Effect of premature birth on long-term systolic blood pressure variability in women

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Abstract

Objective: To investigate the effect of premature birth (PTB) on long-term systolic blood pressure (SBP) variability (SBPV) in women.
Methods: A total of 1974 pregnant women were divided into PTB group and non-PTB (NPTB) group. The SBP standard deviation (SSD) was calculated by four annual SBP values measured in 2006–2007, 2008–2009, 2010–2011, and 2012–2013. SBP coefficient of variation (SCV) was calculated by dividing SSD with mean SBP. Multivariate logistic regression analysis was used to analyze the influence of PTB on long-time SSD and SCV in women.
Results: SSD and SCV of the PTB group (10.95 mm Hg and 9.05%, respectively) were higher than those of the NPTB group (9.81 mm Hg and 8.23%, respectively), but there were no significant differences ($p>0.05$). The number of patients with SSD >9.87 mm Hg and SCV >8.28% in the PTB and NPTB groups was 57 (51.40%) and 62 (55.90%) and 747 (40.10%) and 841 (45.10%), respectively. The number of patients with SSD >9.87 mm Hg and SCV >8.28% in the PTB group was significantly higher than that in the NPTB group ($p<0.05$). Multiple logistic regression analysis showed that after adjusting other risk factors, the PTB group was at a risk of SSD and SCV elevations with OR values of 1.60 (95% CI: 1.06–2.40) and 1.64 (95% CI: 1.10–2.45), respectively.
Conclusion: PTB is a risk factor of long-time SBPV in women, which might be a potential reason for cardiovascular events. Pregnancy may be an important opportunity for early identification of women at an increased risk of cardiovascular disease later in life. *(Anatol J Cardiol 2018; 20: 347-53)*
Keywords: premature birth, blood pressure variability, risk factor

Introduction

Cardiovascular disease (CVD) is one of the leading causes of death in women worldwide (1). The reason behind this is that women experience pregnancy-related complications such as gestational diabetes mellitus, preeclampsia, intrauterine growth retardation, and preterm delivery, which lead to a high risk of CVD (2-7). Therefore, it has been suggested that pregnancy offers an opportunity to identify women at risk of future CVD (8-10). However, whether these pregnancy complications have separate, independent effects on future cardiovascular risk and if so the manner in which their relative and absolute associations differ from each other remain unclear.

Pregnancy and delivery are special physiological processes in women, while premature birth (PTB) is one of the major complications of pregnancy. Premature birth (PTB, delivery in <37 weeks) is responsible for most cases of perinatal mortality and morbidity. Until recently, PTB was thought to have no long-term sequelae for mothers; however, emerging evidence indicates that women with PTB have a 2- to 3-fold increased risk for CVD (7, 11, 12). Mechanisms that could link these conditions are not understood, and whether this association is completely because of hypertension during pregnancy is equivocal (13, 14).

Blood pressure variability (BPV) refers to the degree of blood pressure fluctuations within a certain period of time. In the 18th century, blood pressure was found to be non-constant and fluctuating within a certain range. In 1948, Hammarström et al. (15) first proposed the concept of BPV. However, BPV has been believed to be a normal physiological fluctuation and has not been paid enough attention. In recent years, with increased researches on blood pressure, it has been found that elevated BPV is associated with an increased incidence of hypertension

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resulting in organ damage and cardiovascular and cerebrovascular events (16). It has been found that long-time BPV is affected by age, smoking, elevated blood pressure, and salt sensitivity (17-20). BPV is greater in women than in men (21).

Recent studies have found that the incidence and risk of death due to hypertension and cardiovascular events in women with PTB are higher than those in women with non-PTB (NPTB) (13, 14, 22). However, till date, no studies have investigated the association between PTB and systolic BPV (SBPV). Therefore, the current study was designed to investigate the effect of PTB on long-term SBPV in women.

