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# Visit-to-visit blood pressure variability is associated with gestational hypertension and pre-eclampsia

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ABSTRACT

*Objective:* Visit-to-visit blood pressure variability (VVV) was an independent risk factor for cardiovascular events. In pregnant women whose hemodynamic changes are unique, the role of VVV in hypertensive disorders is still obscure. Therefore, we aimed to investigate the association of VVV with gestational hypertension (GH) and pre-eclampsia (PE).

*Methods:* 14,702 pregnant women were recruited at around 13 weeks of their gestation. VVV during the second, third trimester and the whole pregnancy, were estimated as standard deviation (SD) or coefficient of variation (CV) of systolic blood pressure (SBP) or diastolic blood pressure (DBP). The associations between VVV, GH and PE were assessed by multivariate logistic regression models.

*Results:* 878 and 131 women developed GH and PE, respectively. VVV was significantly higher in GH and PE subjects than normotensive controls, regardless of whichever metric was calculated. In maximally adjusted models, odds ratio (95% confidence interval) of SBP-CV during the whole pregnancy was 1.62 (1.56–1.68) for GH, 1.14 (1.06–1.21) for PE, and 1.51 (1.47–1.56) for either GH or PE. The cooperation of SBP-CV to other risk factors could help in discriminating pregnant women at high risk of GH and PE.

*Conclusions:* VVV during pregnancy, especially SBP-CV, was independently associated with GH and PE. These results suggested that VVV could provide additional information to identify pregnant women at high risk of GH or PE. Further studies exploring prospective association between VVV, GH and PE are warranted.

## 1. Introduction

Gestational hypertension (GH) and pre-eclampsia (PE), which are common hypertensive disorders during pregnancy, affect around 3–8% of all pregnancies [1–4]. GH and PE remain major causes of maternal and perinatal morbidity and mortality [5,6]. Pregnant women with GH and PE are at high risk of cerebrovascular events, placental abruption, organ failure and disseminated intravascular coagulation [4]; fetuses of these mothers are more likely to suffer intrauterine growth restriction, prematurity, intrauterine death and perinatal death [7]. Therefore, it is urgent to find accurate, noninvasive, low-cost predictor for surveillance and early treatment of populations at high risk of GH and PE.

A number of studies have revealed that blood pressure (BP) fluctuates across a wide time scale, from years to months, weeks, days, and even within a 24 h period (beat-to-beat, minute-to-minute, hour-to-hour, and day-to-night changes) [8–10]. Rather than representing 'background noise' or a randomly occurring phenomenon, these variations of BP have been shown to be the result of complex interactions between extrinsic environmental, behavioral factors and intrinsic cardiovascular regulatory mechanisms [8]. Considerable evidence indicated that BP variability carried important diagnostic and prognostic value, and may be as clinically important as absolute BP values

*Abbreviations:* VVV, visit-to-visit blood pressure variability; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; GH, gestational hypertension; PE, pre-eclampsia; SD, standard deviation; CV, coefficient of variation; GDM, gestational diabetes mellitus; BMI, body mass index; AUC, area under curve; IDI, integrated discrimination improvement; NRI, net reclassification improvement

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[11–15]. For example, increased BP variability was suggested to be associated with the development, progression, and severity of organ damage and cardiovascular disease (CVD) [8,11,12,14–17]. Visit-to-visit blood pressure variability (VVV) is a typical type of BP variability. It was demonstrated as random fluctuation around a patient's true underlying BP [14], and was found to be independently associated with risk of CVD and mortality [18]. Rothwell has demonstrated that VVV may be an even stronger predictor of cardiovascular disease than short-term BPV (i.e., ambulatory BPV) in hypertensive subjects [19].

The most important predictor of hypertensive disorders during pregnancy is BP [20]. Maternal hemodynamics begin to change within 5 weeks of gestation, the pattern of BP change during gestation is considered to be unique in pregnant women, and have obvious difference between normotensive and hypertensive pregnancies [21,22]. It was previously reported that short-term BP variability may have predictable value in early diagnosis of hypertensive complications in pregnancy [21,23]. However, evidence of associations between VVV, GH and PE is still lacking. Therefore, our study aims to investigate whether VVV during the second, third trimesters and over pregnancy (from baseline through delivery) differs among pregnant women who remain normotensive and those who develop GH or PE.

