Impact of metabolic risks on preeclampsia among women with different early-pregnancy blood pressures based on 2017 AHA Guidelines: A retrospective study

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Abstract

Objective A blood pressure (BP) of 120-140/80-90 mmHg at <20 weeks' gestation is associated with risks for preeclampsia. We aimed to explore the effect of maternal metabolic risk factors on the strength of the association between blood pressure thresholds based on 2017 American Heart Association (AHA) guidelines and preeclampsia. **Design** Retrospective cohort study. **Setting** The reproductive center is based in Shanghai, China. **Population or Sample** Data from 78,016 women enrolled between 2014 and 2019 from the medical record system of the center were used. **Methods** This retrospective cohort study included 78,016 participants. Preeclampsia prevalence was analyzed among women of four BP categories, stratified by maternal BMI and TG. **Main outcome measures** Incidence of preeclampsia **Results** Maternal BMI and TG showed a dose-response superimposed impact on the relationships between BPs and preeclampsia rates. Although heightened risks for preeclampsia were found in women with normal BMI (18.5-<25 kg/m2) and TG (<90th, 2.04 mM) women at a BP of 120-140 /80-90 mmHg, women with obesity (BMI [?] 25 kg/m2) and (or) high TG ([?] 90th) showed higher rates of preeclampsia. The preeclampsia risk was the highest in women with obesity and high TG at a BP of 130-140/80-90 mmHg and over 140/90 mmHg, which was 6-fold, and 13-fold greater than normotensive women with normal BMI and TG respectively. **Conclusion** Obesity and (or) high TG tended to strengthen the association between BP over 130/80 mmHg and risk of preeclampsia.

Introduction

Preeclampsia is a classic disorder characterized by the onset of hypertension which begins after 20 weeks of pregnancy together with a new onset of significant proteinuria,(1) which is one of the main causes of perinatal morbidity as well as mortality of both the mother and the child. (2-4) Preeclampsia affects around 2.3% to 4% of Chinese pregnant women,(5, 6) and is also related to survivors having substantial risks of developing cardiovascular disease (CVD) and cerebrovascular disease in the long-term. (7, 8) In addition, several lines of evidence have demonstrated that early intervention, such as administering aspirin in small doses, would help significantly lower the risks of mothers developing preeclampsia.(9-11) Therefore, early identification of pregnant women at risk of developing preeclampsia during the first trimester of pregnancy is of the utmost importance to minimize adverse perinatal events,(12) and to initiate appropriate timely therapeutic interventions.(12, 13)

Chronic hypertension and elevated blood pressure before 20 weeks of gestation are associated with an increased risk of pregnant women developing preeclampsia.(14) In 2017, the criteria for the diagnosis of hy-

pertension in non-pregnant adults, recommended by the American College of Cardiology / American Heart Association (ACC/AHA), were reduced to a threshold of 130/80 mmHg, while the previous cutoff value was 140/90 mmHg.(15) Data from a recent large cohort study showed that the lower diagnostic threshold for hypertension in the 2017 ACC/AHA guidelines markedly predicted those women who would go on to develop preeclampsia.(16) Our previous study also found that women with a normal body mass index (BMI) who met diagnostic criteria of the stage 1 hypertension of ACC/AHA Blood Pressure revised guideline were 3 times more likely to develop preeclampsia.(14) However, there is not enough evidence to support the efficacy of lower blood pressure thresholds for identifying women at heightened risk for preeclampsia. (17-21)

The risks of preeclampsia were considered to be screened based on maternal risk factors.(22) Major maternal metabolic risk factors such as being overweight/obese increase the risks of gestational hypertensive disorders.(23) High serum triglyceride (TG) concentrations during the first trimester have been confirmed to increase the risks of preeclampsia independent of BMI.(24) However, previous studies lacked the power to assess robustly whether differences in the preeclampsia risk at different blood pressure thresholds were correlated with different maternal pre-pregnancy BMI and early-pregnancy TG concentrations. Information regarding maternal obesity and high TG concentrations across a range of maternal blood pressure thresholds will be important for the identification of mothers at an increased risk of developing preeclampsia. The current study pooled a big cohort from China to assess the impact of maternal pre-pregnancy BMI and early-pregnancy TG concentrations on the association with increased blood pressure thresholds by applying the 2017 ACC/AHA blood pressure guideline criteria of the risk for preeclampsia.

