

# The relationship between high-normal blood pressure in the first half of pregnancy and the risk of hypertensive disease of pregnancy

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## Abstract

Early warning of hypertensive disorder in pregnancy (HDP) can improve maternal and infant outcomes. However, few studies had evaluated the warning value of high-normal blood pressure (BP) before the onset of HDP. This was a prospective cohort study to investigate the relationship between high-normal BP in the first half of pregnancy and the risk of HDP. According to the maximum BP measured before 20<sup>+6</sup> weeks of gestation, the cohort was divided into three groups: optimal BP (SBP < 120 mmHg and DBP < 80 mmHg), normal BP (120 mmHg ≤ SBP < 130 mmHg or 80 mmHg ≤ DBP < 85 mmHg), and high-normal BP (130 mmHg ≤ SBP < 140 mmHg or 85 mmHg ≤ DBP < 90 mmHg). The relationship between different BP levels in the first half of pregnancy and HDP risk was assessed by general linear models. Ten thousand one hundred and ninety-three normotensive pregnant women with complete information were finally included for data analysis. Among them, 532 pregnant women were diagnosed with HDP, with a total HDP incidence of 5.2%. The incidences in the optimal, normal, and high-normal BP groups were 2.4%, 6.0%, and 21.8%, respectively. Compared to women with optimal BP in the first half of pregnancy, women with high-normal BP had a 445% increased risk of HDP (aRR: 5.45, 95% CI: 4.24–7.00), and even women with normal BP had a 107% increased risk of HDP (aRR: 2.07, 95% CI: 1.68–2.56). This study demonstrated that among low-risk healthy women, women with high-normal BP in the first half of pregnancy had a significantly higher risk of HDP.

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## KEYWORDS

high-normal blood pressure, hypertension disorder in pregnancy, preeclampsia

## 1 | INTRODUCTION

Hypertensive disorder in pregnancy (HDP), including gestational hypertension (GH) and preeclampsia (PE)-eclampsia, is characterized by new onset of hypertension after 20 weeks of gestation. Early warning of HDP, as one of the leading causes of maternal and infant morbidity and mortality,<sup>1</sup> can improve their outcomes. Despite extensive research evaluating the early prediction of HDP, there are currently no screening tests for HDP with sufficient clinical and cost-effectiveness to be widely used in clinical practice.<sup>2-5</sup> This is associated with the complex pathophysiological mechanisms of the disease.<sup>6,7</sup> Blood pressure (BP) was the most easily accessible index of pregnancy examination, and elevated BP was generally the first clinical manifestation of HDP. BP monitoring before the onset of HDP remained one of the most achievable and critical clinical indicators. 130 mmHg  $\leq$  Systolic BP (SBP) < 139 mmHg and/or 80 mmHg  $\leq$  Diastolic BP (DBP) < 90 mmHg was defined as high-normal BP by the European hypertension guidelines<sup>8</sup> and as grade 1 hypertension by the American hypertension guidelines.<sup>9</sup> Nonetheless, little research had evaluated the warning value of high-normal BP before the onset of HDP.<sup>10,11</sup> The study aimed to investigate the risk of HDP in pregnant women with high-normal BP during the first half of pregnancy.

## 2 | METHODS

### 2.1 | Study design

This was a prospective cohort study for singleton normotensive pregnant women in Tianjin, China, since November 2016. This study was approved by the Medical Ethics and Human Clinical Trial Committee of Characteristic Medical Center of PAP (No. PJHEC-2015-A1). Participants had been recruited from 19 community hospitals if they met the inclusion criteria: (1) singleton pregnancy; (2) age at enrollment  $\geq$ 18 years; (3) gestational age at enrollment  $\leq$ 13<sup>+6</sup> weeks; (4) no presence of chronic hypertension, SBP at enrollment <140 mmHg, and DBP at enrollment <90 mmHg. All participants signed a written informed consent form and were followed up according to the routine antenatal examinations procedure, which began at 6–13<sup>+6</sup> weeks of pregnancy (at enrollment), once every 4 weeks to 28–30 weeks, every 2–36 weeks, and then a week until delivery. The follow-up data, such as BP and weight of pregnant women, gestational week at delivery, mode of delivery, the hospital where the newborn was delivered, and neonatal information (length, weight, and Apgar score) were recorded in Tianjin Maternal and Child Health Information Network. Pregnancy outcomes were recorded by the medical record system of the hospitals for delivery. The final diagnosis of HDP was determined by