## 2. Materials and methods

### 2.1. Study population

We investigated 26,429 pregnant women who had regular antenatal examination beginning at around 13 weeks' gestation (baseline) through delivery between January 1th, 2015 and June 30th, 2018 in Maternal and Child Healthcare Center of Taicang, Jiangsu province, China. Later, 2884 women who were diagnosed with hypertension or experienced proteinuria at initial antenatal examination were excluded. We further excluded 7765 patients if there were fewer than three BP measurements in either the second or third trimester. Additionally, 128 subjects with polyembryony were excluded. GH was diagnosed as hypertension (measured twice 6 h apart, ≥140/90 mmHg) that manifested after 20 weeks' gestation without proteinuria [24]. BP of patients with GH generally returns to normal by 12 weeks postpartum. PE was defined as hypertension concurrent with proteinuria (proteinuria > 300 mg on a 24 h urinary collection or ≥1 + on dipstick in two urine samples) after 20 weeks' gestation, or without proteinuria but showed symptoms of thrombocytopenia, impaired liver function, new development of renal insufficiency, pulmonary edema or new onset of cerebral or visual disturbance [24]. In the remained 14,702 subjects, 878 and 131 women were diagnosed by obstetrician according to the diagnostic standard as GH and PE, respectively.

The primary outcome of the current study is GH or PE, second outcome is either GH or PE. The flow chart of the excluding and including process of our study population was illustrated in Fig. 1.

This study was approved by the ethics committee of Soochow University and Maternal and Child Healthcare Center of Taicang.

### 2.2. Data acquisition

When pregnant women started their antenatal examination in Maternal and Child Healthcare Center of Taicang, their baseline information including age, body mass index (BMI), BP, past obsterical history (such as gestation, parturition and abortion in previous pregnancy) were collected. During the following visit, weight gain during pregnancy, and presence or absence of gestational diabetes mellitus (GDM), anemia, hyperthyroidism and hypothyroidism during this time of pregnancy were also collected.

GDM was considered about 28 weeks of gestation, when any of the following criteria were met on the 75 g oral glucose tolerance test: fasting plasma glucose ≥5.1 mmol/L, at 1 h ≥ 10 mmol/L, and at 2 h ≥ 8.5 mmol/L [25]. Weight gain was defined as the difference between the weight at delivery and at baseline. Maternal anemia was defined as hemoglobin at delivery < 110.0 g/L [26].

### 2.3. Blood pressure variability

BP was measured using a calibrated mercury sphygmomanometer following a standardized protocol. All participants were seated in an upright position with back support and were asked to relax for 5 min. A cuff was placed around the non-dominant upper arm, which was supported at the level of the heart, with the bladder midline over the brachial artery pulsation. We assigned average of two sequential BP values to each record, with a minimum two-minute rest period between measurements, then the mean BP values was obtained from each visit.

To acquire VVV, at least six times of BP measurement (≥3 times in the second trimester and ≥3 times in the third trimester) were obtained from each pregnant woman. VVV was determined by standard deviation (SD) or coefficient of variation (CV) of either SBP or DBP by trimester and from baseline through delivery.

### 2.4. Statistical analysis

Baseline data are expressed as Mean ± SD for continuous variables and number (%) for categorical variables. Characteristics of women who developed GH or PE versus those who remained normotensive were compared using Student *t*-test or Chi-square test for continuous and categorical variables, respectively. Longitudinal linear mixed-effects models were used to examine the fluctuation between average BP at baseline and across gestation. We calculated odds ratio (OR) [95% Confidence level (95% Cl)] in three logistic models to evaluate the association of VVV with GH and PE. Model 1 was unadjusted. In model 2, age, BMI at baseline, mean SBP, mean DBP and BP measurement times at each trimester or during the whole pregnancy, and weight gain were adjusted. Based on model 2, Model 3 additionally controlled for gestational age, presence of GDM and anemia, gestation and parturition. Furthermore, *c*-statistics, continuous net reclassification index (NRI), and integrated discrimination improvement (IDI) were generated to evaluate any improvement in risk identification when VVV was added to the established risk factors in logistic models [27,28]. *P*-value < 0.05 was considered statistically significant. For database management and statistical analysis, we used Statistical Analysis System (SAS) software (version 9.4, SAS Institute, Cary, NC, USA).

## 3. Results

### 3.1. Baseline characteristics

A total of 14,702 patients had sufficient BP measurements to evaluate the VVV during pregnancy; 13693, 878 and 131 women with normal BP, GH and PE were identified in our study, respectively.

Characteristics of normotensive, GH subjects and PE subjects were listed in Table 1. Compared to normotensive subjects, both GH and PE subjects had higher BMI values at baseline. Mean gestational age at delivery was 37.53 ± 1.46 weeks in GH subjects, slightly older than that of normotensive women (37.33 ± 1.65 weeks, $P < 0.0001$). GH subjects experienced more weight gain (14.58 ± 5.47 kg) than normotensive women (13.75 ± 4.54 kg), with $P < 0.0001$. Mean SBP at baseline was the highest in GH subjects (114.60 ± 11.19 mmHg), followed by PE subjects (109.00 ± 10.81 mmHg) and then normotensive women (108.10 ± 10.40 mmHg). The same trend was found for DBP.

