proteinuria occurring after the 20th week of gestation. Superimposed PE was defined as chronic hypertension diagnosed prior to pregnancy or prior to the 20th week of gestation, with proteinuria emerging after the 20th week of gestation. Superimposed PE was included in the category of PE in this study. Proteinuria was defined as 300 mg/day from 24 h urine collection. If only test tape was available, repeated semi-quantitative test results of 1+, that represented 30 mg/dl of protein or more, were considered to constitute a positive result.

Statistical Methods

The results are presented as the mean±SD. For multiple

Table 3. Odds Ratio of Blood Pressure Levels in the Second Trimester, Pre-Pregnancy BMI Associated with the Occurrence of Preeclampsia and Gestational Hypertension

	Occurrence of preeclampsia						Occurrence of gestational hypertension					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	Crude odds ratio	(95% CI)	*p* value	Adjusted odds ratio	(95% CI)	*p* value	Crude odds ratio	(95% CI)	*p* value	Adjusted odds ratio	(95% CI)	*p* value
Initial blood pressure levels in the second trimester												
Optimal	1			1			1			1		
Normal	5.6	(2.4–13)	<0.001	5.1	(2.2–12)	<0.001	7.2	(2.7–19)	<0.001	7.0	(2.6–19)	<0.001
High-normal	9.5	(3.7–24)	<0.001	8.3	(3.1–22)	<0.001	7.7	(2.3–25)	<0.001	7.4	(2.1–25)	0.002
Hypertension	20	(6.7–59)	<0.001	16	(5.0–50)	<0.001	24	(7.0–83)	<0.001	22	(6.1–83)	<0.001
Pre-pregnancy BMI												
18.5–24.9	1			1			1			1		
<18.5	0.83	(0.25–2.8)	0.769	1.0	(0.30–3.6)	0.946	0.68	(0.16–2.9)	0.604	0.86	(0.19–3.8)	0.837
25.0–29.9	2.7	(1.2–6.3)	0.017	1.4	(0.59–3.3)	0.451	2.1	(0.75–5.6)	0.160	1.0	(0.36–2.9)	0.950
≥30.0	5.5	(2.0–15)	0.001	2.0	(0.67–5.9)	0.216	3.9	(1.1–14)	0.035	1.3	(0.33–4.8)	0.726

CI, confidence interval; BMI, body mass index.

group comparisons, the homogeneity of variance was assessed using the Levene test. We used one way analysis of variance (ANOVA) to test for the overall differences among groups, followed by Gabriel's method to compare the separate group means when the Levene test was not significant, and followed with the Dunnett-T3 method to compare those when the Levene test was significant. The χ^2 test or Fisher's exact test was used to compare the incidence of the discrete variables. The correlation between two continuous variables was assessed by regression analysis. The contribution of BP and BMI to the development of PE and GH was evaluated using multiple logistic regression analysis. All analyses were performed with the SPSS software package (version 13.0J for Windows, SPSS Inc., Chicago, USA). A level of $p<0.05$ was considered statistically significant.

Results

Of the 1,518 women participating in this study, 304 (20.0%) belonged to the normal BP group, 119 (7.8%) to the high-normal BP group, 41 (2.7%) to the hypertension group, and the remaining 1,054 (69.4%) to the optimal BP group (Table 1). The ages and the rates of nulliparity were not different among the 4 groups. The pre-pregnancy BMIs in the higher BP groups were significantly larger than those in the optimal BP group. Dates of examination were almost equal among the 4 groups. The BP levels in the second trimester were related to the incidence of PE or GH.

Of the 1,518 women, 184 (12.1%) belonged to the underweight group, 155 (10.2%) to the overweight group, 51 (3.4%) to the obese group and the remaining 1,128 (74.3%) to the normal range group (Table 2). The age in the overweight group was the highest among the 4 groups.

The incidence rates of normal BP in women in the underweight, normal range, overweight and obese group were 13.6%, 18.3%, 34.6% and 39.2%, respectively (Fig. 1). The incidence rates of high-normal BP in the same fractions were 3.3%, 6.1%, 21.8% and 19.6%, respectively. The incidence rates of hypertension in the same fractions were 1.1%, 1.8%, 5.8% and 19.6%, respectively. Thus, the incidences of both normal BP and high-normal BP were significantly higher in the overweight group compared to the underweight or normal range group, but the incidence rates did not differ between the overweight and obese group. Conversely, the incidence of hypertension significantly and exponentially increased as the category of pre-pregnancy BMI became more severe. The systolic BP (SBP), diastolic BP (DBP) and MBP were significantly correlated to the pre-pregnancy BMI, respectively ($r=0.392$, $r=0.369$ and $r=0.397$, respectively).

