Dose-response Relationship Between Maternal Blood Pressure in Pregnancy and Preterm Birth: Based on the Monitoring Data of 212,941 Pregnant Women in China

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Research Article

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Abstract

Background: Hypertensive disorders of pregnancy (HDP) is a generally accepted risk factor of preterm birth (PTB). Most related studies focus on the effects of various HDP on pregnancy outcomes. Based on large-scale maternal health monitoring data, this study analyzes the dose-response relationship between maternal Blood pressure (BP) in different trimesters and PTB.

Methods: Through the Maternal and Newborn Health Monitoring System in China, a total of 212,941 single-fetus pregnant women who delivered during 2014-2018 in 13 counties of 6 provinces in China were included in this study. BP level, distribution and changes in each trimester were described with linear trend test. Multivariate logistic regression analysis was performed to estimate the associations between BP groups in different gestational trimesters and PTB. Then a restricted cubic spline (RCS) was used to delineate the dose-response relationships between BP (both diastolic and systolic) during each trimester and PTB.

Results: The overall incidences of HDP and PTB were 7.07% and 4.04% respectively. The detection rates of HDP in the 1st, 2nd and 3rd trimesters were 1.03%, 2.06% and 6.23% respectively. Taking the group of normal BP as reference, the odds ratios(OR) of PTB for the groups of hypertension in the 1st, 2nd and 3rd trimesters was 3.23, 2.70 and 2.05 respectively (P<0.001). Hypotension in 3rd trimester was associated with a 1.5-fold higher risk of PTB (P<0.001). OR of PTB had a nonlinearly U-shaped association with SBP and DBP in the 1st, 2nd and 3rd trimesters.

Conclusions: The risks of PTB varied among pregnant women with the same BP in different trimesters. An increase of BP within the normal range during pregnancy could prevent PTB. Hypotension in 3rd trimester was associated with a high risk of PTB.

Introduction

Preterm birth (PTB) is one of the main causes of perinatal child death and neonatal disease[1]. In previous research[2], a generally accepted risk factor of PTB is hypertensive disorders of pregnancy (HDP), which is a group of medical complications in pregnancy with an elevation of blood pressure (BP), generally accepted as systolic blood pressure (SBP) ≥ 140mmHg and/or diastolic blood pressure (DBP) ≥ 90mmHg. In accordance with usual disease classification, HDP include gestational hypertension, preeclampsia, eclampsia, chronic hypertension with superimposed pre-eclampsia and chronic hypertension in pregnancy[3]. However, most related studies have focused on the effects of various HDP on pregnancy outcomes, and only a few studies have looked at maternal BP as a continuous risk factor of PTB[4–6]. Based on large-scale maternal heath monitoring data, in addition to unconditional logistic regression analysis, this study used restricted cubic spline (RCS) to analyze the dose-response relationship between maternal BP in different phases and PTB, in order to provide more information in identifying the risk of an early birth.

Methods

Study population

The research data were obtained from the Maternal and Newborn Health Monitoring System (MNHMS) set up by the National Center for Women and Children's Health (NCWCH), China CDC for the Maternal and Newborn Health Monitoring Program in 2013. The MNHMS was established to monitor the antenatal health care and pregnancy outcomes of pregnant women who had lived more than 6 months in the 16 districts/counties of eight provinces in China, including essential maternal information, all previous antenatal examination and pregnancy outcomes. Considering the integrity of the monitoring data, this study selected 13 counties and districts from six provinces to analyze the data. The provinces (with counties/districts) are Hebei (Xinhua and Zhengding), Liaoning Province (Lishan, Tiedong and Tai'an), Hubei

(Macheng and Luotian), Fujian (Haicang and Jimei), Sichuan (Gongjing and Rong County) and Yunnan (Tonghai and Huaning). Among them, Macheng and Luotian in Hubei, and Tiedong in Liaoning joined the project in 2016, and Tai'an in Liaoning withdrew in the same year. For the sake of information quality, a number of logical checks were set in the system to avoid input errors. In addition, the staff of NCWCH conducted field supervision on data accuracy every year.

Inclusion/exclusion criteria

Criteria for inclusion in this study were: (1) confinement date from January 1, 2014 to December 31, 2018; (2) residents with relatively complete information. Exclusion criteria were: (1) twin or multiparous pregnancy; (2) fetal deaths or birth sex unknown; (3) maternal deaths; (4) gestational age less than 28 weeks or unknown. In total, the data from 212941 pregnant women were analyzed .