### 3.2. Blood pressure change during pregnancy

SBP and DBP were notably higher throughout pregnancy for women who had hypertensive disorders compared with normotensive women. In normal pregnancies, SBP and DBP slightly decreased from baseline to approximately 19 weeks' gestation and significantly increased from the

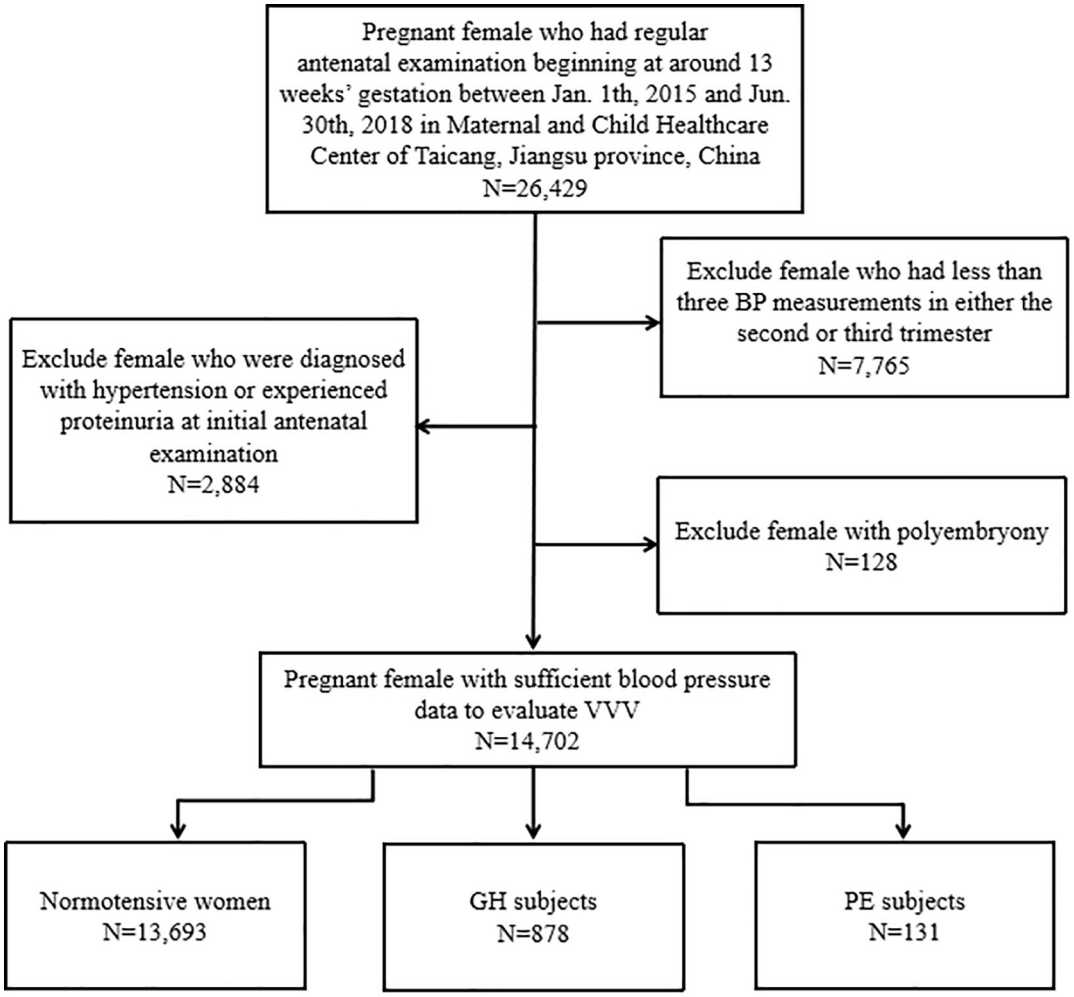


**Fig. 1.** The flow chart of selection process.

second to the third trimester ($P < 0.001$). Similar trends and enlarged increasement were found for women with GH and PE (Supplementary Fig. 1).

### 3.3. Association between VVV and PE and GH

VVV increased from the second to the third trimester in the whole population. During the pregnancy, the increasement of VVV in hypertensive participants was enlarged, compared with normotensive women ($P < 0.001$) (Fig. 2 and Supplementary Table 1 (A and B)).