Methods

Study participants

This is a cohort study involving 1974 pregnant women workers of Kailuan who gave birth between 1976 and 2007 in Kailuan Hospital and had complete medical record of delivery (Registration number: ChiCTR-TNC-1100 1489). Participants were divided into the PTB group (n=111) and NPTB group (n=1863). This study was approved by the Ethics Committee of Kailuan Hospital. All subjects enrolled in the study provided written informed consent. The female workers, who had complete delivery records and completed four annual medical examinations of Kailuan Group in 2006–2007, 2008–2009, 2010–2011, and 2012–2013 were included. The exclusion criteria were patients with a history of stroke (excluding lacunar infarction) or myocardial infarction; missing data on gestational weeks; and missing data on blood pressure of any one of the four medical examinations.

Collection of data on pregnancy and delivery

In the survey, participants were asked to fill in their delivery time and hospital name. The trained medical staff checked the medical records and filled the delivery information including gestational weeks, birth age, delivery time and mode, ante- and post-partum blood pressure, height, weight, fundal height, abdominal circumference and edema, fetal sex, fetal weight, fetal height, fetal survival, laboratory test results (including platelet count, hemoglobin, and urine protein), and complications of the mother and infant (if any).

Medical examination data

Epidemiological survey: A common epidemiological questionnaire was developed, and participants were asked to fill in their individual information. Trained medical staff verified all the items by personal interviews with participants. The survey included collection of the following information: demographic data such as age, ethnicity, and occupation; family history; personal history, such as diet habit, living habit, smoking history, drinking history, and physical exercise; and disease history, such as hypertension, diabetes, coronary heart disease, stroke, and other cardiovascular diseases.

Parameters of anthropometric examinations included height and weight. The examinations were carried out by trained medical staff using standard methods stated in a previous research (23). Body mass index (BMI)=weight (kg)/[height (m)×height (m)].

Blood pressure was measured by physicians strictly as per the standard procedure using a standard mercury sphygmomanometer between 7:00 am and 9:00 am on the day of medical examination. Participants were asked to stop smoking and drinking tea or coffee at least 30 min prior to the measurement and sit and relax for 15 min. Systolic blood pressure (SBP) involved measuring in phase I of Korotkoff, whereas diastolic blood pressure (DBP) involved measuring in phase V of Korotkoff. Measurements were conducted continuously for three times, with an interval of 1–2 min, and the average value was used.

Laboratory testing: Fasting blood (5 mL) was collected from the cubital vein from 7:00 am to 9:00 am on the day of the medical examination from all the participants and stored in two vacuum tubes containing ethylenediaminetetraacetic acid, one with 1 mL and the other with 4 mL of blood. The serum was collected after centrifugation, and the total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), and fasting blood glucose (FBG) levels were measured using Hitachi 7080 Biochemical Analyzer (7080 Automatic Analyzer, HITACHI, Tokyo, Japan), while serum high-sensitivity C-reactive protein (hsCRP) level was tested using immunoturbidimetry. All these measurements were conducted by professional inspectors using reagent kits strictly in accordance with the reagent instruction of the batch quality control.

Diagnostic criteria

Premature diagnostic criteria: According to the clinical diagnosis and treatment recommendation of premature birth, PTB refers to delivery between 28 and 37 weeks (196–258 days) (12).

Hypertension diagnosis criteria: The primary hypertension diagnosis as per the Chinese Hypertension Prevention Guide (2010 edition) refers to patients with SBP ≥140 mm Hg and (or) DBP ≥90 mm Hg without taking any antihypertensive drugs or patients currently using antihypertensive drugs.

Blood pressure variability

This study adopted a long-time BPV (i.e., interannual BPV), which had two representations. One was blood pressure standard deviation and the other was blood pressure coefficient of variation (CV=standard deviation/mean blood pressure×100%). First, the mean SBP of four measurements in the medical examination was considered as the SBP during the years 2006–2007, 2008–2009, 2010–2011, and 2012–2013. The mean and standard deviation of the interannual SBP was calculated according to the four annual SBP values, where SBP standard deviation, DBP standard deviation, SBP coefficient of variance, and DBP coefficient of variance were noted as SSD, DSD (DBP standard deviation), SCV, and DCV, respectively.