Definitions

The 1st trimester is from the beginning of pregnancy to the end of the 12th week, the 2nd trimester is from the 13th week of pregnancy to the end of the 27th week, and the 3rd trimester is from the 28th week of pregnancy to the end of childbirth. The definition of PTB was a birth before the 37th and after the 28th gestational week. The upper limit is agreed globally, whereas the lower limit is different around the world. Many developed countries take the lower limit as 20 weeks or 24 weeks, as against 28 weeks of the Chinese standard in this study[7]. HDP was generally diagnosed when SBP ≥ 140mmHg and/or DBP ≥ 90mmHg[3] once. And hypotension means SBP < 90mmHg and/or DBP < 60mmHg once. BP levels were categorized into five groups following "Diagnosis and Treatment of Hypertension and Pre-eclampsia in pregnancy: A Clinical Practice Guideline in China (2020)"[3], "Internal Medicine (Ninth Edition)" [8] and research needs (Table 1).

Table 1
Group of BP levels (mmHg)

Group	SBP	DBP
Low	< 90	< 60
Normal	90 ~ 119	60 ~ 79
High normal	120 ~ 139	80 ~ 89
General high	140 ~ 159	90 ~ 109
Severe high	≥ 160	≥ 110

Statistical analysis

Data cleaning and analyses were conducted using the Statistical Package for the Social Sciences, version 17.0 (SPSS, Inc., Chicago, Illinois). The highest value of BP readings in each antenatal examination during each trimester was documented. Gestational diabetes mellitus (GDM) was a new index added into the information system in 2016. The missing values of GDM were taken as unchecked, through a single imputation method. T-test was used for quantitative variables, whereas chi-square test was used for categorical variables, and linear trend test was performed for ordinal categorical variables. Influencing factors of HTB are screened as dependent variables, first univariate logistic regression analysis was performed, and then multivariate logistic regression analysis was performed.

Through univariate logistic regression analysis, we found that PTB was affected by biological characteristics (namely maternal age, parity, history of abortion, GMD and neonatal sex), which has been validated in many studies before[2,7,9–13]. Caesarean section, which is closely related to pregnant diseases, also increases the risk of PTB, and is therefore an important confounding factor of HDP and PTB[14]. Thus, the associations between BP and PTB were

assessed after adjustment for the 6 variables above. A RCS function was used to delineate the dose-response relationships between BP (both DBP and SBP) during each trimester and PTB.

Results

Basic characteristics of study pregnant women

Of all 212941 pregnant women, the mean maternal age was 27.93 ± 4.62 years, and the mean gestational weeks at delivery was 38.97 ± 1.44 weeks. We observed that 42.51% of the women were rural residents and 96.34% were of Han nationality. The overall incidence of HDP was 7.07% and the incidence of PTB was 4.04%. There were significant differences ($P < 0.01$) between PTB and full-term births by province, urban-rural area, pregnant age (subgroup), education levels, gravidity, parity, history of abortion (subgroup), GDM, HDP, delivery mode and birth sex.(Table 2)

Table 2
Comparison of maternal basic characteristics between full-term births and PTB [*n*(%) / *n*(*X* ± *SD*)]

Variable	Full-term birth	PTB	χ^2/t	*P* value
Province			52.551	< 0.001
Hebei	58561(28.66)	2637(30.64)		
Liaoning	17699(8.66)	749(8.70)		
Fujian	54139(26.5)	2390(27.77)		
Hubei	28860(14.12)	1170(13.59)		
Sichuan	21073(10.31)	723(8.40)		
Yunnan	24002(11.75)	938(10.90)		
Area			70.082	< 0.001
Urban	117089(57.3)	5324(61.86)		
Rural	87245(42.7)	3283(38.14)		
Maternal age (years)	204334(27.86 ± 4.6)	8607(28.87 ± 5.12)	-19.832	< 0.001
Subgroup of maternal age (years)			362.750	< 0.001
< 25	46270(22.79)	1580(18.47)		
25 ~ 34	138592(68.25)	5718(66.84)		
≥ 35	18208(8.97)	1257(14.69)		
Education level			14.907	0.001
Junior high school or lower	62997(32.34)	2825(34.22)		
Senior high school	57913(29.73)	2331(28.24)		
University or above	73879(37.93)	3099(37.54)		
Ethnicity			0.092	0.762
Han	189113(96.34)	7957(96.4)		
Others	7189(3.66)	297(3.6)		
Gravidity (times)	204334(1.95 ± 1.05)	8607(2.02 ± 1.14)	-6.500	< 0.001
Parity(times)			7.898	0.005
0	118688(58.36)	4870(56.83)		
1~	84681(41.64)	3699(43.17)		
History of abortion(times)	204334(0.50 ± 0.79)	8607(0.56 ± 0.88)	-6.552	< 0.001
Subgroup of history of abortion (times)			44.997	< 0.001
0	105482(64.35)	4312(62.29)		
1 ~ 2	54242(33.09)	2347(33.91)		
≥ 3	4192(2.56)	263(3.8)		