two or more medical experts reviewing medical records. This study excluded pregnant women with the termination of pregnancy for various reasons before 24 weeks of pregnancy, incomplete or illogical enrollment or follow-up information, or a diagnosis of chronic hypertension or chronic hypertension with superimposed PE during the follow-up. Pregnant women who had at least one follow-up data before 20<sup>+6</sup> weeks after enrollment and gave birth before September 2019 were included in the analysis.

### 2.2 | Data collection

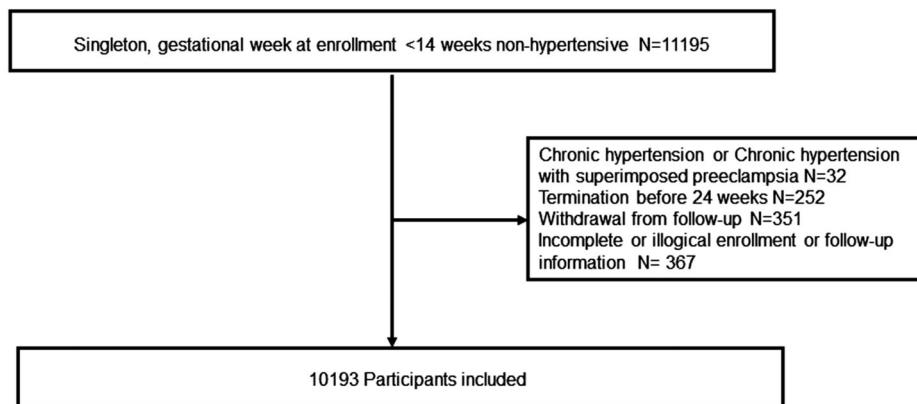
Baseline characteristics, including age, ethnicity (Han which is the ethnic majority in China/other ethnicities), education levels (years of education), family history of hypertension and diabetes, parity (primipara/multipara), previous medical history, and prepregnancy weight, were obtained by predesigned questionnaires. Height and weight at enrollment were simultaneously recorded. Prepregnancy body mass index (BMI) was calculated based on self-reported prepregnancy weight and height at enrollment. Gestational age was calculated according to the last menstrual period and verified with an ultrasound examination in early pregnancy.

BP was measured by using an upper arm electronic sphygmomanometer certified to international standards. Specifically, after a quiet rest for 5 min, the BPs of both upper arms were measured, and the side with the higher BP reading was used as the measuring arm. Besides, the measurement was performed twice, with an interval of 1–2 min. The average of the two readings was taken. If the difference between the two measurements exceeded 5 mmHg, the measurement would be repeated after rest, and the average value of the three readings was recorded.

As previously described, pregnant women who had at least two BP data before 20<sup>+6</sup> weeks were included in the analysis. According to the maximum BP measured before 20<sup>+6</sup> weeks of gestation, the cohort was divided into three groups: optimal (SBP < 120 mmHg and DBP < 80 mmHg), normal (120 mmHg  $\leq$  SBP < 130 mmHg or 80 mmHg  $\leq$  DBP < 85 mmHg), and high-normal (130 mmHg  $\leq$  SBP < 140 mmHg or 85 mmHg  $\leq$  DBP < 90 mmHg).

### 2.3 | Observation outcomes

The diagnostic criteria for HDP were based on the Chinese Guidelines for the Diagnosis and Treatment of Hypertensive Disorders in Pregnancy (2015).<sup>12</sup> GH: SBP  $\geq$  140 mmHg and/or DBP  $\geq$  90 mmHg after 20 weeks of gestation, which returned to normal within 12 weeks after delivery, with a negative urine protein test. PE: GH accompanied by



**FIGURE 1** Study flowchart

any of the following abnormalities: proteinuria  $\geq 0.3$  g/24 h, or a urine protein/creatinine ratio  $\geq 3$ , or a random urine protein  $\geq 1+$ ; or other end-organ dysfunction or fetus involvement. Eclampsia: unexplained seizures that occurred during PE.