Statistical analysis

All the medical examination results were verified by professionals of each hospital and were uploaded in an Oracle 10.2 g database at the Computer Center of Kailuan Hospital. Microsoft Excel 2003 was used to input the childbirth data and a database was created, while SPSS (SPSS Inc., Chicago, Illinois, USA) software was used for statistical analysis. All the measurement data with normal distribution were expressed as mean±standard deviation ($\bar{x}$±s), while independent sample t-test was used to compare data between two groups. All the count data were expressed by n (%), while the χ^2-test was used for comparison between the two groups. Because hsCRP and TG levels were in accordance with skew distribution, their log-transformed results were applied with independent sample t-test for comparison between groups. Multivariate logistic regression method was used to analyze effects of PTB on SSD and SCV, while $p<0.05$ (two-sided test) was considered as statistically significant.

Results

Subject disposition

A total of 3965 Kailuan female employees who gave birth between 1976 and 2007 in the hospital and had complete delivery records were included in the study. Of these, three cases had missing data of gestation weeks, 1788 cases had medical examination less than four times, six cases had histories of stroke and myocardial infarction, and 194 cases participated four times in medical examinations but had incomplete blood pressure data. Eventually, 1974 cases were included for statistical analysis. Based on the presence of PTB history, participants were divided into PTB group (n=111) and NPTB group (n=1863) (Fig. 1).

Baseline data comparison between PTB and NPTB groups

The age of participants at the annual examination between 2006 and 2007 ranged from 23 to 69 years (median, 38 years). The log-transformed TG and pregnancy-induced hypertension (PIH) of the PTB group were significantly higher than those of the NPTB group ($p<0.05$). The age, SBP, DBP, BMI, and hypertension of the PTB group were higher than those of the NPTB group, but the difference was not statistically significant ($p>0.05$). Meanwhile, the TC, HDL, and FBG of the PTB group showed only a decreased trend compared with those of the NPTB group ($p>0.05$) (Table 1).

SD and CV of the PTB and NPTB groups

The mean SSD and DSD values of all participants were 9.87 mm Hg and 6.40 mm Hg, respectively, whereas mean SCV and

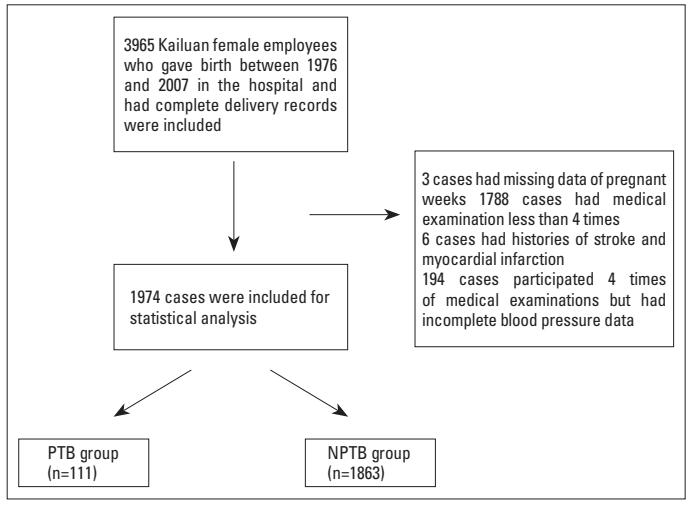

Figure 1. Study flow chart

Table 1. Baseline date from 2006 to 2007 of the PTB and NPTB group ($\bar{x}$±s)

Variable	Total (n=1974)	NPTB group (n=1863)	PTB group (n=111)	*P* value
Age (years)	39.99±7.50	39.94±7.47	40.84±7.97	0.221
SBP (mm Hg)	116.28±17.22	116.19±17.22	117.87±17.08	0.318
DBP (mm Hg)	76.36±10.29	76.28±10.32	77.79±9.69	0.134
BMI (kg/m^2)	23.92±3.78	23.91±3.79	24.16±3.75	0.502
TC (mmol/L)	4.70±0.92	4.71±0.92	4.63±0.94	0.407
HDL (mmol/L)	1.53±0.34	1.53±0.34	1.51±0.33	0.569
FBG (mmol/L)	5.09±1.18	5.09±1.20	5.02±0.86	0.497
lg-hsCRP	-0.33±0.67	-0.33±0.67	-0.35±0.68	0.710
lg-TG	0.01±0.25	0.01±0.25	0.07±0.24	0.018
PIH, n (%)	332 (16.80 %)	297 (15.90%)	35 (31.80%)	<0.001
Hypertension, n (%)	320 (16.20 %)	299 (16.00%)	21 (18.90%)	0.427