Variable	Full-term birth	PTB	χ^2/t	*P* value
GDM			112.776	< 0.001
No	85368(41.78)	3764(43.73)		
Yes	5759(2.82)	391(4.54)		
Unchecked	113207(55.4)	4452(51.73)		
HDP			462.923	< 0.001
No	190082(93.18)	7478(87.11)		
Yes	13913(6.82)	1107(12.89)		
Delivery mode			331.210	< 0.001
Vaginal delivery	113059(55.39)	3903(45.42)		
Caesarean	91071(44.61)	4691(54.58)		
Birth sex			62.715	< 0.001
Male	107248(52.49)	4892(56.84)		
Female	97086(47.51)	3715(43.16)		

BP level distribution in each trimester

The detection rates of HDP in the 1st, 2nd and 3rd trimesters were 1.03%, 2.06% and 6.23% respectively. From the 1st trimester to the 3rd trimester, maternal SBP and DBP increased with averages of 12.46mmHg and 7.56mmHg respectively ($P < 0.001$); the proportion of the first two groups (low and normal) in SBP and DBP gradually dropped while the proportion of the later three groups (high normal, general high and severe high) rose (Table 3).

Table 3
BP level distribution in each trimester

Variable	*N*	*X* ± *SD*(mmHg)	BP group [*n*(%)]				
			Low	Normal	High normal	General high	Severe high
SBP							
1st trimester	120865	106.80 ± 11.08	1998(1.65)	98876(81.81)	19477(16.11)	466(0.39)	48(0.04)
2nd trimester	195181	113.01 ± 11.08	821(0.42)	130883(67.06)	61405(31.46)	1883(0.96)	189(0.10)
3rd trimester	199403	119.26 ± 11.28	149(0.07)	91236(45.75)	101533(50.92)	5812(2.91)	673(0.34)
P value		< 0.001*	< 0.001*	< 0.001*	< 0.001*	< 0.001*	< 0.001*
DBP							
1st trimester	120830	68.17 ± 8.06	6814(5.64)	98793(81.76)	14162(11.72)	1029(0.85)	32(0.03)
2nd trimester	195176	71.03 ± 8.02	6886(3.53)	149286(76.49)	35957(18.42)	2955(1.51)	92(0.05)
3rd trimester	199407	75.73 ± 8.45	2219(1.11)	120274(60.32)	67000(33.60)	9491(4.76)	423(0.21)
P value		< 0.001*	< 0.001*	< 0.001*	< 0.001*	< 0.001*	< 0.001*

* the P value of linear trend test.

Table 4
Unconditional logistic regression analysis modes to estimate the associations between BP in different gestational trimesters and PTB

BP group	*β*	*S.E.*	*Wald* χ^2	*P*	*OR*	95%*CI*
1st trimester						
HDP	1.172	0.094	154.901	< 0.001	3.228	2.684～3.882
Normal					1	
Hypotension	0.000	0.068	0.000	0.998	1.000	0.874～1.143
2nd trimester						
HDP	0.994	0.057	300.476	< 0.001	2.702	2.414～3.023
Normal					1	
Hypotension	-0.056	0.073	0.587	0.444	0.945	0.819～1.091
3rd trimester						
HDP	0.715	0.041	311.314	< 0.001	2.045	1.889～2.214
Normal					1	
Hypotension	0.921	0.088	110.160	< 0.001	2.512	2.115～2.983
Models were adjusted for maternal age, parity, history of abortion, GDM, delivery mode and birth sex.						