## 2.4 | Statistical analyses

Continuous variables were expressed as mean  $\pm$  SD or median (interquartile range, IQR), and one-way ANOVA or the Kruskal–Wallis H test was adopted to analyze the differences between groups. Categorical variables were expressed as percentages or rates, and multiple groups were compared using the  $\chi^2$  test or the Kruskal–Wallis H test. Women with optimal BP in the first half of pregnancy were the reference group, and relative risks (RRs) with 95% confidence intervals (CIs) were obtained using general linear models to analyze the relationship between different BP levels in the first half of pregnancy and the risk of HDP. Moreover, analyses were adjusted regarding maternal age, ethnicity, education level, parity, assisted reproduction technology (ART), family history of hypertension, family history of diabetes, and prepregnancy BMI. All analyses were performed using SPSS version 23.0 (IBM Corp, Armonk, New York, USA) and STATA version 14.0 (Stata Corp, College Station, Texas, USA).  $P < .05$  indicated statistical significance.

## 3 | RESULTS

A total of 11 195 singleton nonhypertensive pregnant women with gestational age at enrollment  $<14$  weeks were enrolled. Among them, 32 women were eventually diagnosed with chronic hypertension or chronic hypertension complicated with PE; 252 women terminated pregnancies for various reasons before 24 weeks; 351 women withdrew from follow-up or were lost to follow-up; 367 women had incomplete enrollment or follow-up information or illogical records. Finally, 10 193 pregnant women were included. The study flowchart is illustrated in Figure 1.

The characteristics of the 10 193 participants are presented in Table 1. The number of pregnant women with optimal BP, normal BP,

and high–normal BP were 5700 (55.9%), 3713 (36.4%), and 780 (7.7%), respectively. The average age was 30.6 years old. The proportion of Han ethnicity, which was the ethnic majority in China, college-educated and primipara accounted for 96.0%, 72.3%, and 69.5%, respectively. The average gestational age of enrollment was about 11 weeks, and the average number of follow-up visits after enrollment was  $2.2 \pm 0.6$ . There were significant differences among the three groups in all baseline indicators except for the proportion of primipara. With the increase in the levels of BP, maternal height, weight, and prepregnancy BMI increased. Pregnant women with high–normal BP were the oldest while exhibiting the lowest education level and the highest proportion of family history of hypertension, family history of diabetes, and assisted reproductive technology (ART).

Five hundred and thirty-two pregnant women were finally diagnosed with HDP, including 186 with GH and 346 with PE/eclampsia. The incidence of HDP in the total population, optimal BP, normal BP, and high–normal BP groups was 5.2%, 2.4%, 6.0%, and 21.8%, respectively. Pregnant women with high–normal BP were more likely to have cesarean sections, with the shortest gestational age at delivery and length of their newborns.

The study revealed that risk factors for HDP included primipara, high prepregnancy BMI, and higher BP levels (Table 2). The risk of HDP in primiparas was 1.57 times higher than that in multiparous women (aRR 1.57, 95% CI: 1.27, 1.93), and high prepregnancy BMI was a risk factor for HDP (aRR 1.10, 95% CI: 1.08, 1.12). After adjustment of potential confounding factors such as age, ethnicity, education level, primigravida, ART, family history of hypertension and diabetes, and prepregnancy BMI, the present study revealed that compared to women with optimal BP in the first half of pregnancy, women with high–normal BP had a 445% increased risk of progression to HDP (aRR: 5.45, 95% CI: 4.24–7.00), and even women with normal BP had a 107% increased risk of HDP (aRR: 2.07, 95% CI: 1.68–2.56).