Age - age at examination, SBP - systolic blood pressure, DBP - diastolic blood pressure, BMI - body mass index, TC - total cholesterol, HDL - high-density lipoprotein, FBG - fasting blood glucose, lg-hsCRP - log-transformed high-sensitivity C-reactive protein, lg-TG - log-transformed triglyceride, 1 mm Hg = 0.133 kPa, PIH - pregnancy-induced hypertension

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Table 2. SD and CV values of the PTB and NPTB groups ($\bar{x}\pm s$)

Variable	Total (n=1974)	NPTB group (n=1863)	PTB group (n=111)	*P* value
SSD (mm Hg)	9.87±6.28	9.81±6.34	10.95±5.04	0.064
DSD (mm Hg)	6.40±3.13	6.38±3.08	6.68±3.94	0.329
SCV (%)	8.28±4.36	8.23±4.39	9.05±3.80	0.053
DCV (%)	8.24±3.82	8.23±3.78	8.41±4.50	0.625
SSD >9.87 mm Hg, n (%)	804 (40.70%)	747 (40.10%)	57 (51.40%)	0.022
DSD >6.40 mm Hg, n (%)	815 (41.30%)	770 (41.30%)	45 (40.50%)	0.921
SCV >8.28 %, n (%)	903 (45.70%)	841 (45.10%)	62 (55.90%)	0.031
DCV >8.24 %, n (%)	836 (42.40%)	785 (42.10%)	51 (45.90%)	0.431

SD - standard deviation, CV - coefficient of variation, SSD - systolic blood pressure standard deviation, DSD - diastolic blood pressure standard deviation, SCV - systolic blood pressure coefficient of variance, DCV - diastolic blood pressure coefficient of variance

Table 3. Multivariate logistic regression analysis of SSD

Model	Risk factor	B	SE	Wald	*P*	OR (95% CI)
Model 1	Premature birth	0.456	0.196	5.418	0.020	1.58 (1.08~2.31)
Model 2	Premature birth	0.438	0.204	4.621	0.032	1.55 (1.04~2.31)
	Age	0.065	0.007	94.818	0.000	1.07 (1.05~1.08)
	Body mass index	0.043	0.013	11.493	0.001	1.04 (1.02~1.07)
Model 3	Premature birth	0.469	0.208	5.101	0.024	1.60 (1.06~2.40)
	Age	0.055	0.007	56.613	0.000	1.06 (1.04~1.07)
	Body mass index	0.035	0.014	6.087	0.014	1.04 (1.01~1.06)
	Total cholesterol	0.127	0.061	4.333	0.037	1.14 (1.01~1.28)
	Hypertension	0.488	0.137	12.682	0.000	1.63 (1.25~2.13)

Model 1: PTB was the independent variable; Model 2: Age and BMI were corrected on the basis of Model 1; Model 3: TC, HDL, FBG, lg-CRP, lg-TG, PIH, and hypertension were corrected on the basis of Model 2.
TC - total cholesterol, HDL - high-density lipoprotein, FBG - fasting blood glucose, lg-CRP - log-transformed C-reactive protein, lg-TG - log-transformed triglyceride, PIH - pregnancy-induced hypertension

DCV values were 8.28% and 8.24%, respectively. Number of patients with SSD >9.87 mm Hg and DSD >6.40 mm Hg was 804 (40.70%) and 815 (41.30%), respectively, whereas number of patients with SCV >8.28% and DCV >8.24% was 903 (45.70%) and 836 (42.40%), respectively. Number of patients with SSD >9.87 mm Hg and SCV >8.28% in the PTB group was higher than that in the NPTB group ($p<0.05$). Number of patients with SSD, SCV, DSD, DCV, and DCV >8.24% in the PTB group was higher than that in the NPTB group, but the differences were not statistically significant ($p>0.05$). Number of patients with DSD >6.40 mm Hg in the PTB group was lower than that in the NPTB group without any statistically significant difference ($p>0.05$) (Table 2).