Association between BP in each gestational trimester and PTB

Taking the group of normal BP as reference, the groups with HDP in the 1st, 2nd and 3rd trimesters showed a 2.23-fold, a 1.70-fold and a 1.05-fold increased risk of PTB respectively ($P < 0.001$). The risk was highest in the 1st trimester and lowest in the 3rd trimester. Hypotension in the 1st and 2nd trimesters was not associated with PTB ($P > 0.05$), whereas hypotension in the 3rd trimester was associated with a 1.5-fold higher risk of PTB ($P < 0.001$).

Dose-response relationship between BP in each gestational trimester and PTB

A RCS model was used to analyze the association between BP in each gestational trimester and PTB, with baselines of SBP and DBP at 120mmHg and 80mmHg respectively (OR = 1). Adjusted for maternal age, parity, history of abortion, GDM, delivery mode and birth sex, OR of PTB had a nonlinearly U-shaped association with SBP and DBP in the 1st, 2nd and 3rd trimesters ($P_{nonlinear}$<0.001, Fig. 1). The lowest points of SBP and DBP in the 1st and 2nd trimesters were 100mmHg and 70mmHg respectively; the OR changed insignificantly with a decreased BP but ascended with an increased BP. In the 3rd trimester, with the lowest points of SBP and DBP at 130mmHg and 80mmHg respectively, the OR always ascended when BP changed.

Discussion

BP level during pregnancy

According to relevant studies, the incidence of HDP ranges from 5–10% in the population worldwide[15–17]. In 2011, a multicenter cross-sectional retrospective survey of almost 110,000 pregnant women revealed a 5.22% prevalence of HDP

in China[18]. This study reported a 7.07% incidence of HDP based on the monitoring data of BP of 212,941 pregnant women in China, which was essentially consistent with the results of previous studies.

The conclusions on maternal BP changes during each trimester in normal pregnancy varied in research in China and abroad. Some research suggested there were lower BP in 2nd trimester and an elevation in 3rd trimester[19]; some found a significant drop in BP around a stage in 2nd trimester, followed by an increase toward term[20–21]; some considered a gradually rising trend during the whole pregnancy[22]. For pregnant women with abnormal BP, this study showed increases in SBP and DBP and a higher rate of HDP from 1st and 2nd trimester to the 3rd (but specific gestational weeks not involved), which was similar to some research results[22] above.

Effect of HDP in each trimester on PTB

The logistic regression analysis indicated that a lower risk of PTB was associated with HDP at older gestational ages. The highest risk of PTB was associated with HDP in the 1st trimester (OR = 3.23), which was higher than the risk in the 2nd trimester (OR = 2.70) and in the 3rd trimester (OR = 2.05). The associations between HDP in each trimester and the risk of PTB vary in different studies. Some studies have suggested that the highest risk is in the 2nd trimester (RR = 2.55), with a lower risk in the 3rd trimester (RR = 1.90) and the lowest risk in the 1st trimester (RR = 1.15)[14], which was partly comparable to our results. In contrast, some studies have suggested that the lowest risk is in the 2nd trimester (OR = 0.75), with a higher risk in the 1st trimester (OR = 1.35) and the highest risk in the 3rd trimester (OR = 1.44)[23].

In our study, the dose-response relationship was assessed using a RCS model, with a baseline of SBP and DBP at 120mmHg and 80mmHg respectively. In the 1st and 2nd trimesters, ORs were almost 2.0 for SBP of 140mmHg and DBP of 90mmHg, which were significantly higher than in the 3rd trimester (OR ≈ 1.414); but individuals with SBP of 170mmHg or above and DBP of 100mmHg or above in the 3rd trimester had a higher risk of PTB than in the 1st and 2nd trimesters. A birth cohort study that recruited 3474 pregnant women in Ma'anshan China in 2013 and 2014 assessed the dose-response relationships between BP during each trimester (SBP at 110-145mmHg and DBP at 60-100mmHg) and the risk of PTB[5]. A higher risk was revealed in the 3rd trimester than in the 1st and 2nd trimesters for SPB at 140-145mmHg and DBP at 90-100mmHg, which was inconsistent with our study. Sample sizes and adjustment factors might account for this inconsistency.