## 4 | DISCUSSIONS

This study demonstrated that more than one-fifth of pregnant women with high–normal BP ( $130 \text{ mmHg} \leq \text{SBP} < 139 \text{ mmHg}$  and/or

**TABLE 1** The descriptive characteristics of pregnancies with different blood pressure levels in the first half of pregnancy characteristic

Characteristic	Total (n = 10 193)	Optimal BP n = 5700 (55.9%)	Normal BP n = 3713 (36.4%)	High-normal BP n = 780 (7.7%)	P value
Age (year)	30.6 ± 3.8	30.5 ± 3.8	30.6 ± 3.8	31.1 ± 3.9	<0.001
Ethnicity (Han)	9788 (96.0%)	5472 (96.0%)	3554 (95.7%)	762 (97.7%)	0.037
Education level (year)					0.001
≤12	1741 (17.1%)	963 (16.9%)	619 (16.7%)	159 (20.4%)	
13–16	7373 (72.3%)	4093 (71%).8	2715 (73.1%)	565 (72.4%)	
>16	1079 (10.6%)	644 (11.3%)	379 (10.2%)	56 (7.2%)	
Primipara (%)	7085 (69.5%)	3937 (69.1%)	2586 (69.6%)	562 (72.1%)	0.231
ART (%)	199 (2.0%)	96 (1.7%)	77 (2.1%)	26 (3.3%)	0.006
Family history of hypertension	2128 (20.9%)	1084 (19.0%)	828 (22.3%)	216 (27.7%)	<0.001
Family history of diabetes	946 (9.3%)	479 (8.4%)	373 (10.0%)	94 (12.1%)	<0.001
Height (cm)	162.8 ± 5.0	162.5 ± 4.9	163.0 ± 4.9	163.7 ± 5.3	<0.001
Prepregnancy weight (kg)	58.7 ± 10.1	56.2 ± 8.7	60.5 ± 10.0	67.8 ± 12.6	<0.001
Prepregnancy BMI (kg/m <sup>2</sup> )	21.3 (19.6,24.0)	20.8 (19.1,22.9)	22.2 (20.3,24.6)	24.8 (22.0,27.8)	<0.001
GW at enrollment, week	11 <sup>+1</sup> ± 1 <sup>+4</sup>	11 <sup>+1</sup> ± 1 <sup>+4</sup>	11 <sup>+0</sup> ± 1 <sup>+4</sup>	11 <sup>+1</sup> ± 1 <sup>+4</sup>	0.037
SBP at enrollment, mmHg	106.7 ± 10.8	101.3 ± 7.8	111.7 ± 9.3	121.9 ± 10.8	<0.001
DBP at enrollment, mmHg	68.1 ± 7.8	64.5 ± 5.5	71.8 ± 7.4	76.8 ± 8.5	<0.001
Maximum SBP	113.8 ± 9.6	107.6 ± 6.9	119.7 ± 4.0	131.3 ± 5.9	<0.001
Maximum DBP	72.4 ± 7.4	68.1 ± 5.3	77.0 ± 5.2	81.8 ± 6.6	<0.001
Visits after enrollment	2.2 ± 0.6	2.1 ± 0.6	2.3 ± 0.7	2.3 ± 0.7	<0.001
HDP (%)	532 (5.2%)	139 (2.4%)	223 (6.0%)	170 (21.8%)	<0.001
GH	186 (1.8%)	32 (0.6%)	78 (2.1%)	76 (9.7%)	
PE	346 (3.4%)	107 (1.9%)	145 (3.9%)	94 (12.1%)	
GW at delivery, week	39 <sup>+2</sup> ± 1 <sup>+3</sup>	39 <sup>+2</sup> ± 1 <sup>+2</sup>	39 <sup>+1</sup> ± 1 <sup>+3</sup>	38 <sup>+6</sup> ± 1 <sup>+5</sup>	<0.001
Mode of delivery					<0.001
Natural delivery	5187 (50.9%)	3036 (53.3%)	1835 (49.4%)	316 (40.5%)	
Cesarean section	5006 (49.1%)	2664 (46.7%)	1878 (50.6%)	464 (59.5%)	
Neonatal outcome					
Birth length, cm	50.0 ± 1.8	50.1 ± 1.6	50.1 ± 1.8	49.9 ± 2.2	0.005
Birth weight, g	3344.1 ± 457.2	3335.6 ± 437.6	3356.8 ± 465.2	3345.7 ± 549.0	0.088
Apgar score at 5 min	10 (9,10)	10 (9,10)	10 (9,10)	10 (9,10)	0.796

Abbreviations: ART, assisted reproductive technology; BMI, body mass index; DBP, diastolic blood pressure; GH, gestational hypertension; GW, gestational week; Han ethnicity, the ethnic majority in China; HDP, hypertensive disorder in pregnancy; PE, preeclampsia; SBP, systolic blood pressure.