We then estimated the associations between VVV and hypertensive outcomes by multiple logistic regression models (Table 2). After controlling for covariates (age, BMI at baseline, mean SBP, mean DBP and BP measurement times at each trimester or during pregnancy, weight gain, gestational age, presence of GDM and anemia, gestation and parturition), VVV derived from SBP was independently associated with both GH and PE; but VVV from DBP failed to reach significance. In maximally adjusted logistic regression models, SBP-CV during the whole pregnancy yielded the largest ORs for PE (OR = 1.14, 95%CI = 1.06–1.21), and this metric was still significant for GH (OR = 1.62, 95%CI = 1.56–1.68) and either GH or PE (OR = 1.51, 95%CI = 1.47–1.56).

### 3.4. Additional discriminative information of VVV

We further examined whether adding CV of SBP to a logistic regression model consisting of other factors could improve identification of subject at risk of GH or PE. As shown in Table 3, adding CV of SBP to model 3 including age, BMI at baseline, mean SBP, mean DBP and BP measurement times during pregnancy, weight gain, gestational age, presence of GDM and anemia, gestation and parturition, the discriminative ability for GH (*c*-statistics increased from 0.868 to 0.919; NRI = 96.59%; IDI = 11.65%; $P < 0.0001$) and either GH or PE (*c*-statistics increased from 0.837 to 0.884; NRI = 84.50%; IDI = 10.26%; $P < 0.0001$) were significantly increased. Significantly elevated NRI and IDI values were also obtained for PE (NRI = 16.01%, $P = 0.068$; IDI = 0.21%, $P = 0.0009$).

## 4. Discussion

GH and PE are major contributors to maternal and perinatal morbidity and mortality [4]. We revealed associations between VVV and hypertensive outcomes. These associations were independent and additive to absolute values of BP. Furthermore, the improved risk reclassification of GH and PE after incorporating VVV to traditional variables, suggested that serial assessment of BP and VVV during pregnancy may facilitate clinical management decision.

Previously, it was reported that VVV presented as SD of SBP was significantly higher in hypertensive patients than in normotensive subjects throughout pregnancy in Korea [29]. The current study found similar result and further revealed that VVV, especially SBP-CV, was an independent risk factor of GH and PE.

Increased VVV may be a marker of low artery elasticity [30] and increased arterial stiffness [31]. High VVV could represent an inability

**Table 1**
Baseline characteristics of normotensive, GH and PE subjects during pregnancy (Participants included, N = 14702).

| Variable* | Normotensive subjects (N = 13693) | GH subjects (N = 878) | *P*-value | PE subjects (N = 131) | *P*-value |
|---|---|---|---|---|---|
| Age (years) | 27.14 ± 4.28 | 27.26 ± 4.85 | 0.481 | 27.52 ± 4.61 | 0.316 |
| Body mass index at baseline (kg/m$^2$) | 21.43 ± 2.92 | 23.13 ± 3.79 | < 0.0001 | 22.21 ± 3.35 | 0.009 |
| Gestational age (week) | 37.33 ± 1.65 | 37.53 ± 1.46 | < 0.0001 | 37.56 ± 1.57 | 0.112 |
| Primipara (n, %) | 7112 (51.94%) | 499 (56.83%) | 0.005 | 61 (46.56%) | 0.253 |
| GDM (n, %) | 2713 (19.81%) | 224 (25.51%) | < 0.0001 | 24 (18.32%) | 0.742 |
| Hyperthyroidism (n, %) | 92 (0.67%) | 7 (0.80%) | 0.668 | 0 (0.00%) | 1.000 |
| Hypothyroidism (n, %) | 143 (1.04%) | 10 (1.14%) | 0.732 | 1 (0.76%) | 1.000 |
| Abortion in previous pregnancy (n, %) | 1824 (13.32%) | 125 (14.24%) | 0.443 | 19 (14.50%) | 0.869 |
| Mean SBP during pregnancy (mmHg) | 112.90 ± 7.51 | 123.60 ± 6.95 | < 0.0001 | 116.10 ± 8.97 | < 0.0001 |
| Mean DBP during pregnancy (mmHg) | 69.03 ± 5.36 | 76.78 ± 5.42 | < 0.0001 | 71.69 ± 6.69 | < 0.0001 |
| Mean SBP at baseline (mmHg) | 108.10 ± 10.40 | 114.60 ± 11.19 | < 0.0001 | 109.00 ± 10.81 | 0.296 |
| Mean DBP at baseline (mmHg) | 67.36 ± 11.00 | 72.31 ± 8.90 | < 0.0001 | 68.83 ± 8.61 | 0.054 |
| Mean SBP in 2nd trimester (mmHg) | 109.40 ± 8.53 | 117.50 ± 9.26 | < 0.0001 | 111.80 ± 9.43 | 0.004 |
| Mean SBP in 3rd trimester (mmHg) | 115.50 ± 8.20 | 128.00 ± 7.05 | < 0.0001 | 119.30 ± 10.42 | < 0.0001 |
| Mean DBP in 2nd trimester (mmHg) | 66.68 ± 6.20 | 72.55 ± 6.99 | < 0.0001 | 69.20 ± 7.05 | < 0.0001 |
| Mean DBP in 3rd trimester (mmHg) | 70.76 ± 5.86 | 79.85 ± 5.61 | < 0.0001 | 73.62 ± 7.57 | < 0.0001 |
| Weight gain (kg) | 13.75 ± 4.54 | 14.58 ± 5.47 | < 0.0001 | 13.62 ± 4.67 | 0.741 |
| SBP-SD during pregnancy (mmHg) | 8.38 ± 2.70 | 10.73 ± 3.33 | < 0.0001 | 9.56 ± 3.69 | 0.0004 |
| SBP-CV during pregnancy (%) | 7.46 ± 2.46 | 8.76 ± 2.94 | < 0.0001 | 8.21 ± 3.06 | 0.006 |
| DBP-SD during pregnancy (mmHg) | 6.42 ± 2.05 | 7.93 ± 2.52 | < 0.0001 | 6.72 ± 2.34 | 0.152 |
| DBP-CV during pregnancy (%) | 9.36 ± 3.11 | 10.46 ± 3.62 | < 0.0001 | 9.39 ± 3.27 | 0.906 |
| SBP-SD in 2nd trimester (mmHg) | 6.79 ± 3.30 | 7.62 ± 3.90 | < 0.0001 | 7.62 ± 3.96 | 0.018 |
| SBP-CV in 2nd trimester (%) | 6.22 ± 3.03 | 6.51 ± 3.34 | 0.013 | 6.82 ± 3.51 | 0.055 |
| SBP-SD in 3rd trimester (mmHg) | 7.29 ± 3.17 | 9.30 ± 4.13 | < 0.0001 | 8.03 ± 4.02 | 0.037 |
| SBP-CV in 3rd trimester (%) | 6.35 ± 2.82 | 7.35 ± 3.45 | < 0.0001 | 6.77 ± 3.35 | 0.156 |
| BP measurement times in 2nd trimester | 3.91 ± 0.44 | 3.88 ± 0.49 | 0.070 | 3.91 ± 0.47 | 0.899 |
| BP measurement times in 3rd trimester | 5.46 ± 1.51 | 5.54 ± 1.48 | 0.107 | 5.44 ± 1.52 | 0.851 |
| BP measurement times during the whole pregnancy | 9.37 ± 1.60 | 9.43 ± 1.57 | 0.333 | 9.34 ± 1.62 | 0.832 |