Finally individuals with HDP are prone to have PTBs through systemic vasospasm and vascular endothelial injury, which may lead to placental hypoperfusion and placental dysfunction, and result in intrauterine growth retardation, fetal distress and placenta abruption[9,24–25]. The mechanism of associations between HDP in different trimesters and the risk of PTB remains unclear and requires further study. It may be pertinent that pregnant women with HDP in the 1st and 2nd trimesters are prone to have pregnancy complications such as cardiovascular disease, which can lead to a higher BP level in 3rd trimester[26–28]. On the other hand, a lower risk of PTB may reflect drug therapy and BP management after detection of HDP in the 1st trimester, which would avoid more adverse outcomes[29].

Effect of normal BP on PTB

The results of dose-response relationship using RCS model suggest that the risks of PTB were lowest for SBP at 100mmHg and DBP at 75mmHg in the 1st and 2nd trimesters and for SBP at 130mmHg and DBP at 80mmHg in the 3rd trimester, which means that the same BP level in different trimesters leads to distinct risks of PTB. A birth cohort study of 3473 pregnant women in Ma'anshan (SBP at 110-145mmHg and DBP at 60-100mmHg during pregnancy)[5] showed the lowest risks of PTB for SBP at 110mmHg and DBP at 70mmHg in the 1st and 2nd trimesters and for SBP at 120mmHg and DBP at 60mmHg in the 3rd trimester. Although the results were inconsistent with our study, the same BP level in different trimesters also led to distinct risks of PTB. The inconsistency may lie in the sample sizes and different adjustment factors.

Normal pregnancy is generally considered as a physiological state of adaptation to blood volume overload[30]. Higher BP level with advanced gestational ages might be response to an increase of blood volume during pregnancy[19]. In fact, one study concluded that a rise of 30mmHg in SBP and/or 15mmHg in DBP was not a risk factor of adverse outcome among women without HDP during pregnancy[31]. Therefore, an increase of BP within normal range might be a state of physiological adaptation in order to prevent adverse outcomes such as PTB instead.

Effect of hypotension in the 3rd trimester on PTB

The results of logistic regression analysis showed that the OR for PTB by hypotension was 2.51 in the 3rd trimester. Similarly, the dose-response relationship using the RCS model reflected the fact that the risk of PTB was higher when maternal SBP and DBP decreased in the last trimester. The OR reached 2.0 for SBP at 90mmHg and DBP at 60mmHg, and 4.0 for SBP at 80mmHg and DBP at 50mmHg. That means hypotension in the 3rd trimester led to a quite high risk of PTB. A case-control study abroad found no associations between maternal hypotension and adverse birth outcomes such as PTB and low birthweight[32], which differed from the result in our study. However, these studies are not directly comparable because this case-control study did not focus on hypotension in the last trimester specifically. There are few studies about the effects of hypotension in each trimester on the risk of PTB, which thus await further study.

Strengths and limitations

As distinct from most previous studies on classifying BP level and focusing on HDP only, this study assessed the dose-response relationships between BP in different trimesters and PTB. Using large-scale population monitoring data, we took maternal BP as a continuous variable with a relatively new research method. A nearly nonlinearly U-shaped association was found, which provides some scientific basis for identifying the risk of PTB more exactly, managing BP during each trimester and preventing PTB. Nevertheless, since only the highest value of BP readings during per trimester was involved in the analysis, fluctuations of BP were not included in the analysis. This may be a limitation on the study.

Conclusion

The dose-response relationships between BP (SBP and DBP) in different trimesters and PTB presented a nearly nonlinear U-shape. The risks of PTB varied among pregnant women with the same level of BP in different trimesters, which suggests that it may be necessary to deal with BP differently during each gestational period. As a state of physiological adaptation, an increase of BP in normal range during pregnancy could prevent adverse outcomes such as PTB. Hypotension in the 3rd trimester was associated with a quite high risk of PTB, which needs further research.

Declarations

Data Availability Statement

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study.

Ethics approval and consent to participate

Approved by the Ethics Committee of National Center for Women and Children's Health (No.FY2015-007).

Consent for publication

The authors and the center agree to publish.

Competing Interests

The authors have no conflicts of interest to declare.

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Authors' contributions

The first author Wei Zhao substantial contribute to the conception or design, the acquisition, analysis, and interpretation of data for the work, and drafting the work. The corresponding author Jiangli Di substantial contribute to revising it critically for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the the accuracy or integrity of any part of the work are appropriately investigated and resolved. The author Xiao Gong substantial contribute to analysis, and interpretation of data for the work. Aiqun Huang, Qi Yang and Huanqing Hu substantial contribute to the acquisition of data for the work. Sidi Chen substantial contribute to the translation of the work.