85 mmHg ≤ DBP < 90 mmHg) in the first half of pregnancy eventually progressed to HDP. Although BP, especially mean arterial pressure (MAP), was one of the indicators for predicting HDP in early pregnancy,<sup>3,7</sup> there was still no consensus on how much BP should be regarded as “warning” BP and when “warning” BP needed to be monitored. The present study suggested that high clinical attention should be paid to strengthen the monitoring of such pregnant women and evaluate their risk of HDP if the BP of pregnant women was “warning” before 20<sup>+6</sup> weeks of gestation, that was, the BP reached the high-normal BP range.

Traditional methods of predicting HDP based on maternal demographic characteristics and medical history are unreliable.<sup>2,4</sup> More-

over, the screening scheme combining maternal factors, MAP, uterine artery plasticity index (PI), and serum placental derived growth factor (PLGF) in the first trimester has good accuracy in predicting HDP.<sup>13,14</sup> However, the measurement of PI requires standardized training for sonographers, the measurement of PLGF needs to be performed in a standardized laboratory and requires a certain cost, while the measurement of BP only demands simple training for community physicians.<sup>13</sup> Therefore, BP monitoring has strong applicability and is cost-effective. By using data from routine prenatal examinations, this prospective cohort study avoided the selection bias of retrospective studies and concluded that pregnant women with pre-hypertensive BP during the first half of pregnancy were at high risk of HDP, which

**TABLE 2** The relationship between maternal characteristics and the risk of HDP

	cRR (95%CI)	P value	aRR (95%CI)	P value
Age (year)	1.02 (1.00–1.04)	0.112	1.01 (0.99–1.04)	0.260
Ethnicity (Han)	1.53 (0.91–2.58)	0.109	1.34 (0.81–2.22)	0.248
Education level (year)				
≤12	Reference		Reference	
13 to 16	0.96 (0.77–1.19)	0.685	0.99 (0.79–1.23)	0.896
>16	0.61 (0.42–0.88)	0.009	0.74 (0.51,1.08)	0.116
Primipara (yes vs. no)	1.46 (1.20–1.78)	<0.001	1.57 (1.27,1.93)	<0.001
ART (yes vs. no)	1.96 (1.28–3.00)	0.002	1.46 (0.96,2.23)	0.076
Family history of hypertension	1.39 (1.16–1.67)	<0.001	1.17 (0.97,1.41)	0.092
Family history of diabetes	1.29 (1.00–1.67)	0.052	0.97 (0.75–1.25)	0.824
Prepregnancy BMI, (kg/m <sup>2</sup> )	1.16 (1.15,1.18)	<0.001	1.10 (1.08–1.12)	<0.001
Blood pressure level				
Optimal	Reference		Reference	
Normal	2.46 (2.00–3.03)	<0.001	2.07 (1.68–2.56)	<0.001
High-normal	8.94 (7.24–11.04)	<0.001	5.45 (4.24–7.00)	<0.001

Abbreviations: aRR, adjusted relative risk; ART, assisted reproductive technology; BMI, body mass index; cRR, crude relative risk; Han ethnicity, the ethnic majority in China.

was consistent with other studies. A multicenter retrospective cohort study conducted in China discovered that women with high-normal BP at 14–19 weeks of gestation occupied about 8.3% of the total number of pregnant women. Additionally, their risk of PE was higher than that of pregnant women with optimal BP (OR: 4.028, 95% CI: 3.377, 4.804).<sup>10</sup> Another retrospective single-center cohort study in Japan<sup>11</sup> implied that around 4.4% of pregnant women had high-normal BP at 14–19 weeks of pregnancy, and the incidence of HDP in such pregnant women was 20.4%. Moreover, high-normal BP at 14–19 weeks of gestation was an independent risk factor for GH and PE. Although high-normal BP in pregnancy is currently classified as normal, such women are at significantly increased risk of developing HDP as shown in the above studies. Further investigation should be performed to determine the optimal threshold of abnormal BP during pregnancy.<sup>15</sup>