Multivariate logistic regression analysis of SSD

Because there was no exact cutoff value for SSD, the mean value of SSD of the total participants was adopted as the cutoff value. SSD ≥9.87 mm Hg (i.e., the value was 0 for SSD <9.87 mm Hg, whereas value was 1 for SSD ≥9.87 mm Hg) was set as a dependent variable, whereas PTB, age, BMI, TC, HDL, FBG, hsCRP, TG, PIH, and hypertension were set as independent variables. Model 1: PTB was set as an independent variable and NPTB as the control. The results showed that PTB was a risk factor for SSD ≥9.87 mm Hg and OR value was 1.58 (95% CI: 1.08–2.31, $p<0.05$). Model 2: Age and BMI were adjusted based on Model 1, and the results indicated that PTB was a risk factor for SSD ≥9.87 mm Hg and OR value was 1.55 (95% CI: 1.04–2.31, $p<0.05$). Model 3: TC, HDL, FBG, hsCRP, TG, PIH, and hypertension were adjusted on the basis of Model 2, and the results showed that PTB was a risk factor for SSD ≥9.87 mm Hg and OR value was 1.60 (95% CI: 1.06–2.40, $p<0.05$) (Table 3).

Multivariate logistic regression analysis of SCV

Because there was no exact cutoff value for SCV, the mean value of SCV of the total participants was adopted as the cut-

Table 4. Multivariate logistic regression analysis of SCV

Model	Risk factor	B	SE	Wald	*P*	OR (95% CI)
Model 1	Premature birth	0.441	0.197	5.026	0.025	1.55 (1.06~2.29)
Model 2	Premature birth	0.437	0.199	4.804	0.028	1.55 (1.05~2.29)
	Age	0.032	0.006	26.66	0.000	1.03 (1.02~1.05)
Model 3	Premature birth	0.496	0.203	5.951	0.015	1.64 (1.10~2.45)
	Age	0.031	0.007	20.721	0.000	1.03 (1.02~1.05)

Model 1: PTB was the independent variable; Model 2: AGE and BMI were corrected on the basis of Model 1; Model 3: TC, HDL, FBG, lg-CRP, lg-TG, PIH, and hypertension were corrected on the basis of Model 2.
TC - total cholesterol, HDL - high-density lipoprotein, FBG - fasting blood glucose, lg-CRP - log-transformed C-reactive protein, lg-TG - log-transformed triglyceride, PIH - pregnancy-induced hypertension

off value. SCV ≥8.28 mm Hg (i.e., the value was 0 for SCV <8.28 mm Hg, whereas value was 1 for SCV ≥8.28 mm Hg) was set as a dependent variable, whereas PTB, age, BMI, TC, HDL, FBG, hsCRP, TG, PIH, and hypertension were adopted as independent variables. Model 1: PTB was set as an independent variable and NPTB as the control. The results showed that PTB was a risk factor for SCV ≥8.28 mm Hg and OR value was 1.55 (95% CI: 1.06–2.29, p<0.05). Model 2: Age and BMI were adjusted based on Model 1, and the results indicated that PTB was a risk factor for SCV ≥8.28 mm Hg and OR value was 1.55 (95% CI: 1.05–2.29, p<0.05). Model 3: TC, HDL, FBG, hsCRP, TG, PIH, and hypertension were adjusted on the basis of Model 2, and the results showed that PTB was a risk factor for SCV ≥8.28 mm Hg and OR value was 1.64 (95% CI: 1.00–2.45, p<0.05) (Table 4).

Discussion

PTB is a complication during the perinatal stage, and its incidence is on the rise across the world (24). Incidence of PTB in some developed countries is 5%–9% (25), whereas the incidence in China is 5%–15%. Recent studies have shown that women with a history of PTB presented higher incidence of diabetes (24), cardio-cerebrovascular diseases (14), and hypertension (22) for a long-term or after childbirth. However, no studies have reported the impact of PTB on long-term SBPV in women.