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Figures

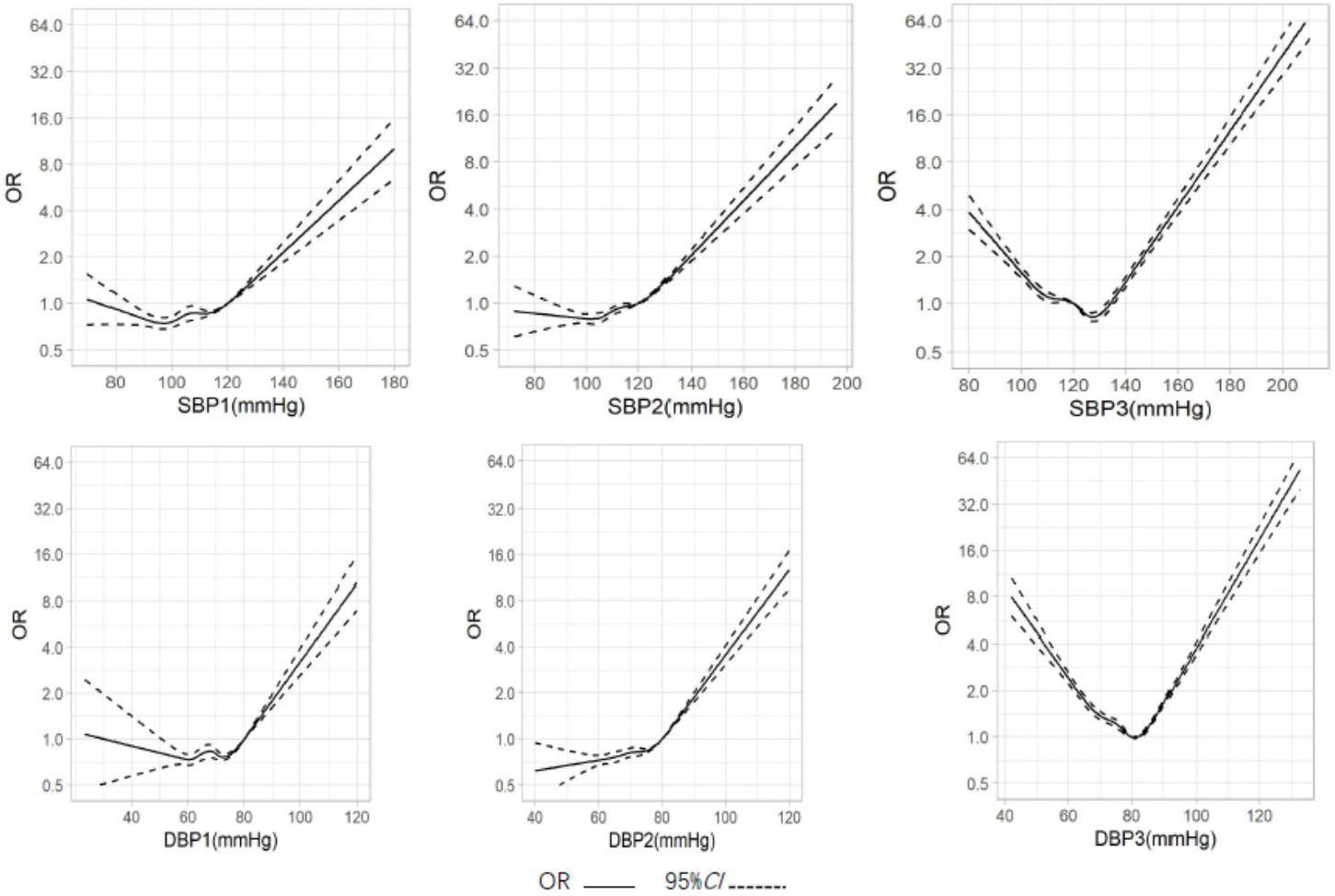

Figure 1

RCS models to analyze the dose-response relationship between maternal SBP and DBP and PTB OR 95%CI (SBP1, SBP2 and SBP3 means SBP in the 1st trimester, 2nd trimester and 3rd trimesters respectively; DBP1, DBP2 and DBP3 mean DBP in the 1st trimester, 2nd trimester and 3rd trimesters respectively)