As a routine monitoring index in prenatal care and a key indicator for the diagnosis of HDP, BP reflects subclinical vascular status among young adults.<sup>16</sup> Regular BP measurement can help early warning of HDP, which is often asymptomatic in the first and second trimesters.<sup>7,14,17,18</sup> This study revealed that among so-called normotensive women, the risk of HDP increased as BP levels in the first half of pregnancy raised, reflecting that some women with HDP had underlying vascular dysfunction before pregnancy and early pregnancy. Foo and colleagues demonstrated that women with PE exhibited a relative increase in MAP and peripheral resistance and a decrease in cardiac output and index before pregnancy.<sup>19</sup> The function of peripheral arteries (such as fundus arteries and brachial arteries) was impaired in the first trimester. This also applied to GH because GH and PE had the same risk factors for cardiovascular disease. Specifically, about 25% of GH eventually progressed to PE. The earlier the gestational age when BP rise occurred, the greater the chance of PE.<sup>20</sup>

Nobles and colleagues suggested that a small increase in BP from prepregnancy to early pregnancy was associated with an increased risk of PE and GH, while women with PE may have a more significant increase in BP soon after conception (about 4 weeks).<sup>21</sup> This may be correlated with prepregnancy subclinical vascular dysfunction and an increase in circulating antiangiogenic factors such as soluble vascular endothelial growth factor receptor-1 (sFlt-1) during the first trimester.<sup>21,22</sup>

Our study further confirmed that primipara and high prepregnancy BMI were associated with the risk of HDP, which was consistent with previous studies.<sup>2,4,23</sup> However, our study failed to verify the correlation between ART and the risk of HDP. Since this study was aimed at low-risk groups, ART accounted for a small proportion, and the statistical power was insufficient. Thus, it cannot be ruled out that the incidence of PE in this population was reduced by oral aspirin. The findings of this study were consistent with those of the above-mentioned retrospective study of Asian populations. Considering that Asian pregnant women have approximately 4% lower MAP levels than the Caucasian population,<sup>24</sup> it remains unclear whether the results of this study can apply to other populations. This study, however, is subject to several limitations. Physiological and pathological changes during pregnancy may affect the accuracy of electronic sphygmomanometers.<sup>25</sup> Due to the limitations of the conditions at the time, the study did not use electronic sphygmomanometers certified for pregnant women, so there may be some measurement bias in BP measurement. Out-of-office (ambulatory or home) BP monitoring was not introduced in this study. Hence, the influence of masked hypertension on the study conclusion cannot be excluded. Additionally, the conclusion may be influenced by other factors such as the lack of smoking status of pregnant women and records of drug use during



pregnancy like aspirin or low molecular weight heparin, and prepregnancy BMI reliance on maternal self-report. Nevertheless, the present study, as a large prospective cohort study, provided robust epidemiological evidence for the role of high-normal BP in the first half of pregnancy in the early warning value of HDP.

## 5 | CONCLUSIONS

Our study demonstrated that among the low-risk healthy cohort, women with high-normal BP ( $130 \text{ mmHg} \leq \text{SBP} < 139 \text{ mmHg}$  and/or  $85 \text{ mmHg} \leq \text{DBP} < 90 \text{ mmHg}$ ) in the first half of pregnancy had a significantly higher risk of HDP. Pregnant women with HDP may have subclinical vascular endothelial dysfunction before the onset of symptoms. Furthermore, a slight increase in BP during this period may be a sensitive index of HDP.

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## CONFLICTS OF INTEREST

The authors report no conflicts of interest. All participants agreed to participate in the study and signed a written informed consent. The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

## AUTHOR CONTRIBUTIONS

Yu-Ming Li, Ning Yang, Wei Cai, and Xiao-Yi Zou conceive and designed the study, Xiao-Yi Zou, Wei Cai, Xiu-Long Niu, and Xin Zhang acquired the data, Yu-Ming Li, Xiao-Yi Zou, Ning Yang, Wei Cai, and Mao-Ti Wei analyzed and interpreted the data, and revised the article critically for important intellectual content together, Xiao-Yi Zou and Ning Yang drafted the article. All the authors approved the version to be published.

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