*SD*, standard deviation; *CV*, coefficient of variation; *GDM*, gestational diabetes mellitus; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *PE*, pre-eclampsia; *GH*, gestational hypertension.

* Baseline stands for the time (around 13 weeks of gestation) that individuals firstly visited Maternal and Child Healthcare Center of Taicang.

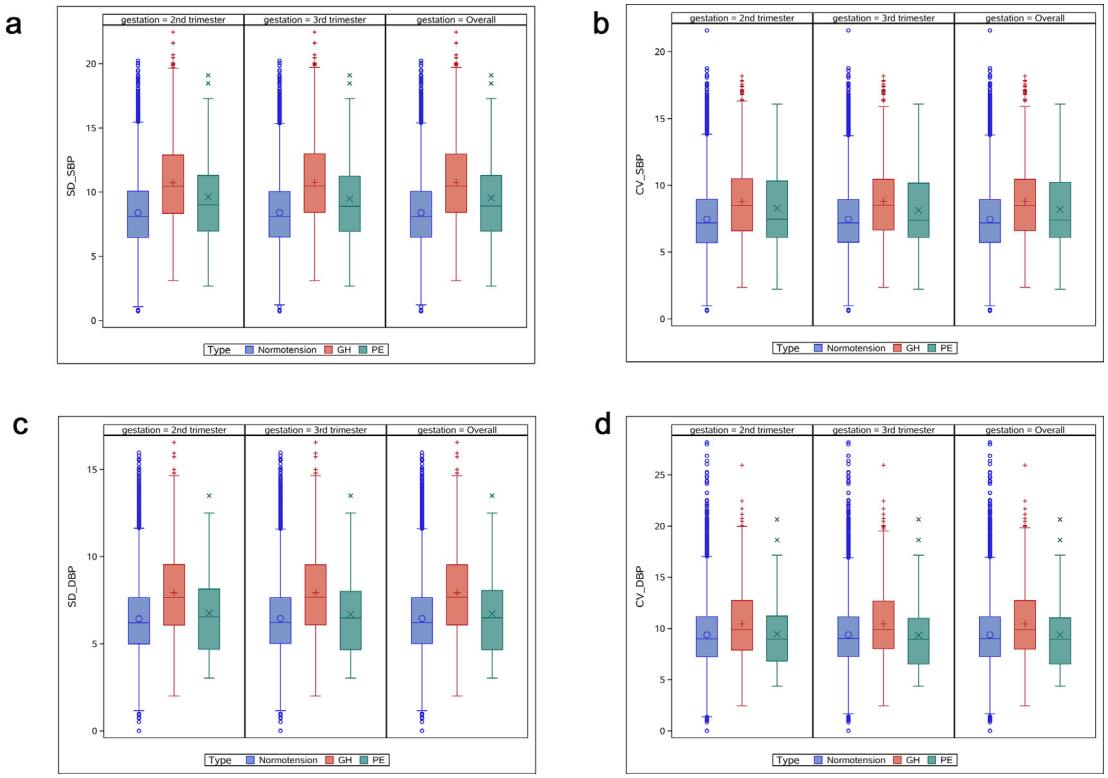


**Fig. 2.** Visit-to-visit blood pressure variability by presence of hypertensive disorders during pregnancy. Panel A: SD of SBP; Panel B: CV of SBP; Panel C: SD of DBP; Panel D: CV of DBP.