It was found in the present study that the number of patients with SSD >9.87 mm Hg in the PTB group was higher than that in the NPTB group. Similarly, in the logistic regression analysis of SSD, the risk of SSD elevation in PTB group was 1.60 (95% CI: 1.06–2.40) times that in the NPTB group after adjusting other factors. These results have indicated that PTB is an independent risk factor for long-term SBPV elevation in women.

SD is based on the mean blood pressure, which means its value is influenced by the mean blood pressure. However, CV is the ratio of SD over the mean blood pressure, which excludes the effect of blood pressure (26). In the current study, it was found that the number of patients with SCV >8.28% in the PTB group was higher than that in the NPTB group. Logistic regression analysis of SCV showed that the risk of SCV elevation in the PTB group was 1.64 (95% CI: 1.10–2.45) times that in the NPTB group after adjusting other factors. These results indicate that PTB is an independent risk factor for long-term SBPV elevation in women after excluding the effect of mean blood pressure. Muntner et al. (21) found that long-term BPV in women was higher than that in men, but they did not propose any explanation for this phenomenon. PTB is a unique complication of pregnancy and delivery in women. Increased SSD and SCV in the PTB group in this study may explain the reason for higher SBPV in women than in men.

In addition, age and hypertension were involved in the SSD logistic regression model, and their OR values were 1.06 (1.04–1.07) and 1.63 (1.25–2.13), respectively, indicating that these factors together with PTB could promote elevation of BPV. Similarly, studies on elderly population by Chowdhury et al. (27) showed that age was also a risk factor for long-term BPV and its OR value was 1.55 (1.16–2.05). Muntner et al. (21) also found that long-term BPV could gradually increase with increase in blood pressure.

The current observational study cannot be used to explore the mechanism of long-term SBPV elevation in women with PTB; however, other studies have already shown that atherosclerosis may cause BPV elevation, while dyslipidemia is the main factor for atherosclerosis. Catov et al. (28, 29) have stated that women with PTB may present atherosclerosis before giving birth, which induces excessive deposition of blood lipid in the vascular wall as well as artery intima injury and endothelial dysfunction. This results in decreased vascular compliance and increased blood pressure fluctuations and thus presents BPV elevation. Pitiphat et al. (30) have proved that increase of serum CRP concentration during pregnancy is associated with PTB. High concentration of CRP may increase the release of endothelin-1 and reduce synthesis of nitric oxide by inhibiting endothelium-derived nitric oxide synthase, which influences the vasorelaxant activity and accelerates the process of atherosclerosis and finally results in decreased vascular compliance and BPV elevation.

Study limitations

There are some limitations of our study. First, patients with PTB were not grouped for comparison analysis due to a small

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number of cases. Second, only four annual SBP values were used to calculate SBPV, which might affect the accuracy of SSD and SCV. However, Shimbo et al. (31) only adopted three annual blood pressures to calculate annual BPV when they studied factors affecting annual BPV in postmenopausal women. Finally, a 2-year interval in blood pressure measurement may affect the repeatability of BPV. Chen et al. (32) have investigated the effects of low birth weight on annual BPV and adopted blood pressure measurement at an interval of 2-3 years. European Carotid Surgery Trial (33) found a good repeatability in BPV when the blood pressure measurement interval was 1 year and blood pressure was measured once at each visit. The present study involved the measurement of blood pressure for three times at each visit, which might result in even better repeatability in measuring annual BPV. In addition, medical examinations were conducted in chronological order with respect to the first examination, thereby eliminating the impact of seasonal variability and evaluating the impact of PTB on long-term SBPV in women in a better way.

Conclusion

In conclusion, our study investigated the influence of PTB on long-term SBPV in women, which might be the potential reason behind cardiovascular events. Pregnancy may provide an opportunity to identify women at an increased risk of CVD relatively early in life.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – S.W., X.Y.; Design – S.W., X.Y.; Supervision – L.S., H.Z.; Fundings – N/A; Materials – H.Z., S.W.; Data collection &/or processing – J.N., Y.W.; Analysis &/or interpretation – S.A., H.Z.; Literature search – S.A., J.N., Y.W.; Writing – L.S., S.A.; Critical review – L.S., X.Y.; Definition of intellectual content – S.A., J.N., Y.W.

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