We performed multivariate analyses to determine whether the pre-pregnancy BMI levels were associated with the development of PE or GH, independent of BP levels in the second trimester. Both the BP levels and pre-pregnancy BMI levels were significantly associated with the occurrence of PE in univariate logistic regression analysis (Table 3). However, pre-pregnancy BMI levels were not associated with the occurrence of PE after removing the effect of the BP levels. Similarly, although both the BP levels and obesity were significantly associated with the occurrence of GH in univariate analysis, the association of obesity with GH disappeared after removing the effect of the BP levels (Table 3). Only the BP levels in the second trimester remained significantly associated with the later occurrence of both PE and GH.

Next, we performed multivariate analyses to determine whether the pre-pregnancy BMI as continuous data was associated with the development of PE or GH, independent of SBP as continuous data in the second trimester. Both the SBP and pre-pregnancy BMI were significantly associated with

Table 4. Odds Ratio of Systolic Blood Pressure in the Second Trimester, Pre-Pregnancy BMI Associated with the Occurrence of Preeclampsia and Gestational Hypertension

	Occurrence of preeclampsia						Occurrence of gestational hypertension					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	Crude odds ratio	(95% CI)	*p* value	Adjusted odds ratio	(95% CI)	*p* value	Crude odds ratio	(95% CI)	*p* value	Adjusted odds ratio	(95% CI)	*p* value
Systolic blood pressure in the second trimester												
By increment of 5 mmHg	1.5	(1.3–1.7)	<0.001	1.5	(1.3–1.7)	<0.001	1.5	(1.3–1.8)	<0.001	1.5	(1.3–1.7)	<0.001
Pre-pregnancy BMI												
By increment of 5 kg/m^2	1.9	(1.4–2.6)	<0.001	1.2	(0.83–1.7)	0.361	2.0	(1.4–2.8)	<0.001	1.3	(0.83–1.9)	0.272

CI, confidence interval; BMI, body mass index.

Table 5. Odds Ratio of Mean Blood Pressure of ≥80 mmHg in the Second Trimester, Pre-Pregnancy BMI of ≥23.6 kg/m^2 Associated with the Occurrence of Preeclampsia and Gestational Hypertension

	Occurrence of preeclampsia						Occurrence of gestational hypertension					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	Crude odds ratio	(95% CI)	*p* value	Adjusted odds ratio	(95% CI)	*p* value	Crude odds ratio	(95% CI)	*p* value	Adjusted odds ratio	(95% CI)	*p* value
Mean blood pressure in the second trimester (mmHg)												
<80	1			1			1			1		
≥80	7.0	(2.5–20)	<0.001	6.3	(2.2–18)	<0.001	11	(2.5–45)	0.001	9.8	(2.3–42)	0.002
Pre-pregnancy BMI (kg/m^2)												
<23.6	1			1			1			1		
≥23.6	2.2	(1.1–4.4)	0.019	1.5	(0.75–2.9)	0.257	2.1	(0.97–4.6)	0.061	1.3	(0.61–3.0)	0.462

CI, confidence interval; BMI, body mass index.

the occurrence of PE in univariate logistic regression analysis (Table 4). However, pre-pregnancy BMI was not associated with the occurrence of PE after removing the effect of the SBP. Similarly, although both the SBP and pre-pregnancy BMI were significantly associated with the occurrence of GH in univariate analysis, the association of pre-pregnancy BMI with GH disappeared after removing the effect of the SBP (Table 4). Only the SBP in the second trimester remained significantly associated with the later occurrence of both PE and GH.

We also performed multivariate analyses to determine whether either of the two pre-pregnancy BMI categories divided by an arbitrary pre-pregnancy BMI of 23.6 according to Tomoda *et al*. (*18*) was associated with the development of PE or GH, independent of the two MBP groups divided by an arbitrary MBP of 80 mmHg in the second trimester (*18*). Both a large MBP and a large pre-pregnancy BMI were significantly associated with the occurrence of PE in univariate logistic regression analysis (Table 5). However, a large pre-pregnancy BMI was not associated with the occurrence of PE after removing the effect of BP. Both univariate and multivariate analysis indicate that large MBP was significantly associated with the occurrence of GH. The risk of the occurrence of GH was higher in the large pre-pregnancy BMI group than in the small pre-pregnancy BMI group, but without statistical significance.