**Table 2**
Association of visit-to-visit blood pressure variability (VVV) with GH, PE, and either GH or PE.

| Gestational age | Metric of VVV | Model 1* | | Model 2* | | Model 3* | |
|---|---|---|---|---|---|---|---|
| | | OR (95%Cl) | *P*-value | OR (95%Cl) | *P*-value | OR (95%Cl) | *P*-value |
| *GH* | | | | | | | |
| 2nd trimester | SBP-SD (mmHg) | 1.07 (1.05–1.09) | < 0.0001 | 1.05 (1.03–1.08) | < 0.0001 | 1.05 (1.03–1.08) | < 0.0001 |
| | SBP-CV (%) | 1.03 (1.01–1.05) | 0.008 | 1.08 (1.05–1.10) | < 0.0001 | 1.08 (1.05–1.10) | < 0.0001 |
| | DBP-SD (mmHg) | 1.07 (1.04–1.09) | < 0.0001 | 1.05 (1.02–1.08) | 0.0003 | 1.05 (1.03–1.08) | 0.0002 |
| | DBP-CV (%) | 1.00 (0.99–1.02) | 0.659 | 1.05 (1.03–1.07) | < 0.0001 | 1.05 (1.03–1.07) | < 0.0001 |
| 3rd trimester | SBP-SD (mmHg) | 1.17 (1.15–1.20) | < 0.0001 | 1.34 (1.31–1.38) | < 0.0001 | 1.34 (1.31–1.38) | < 0.0001 |
| | SBP-CV (%) | 1.11 (1.09–1.14) | < 0.0001 | 1.41 (1.37–1.46) | < 0.0001 | 1.41 (1.37–1.45) | < 0.0001 |
| | DBP-SD (mmHg) | 1.18 (1.15–1.21) | < 0.0001 | 1.36 (1.32–1.40) | < 0.0001 | 1.36 (1.32–1.40) | < 0.0001 |
| | DBP-CV (%) | 1.05 (1.03–1.07) | < 0.0001 | 1.24 (1.21–1.27) | < 0.0001 | 1.24 (1.21–1.27) | < 0.0001 |
| Overall | SBP-SD (mmHg) | 1.29 (1.27–1.32) | < 0.0001 | 1.49 (1.45–1.54) | < 0.0001 | 1.49 (1.44–1.54) | < 0.0001 |
| | SBP-CV (%) | 1.20 (1.17–1.23) | < 0.0001 | 1.62 (1.57–1.69) | < 0.0001 | 1.62 (1.56–1.68) | < 0.0001 |
| | DBP-SD (mmHg) | 1.34 (1.31–1.38) | < 0.0001 | 1.57 (1.51–1.63) | < 0.0001 | 1.57 (1.51–1.63) | < 0.0001 |
| | DBP-CV (%) | 1.11 (1.08–1.13) | < 0.0001 | 1.40 (1.36–1.44) | < 0.0001 | 1.40 (1.36–1.44) | < 0.0001 |
| *PE* | | | | | | | |
| 2nd trimester | SBP-SD (mmHg) | 1.07 (1.02–1.12) | 0.008 | 1.06 (1.01–1.11) | 0.018 | 1.06 (1.01–1.11) | 0.019 |
| | SBP-CV (%) | 1.06 (1.01–1.12) | 0.031 | 1.07 (1.01–1.13) | 0.015 | 1.07 (1.01–1.12) | 0.017 |
| | DBP-SD (mmHg) | 1.04 (0.98–1.11) | 0.173 | 1.04 (0.97–1.10) | 0.287 | 1.04 (0.97–1.10) | 0.279 |
| | DBP-CV (%) | 1.01 (0.97–1.06) | 0.526 | 1.02 (0.98–1.07) | 0.306 | 1.02 (0.98–1.07) | 0.298 |
| 3rd trimester | SBP-SD (mmHg) | 1.06 (1.01–1.11) | 0.030 | 1.06 (1.01–1.12) | 0.015 | 1.06 (1.01–1.11) | 0.020 |
| | SBP-CV (%) | 1.04 (0.98–1.10) | 0.156 | 1.07 (1.01–1.14) | 0.022 | 1.07 (1.01–1.13) | 0.029 |
| | DBP-SD (mmHg) | 0.98 (0.92–1.05) | 0.647 | 1.00 (0.93–1.07) | 0.910 | 0.99 (0.93–1.07) | 0.859 |
| | DBP-CV (%) | 0.97 (0.93–1.02) | 0.287 | 1.00 (0.95–1.05) | 0.980 | 1.00 (0.95–1.05) | 0.936 |
| Overall | SBP-SD (mmHg) | 1.13 (1.07–1.19) | < 0.0001 | 1.13 (1.07–1.19) | < 0.0001 | 1.13 (1.06–1.19) | < 0.0001 |
| | SBP-CV (%) | 1.10 (1.04–1.18) | 0.002 | 1.14 (1.07–1.22) | < 0.0001 | 1.14 (1.06–1.21) | 0.0001 |
| | DBP-SD (mmHg) | 1.05 (0.97–1.13) | 0.271 | 1.05 (0.97–1.14) | 0.226 | 1.05 (0.97–1.14) | 0.260 |
| | DBP-CV (%) | 1.00 (0.94–1.05) | 0.903 | 1.03 (0.97–1.09) | 0.307 | 1.03 (0.97–1.09) | 0.345 |
| *Either GH or PE* | | | | | | | |
| 2nd trimester | SBP-SD (mmHg) | 1.07 (1.05–1.09) | < 0.0001 | 1.05 (1.03–1.07) | < 0.0001 | 1.05 (1.03–1.08) | < 0.0001 |
| | SBP-CV (%) | 1.04 (1.01–1.06) | 0.001 | 1.07 (1.05–1.10) | < 0.0001 | 1.07 (1.05–1.10) | < 0.0001 |
| | DBP-SD (mmHg) | 1.06 (1.04–1.09) | < 0.0001 | 1.05 (1.02–1.08) | 0.0003 | 1.05 (1.02–1.08) | 0.0002 |
| | DBP-CV (%) | 1.01 (0.99–1.02) | 0.518 | 1.05 (1.03–1.06) | < 0.0001 | 1.05 (1.03–1.07) | < 0.0001 |
| 3rd trimester | SBP-SD (mmHg) | 1.16 (1.14–1.18) | < 0.0001 | 1.29 (1.26–1.32) | < 0.0001 | 1.29 (1.26–1.32) | < 0.0001 |
| | SBP-CV (%) | 1.11 (1.09–1.13) | < 0.0001 | 1.34 (1.31–1.38) | < 0.0001 | 1.34 (1.31–1.38) | < 0.0001 |
| | DBP-SD (mmHg) | 1.16 (1.13–1.18) | < 0.0001 | 1.29 (1.25–1.33) | < 0.0001 | 1.29 (1.25–1.33) | < 0.0001 |
| | DBP-CV (%) | 1.04 (1.02–1.06) | < 0.0001 | 1.19 (1.17–1.22) | < 0.0001 | 1.19 (1.17–1.22) | < 0.0001 |
| Overall | SBP-SD (mmHg) | 1.28 (1.25–1.31) | < 0.0001 | 1.42 (1.38–1.46) | < 0.0001 | 1.41 (1.38–1.45) | < 0.0001 |
| | SBP-CV (%) | 1.19 (1.16–1.22) | < 0.0001 | 1.52 (1.47–1.57) | < 0.0001 | 1.51 (1.47–1.56) | < 0.0001 |
| | DBP-SD (mmHg) | 1.31 (1.27–1.35) | < 0.0001 | 1.46 (1.41–1.51) | < 0.0001 | 1.46 (1.41–1.51) | < 0.0001 |
| | DBP-CV (%) | 1.09 (1.07–1.11) | < 0.0001 | 1.32 (1.29–1.35) | < 0.0001 | 1.32 (1.29–1.35) | < 0.0001[f] |

[f] *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *GDM*, gestational diabetes mellitus; *SD*, standard deviation; *CV*, coefficient of variation; *PE*, pre-eclampsia, *GH*, gestational hypertension. *Model 1: Unadjusted model; *Model 2: Adjusted for Age, BMI at baseline, mean SBP, mean DBP and BP measurement times at each trimester or during pregnancy, weight gain; *Model 3: Further adjusted for Gestational age, Presence of GDM and anemia, Gestation and Parturition.