Finally, we performed univariate analysis to determine whether the net change in BMI was associated with the development of PE or GH. Large ΔBMI was not associated with the occurrence of PE or GH ($p=1.000$, $p=0.632$, respectively). The frequency of large ΔBMI was not different among the BP groups in the second trimester ($p=0.104$).

Discussion

In this study, it was shown that normal BP, high-normal BP and hypertension in the second trimester were associated with the later occurrence of PE and GH. This held true after removing the effect of pre-pregnancy BMI levels. These observations clearly indicate that the BP levels themselves are risk factors for both PE and GH independent of pre-pregnancy BMI levels.

In our previous studies, we found that women with a MBP of ≥86 mmHg in the first trimester developed PE more frequently compared with those with a MBP of <86 mmHg (*10*). Moutquin *et al*. (*20*) reported that the DBP and MBP in women who developed PE were significantly elevated from the 9–12 weeks until delivery by at least 10 mmHg compared with those who developed neither PE nor GH. Sibai *et al*. (*21*) reported that the incidence of PE was 8.9% among women whose SBP was 120–134 mmHg at 13–27 weeks of gestation, whereas it was 2.8% among women whose SBP was <100 mmHg. These findings indicated that women who ultimately had PE or GH had had significantly higher SBP, DBP, and MBP during the first and second trimesters than women who remained normotensive.

Previous researchers have shown that obesity is a risk factor for the later occurrence of PE and GH (*12–14*). Thadhani *et al*. (*13*) reported that women with a pre-pregnancy BMI ≥30 kg/m^2 had a multivariate relative risk of 2.1 for the development of PE and 2.6 for the development of GH as compared with lean women. A recent systematic review showed that the risk of PE doubled with each 5–7 kg/m^2 increment in pre-pregnancy BMI (*14*). The present univariate analysis once again showed that obesity in the pre-pregnancy period was associated with the later onset of PE and GH; the crude odds ratios were 5.6 for PE and 4.0 for GH. It is not known, however, whether obesity *per se* poses a high risk for PE/GH, or whether obesity increases the risk of PE/GH *via* the high occurrence of an increased BP level.

To the best of our knowledge, there have been only two reports addressing the effects of both the BP levels during pregnancy and pre-pregnancy BMI levels on the occurrence of PIH (*i.e.*, PE or GH) (*18*, *21*). Sibai *et al*. (*21*) reported that both SBP and pre-pregnancy relative weight were independent risk factors for PE. Tomoda *et al*. (*18*) reported that a MBP ≥80 mmHg and a BMI ≥23.6 kg/m^2 were independent risk factors for PIH. Thus, these earlier researchers claimed that not only the BP during pregnancy, but also the pre-pregnancy relative weight/BMI may independently affect the occurrence of PE or GE, although the statistical analyses in these previous studies had several weaknesses: first, the effect of BP levels was simply evaluated using SBP (*21*), or using dichotomous variables divided by arbitrary MBP (*18*); second, the outcome was evaluated for PIH as a whole, making no special consideration of the different clinical conditions of PE and GH (*18*), or for only PE without considering GH (*21*); and third, the effect of risk factors was analyzed using multiple regression analysis with discrete variables (*18*), or using multiple logistic regression analysis with partly continuous variables (*21*). In the present study, however, the effect of obesity on the later occurrence of PE and GH disappeared after removing the effect of the BP levels in the second trimester. To compare our data with those of these previous studies, we also analyzed our data using almost the same variables that were used in the previous two reports (Tables 4, 5). According to a multiple logistic regression analysis using the SBP and pre-pregnancy BMI as continuous data, the effect of pre-pregnancy BMI on the later occurrence of PE disappeared after excluding the effect of the SBP in the second trimester. According to multiple logistic regression analysis with an MBP ≥80 mmHg and a BMI ≥23.6 kg/m^2 as dichotomous variables, the effect of BMI on the later occurrence of PE or GH also disappeared after excluding the effect of an MBP ≥80 mmHg in the second trimester. Thus, our results suggest that being overweight or obese may not be an independent risk factor for the later occurrence of either PE or GH. Therefore, obesity itself may not be the culprit for the later occurrence of PE and GH. Further studies on a larger population may be necessary to determine the effects of both pre-pregnancy BMI and the BP during pregnancy on the development of PE and GH.

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