to maintain hemodynamic homeostasis and may have negative impacts on the vascular system [32]. Meanwhile, it was speculated that patients with greater VVV were more likely to have cardiovascular target organ damage, which would make them more susceptible to all CVD events [16]. What's important, the main pathognomonic factors of hypertensive disorders in pregnancy are considered to be cardiovascular maladaptation and vasoconstriction due to abnormal placental vasculature [33]. Placental under perfusion causes the release of antiangiogenic factors and other substances that can cause maternal endothelial dysfunction [34], and thus increase VVV. Studies found that patients with GH or PE had elevated sympathetic nervous activity, which may also influence hyemodynamic instability, and eventually VVV [35].

Our research has several strengths. First, original data were obtained in a general pregnant population rather than selected persons recruited for clinical trials. Second, the sample size of the current study is relatively large and could lead to relatively reliable results. Several limitations are also apparent. First, subjects were not all regularly followed to have BP measurements, and there were variations between visits at each time point and between subjects. In order to minimize the variance, we excluded women who performed BP measurements fewer than three BP measurements in either the second or third trimester. Second, based on the policy of antenatal care in Taicang City, two or three times of antenatal examination are recommended for general pregnant women before 20 weeks' gestation. In our study population, only 768 subjects had sufficient blood pressure measurements (three times or more) to calculate VVV before 20 weeks' gestation. Thus we could not estimate prospective associations between VVV and GH/PE. Third, given the observational nature of our study, our findings do not confirm an unequivocal association between increased VVV and risk of GH and PE. Further studies to explore prospective association between VVV, GH and PE are warrant.

Based on the current research, VVV was associated with increased risk of developing GH or PE during pregnancy, suggesting serial assessment of BP may be helpful to identify pregnant women at high risk of GH or PE. Further studies to explore standardized approach to measure VVV for practical usage are warrant.

**Table 3**
Reclassification and additional discriminative ability for GH, PE, and either GH or PE by CV of SBP among pregnant women.

| Complications | Model | C-statistics | | Continuous NRI, % | | IDI, % | |
|---|---|---|---|---|---|---|---|
| | | Estimate (95% Cl) | *P*-value | Estimate (95% Cl) | *P*-value | Estimate (95% Cl) | *P*-value |
| GH | Model 2 | 0.866 (0.854–0.879) | | Reference | | Reference | |
| | Model 2 + SBP_CV | 0.918 (0.909–0.928) | < 0.0001 | 96.63 (90.33–102.93) | < 0.0001 | 11.78 (10.48–13.08) | < 0.0001 |
| | Model 3 | 0.868 (0.855–0.880) | | Reference | | Reference | |
| | Model 3 + SBP_CV | 0.919 (0.909–0.928) | < 0.0001 | 96.59 (90.29–102.88) | < 0.0001 | 11.65 (10.35–12.96) | < 0.0001 |
| PE | Model 2 | 0.600 (0.550–0.651) | | Reference | | Reference | |
| | Model 2 + SBP_CV | 0.612 (0.559–0.664) | 0.551 | 19.50 (2.31–36.69) | 0.026 | 0.23 (0.10–0.36) | 0.0004 |
| | Model 3 | 0.625 (0.573–0.677) | | Reference | | Reference | |
| | Model 3 + SBP_CV | 0.637 (0.584–0.690) | 0.434 | 16.01 (-1.17–33.18) | 0.068 | 0.21 (0.08–0.33) | 0.0009 |
| Either GH or PE | Model 2 | 0.835 (0.821–0.849) | | Reference | | Reference | |
| | Model 2 + SBP_CV | 0.883 (0.870–0.895) | < 0.0001 | 84.00 (77.96–90.03) | < 0.0001 | 10.41 (9.31–11.51) | < 0.0001 |
| | Model 3 | 0.837 (0.823–0.851) | | Reference | | Reference | |
| | Model 3 + SBP_CV | 0.884 (0.872–0.896) | < 0.0001 | 84.50 (78.48–90.53) | < 0.0001 | 10.26 (9.16–11.36) | < 0.0001 |

*NRI*, net reclassification improvement ; *IDI*, integrated discrimination improvement ; *SBP,* systolic blood pressure; *GDM,* gestational diabetes mellitus; *CV,* coefficient of variation; *PE*, pre-eclampsia; *GH,* gestational hypertension.
*Model 2: Adjusted for Age, BMI at baseline, mean SBP, mean DBP and BP measurement times during pregnancy, weight gain.
*Model 3: Further adjusted for Gestational age, Presence of GDM and anemia, Gestation and Parturition.

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## Conflict of interest

No potential conflicts of interest were reported by the authors.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.09.009.

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