Methods

Study population

This retrospective cohort study was performed in Shanghai International Peace Maternity and Child Health Hospital (IPMCH), with approval from the research ethics committee at IPMCH as well as written informed consent provided by all participants before initiation of the study. Data were collected from the electronic medical record system of IPMCH. The study was designed based on in-hospital deliveries from Jan 2014 to Dec 2019 (**Figure 1**). A total of 78,710 births in this center were taken into consideration and analyzed. The exclusion criteria were: (1) fetal abnormalities; (2) women with renal disease; (3) women with a family history of hyperlipidemia; (4) women with diabetes mellitus. In all, a total of 78,016 eligible cases were included in the analysis.

Data collection and measures

Data for each delivery in the center were recorded on the electronic medical system. Maternal baseline characteristics including medical and reproductive histories were collected at the first antenatal visit during 9 to 14 weeks of gestation. Pre-pregnancy weight data were collected from records of pre-pregnancy physical examinations within 1 year and BMI was calculated at the first antenatal care visit. Women with a BMI [?] 25 kg/m^2 were defined as obese.

Maternal blood pressure was measured based on a previous study.(14) Clinical serological examinations were required at the first prenatal care visit before 14 weeks of gestation. Blood samples from all participants were collected in fasting conditions between 7:00 am and 9:00 am. Serum was separated and stored at -40 until analyzed further. TG concentrations were performed by enzymatic assay (Roche Diagnostics, Mannheim, Germany) and a Cobas c702 analyzer. The inter-assay coefficient of variations was $< 2.5\%$ for TGs. The cut-off point of maternal TG at the 90$^{\text{th}}$ (2.04 mM) percentile was defined according to our previous study.

Definitions of outcomes and risk factors

Diagnoses and the following definitions were in alignment with ICD-9 and ICD-10 codes [International Classification of Diseases, Ninth (1996) and Tenth (1997–2010) Revisions]. Preeclampsia was defined as the combination of gestational hypertension plus proteinuria ([?] 300 mg/24 h or $>$ 2+ by dipstick on 2 or more occasions) occurring after 20 weeks of gestation.(15) The superimposed preeclampsia was defined as those who developed preeclampsia with concomitant chronic hypertension, based on the revised criteria of the

International Society for the Study of Hypertension in Pregnancy (ISSHP) in 2018. (25) According to the revised recommendations for gestational hypertension diagnosis from the ACC/AHA Task Force,(15) normal blood pressure was defined as systolic blood pressure (SBP) $<$ 120 mmHg or diastolic blood pressure (DBP) $<$ 80 mmHg; elevated blood pressure as SBP between 120 and 129 mmHg or DBP $<$ 80 mmHg; stage 1 hypertension as SBP between 130 and 139 mmHg or DBP measurement between 80 and 89 mmHg; stage 2 hypertension as SBP measurement $>$ 140 mmHg or DBP measurement $>$ 90 mmHg.

The main outcome measures in the analysis included early-pregnancy maternal TG concentrations and pre-pregnancy BMI. Other risk factors included maternal age, early-pregnancy BMI, education (years), birthplace (immigrant or resident), parity (1 or above 2), and ethnicity (Han Chinese or other) (**Table 1**).

Statistical analysis

Maternal TG concentrations and early-pregnancy BMI are presented as medians and quartile 1 and quartile 3 categorical variables as frequencies with proportions. Multilevel linear regression models were employed to assess associations between maternal baseline characteristics, early-pregnancy BMI, and maternal TG concentrations among the maternal early-pregnancy blood pressure groups. Logistic regression was used to estimate odds ratios with 95% CI for risk of preeclampsia in women with stage 1 and stage 2 hypertension, and elevated blood pressure compared with normal blood pressure for women with or without risk factors.

Multivariable analyses were adjusted for potential confounders. Maternal age ([?] 24, 25-29, 30-34, or [?] 35 years), parity (nulliparous, parous), education ([?] 12, 13-17, or [?] 18 years), birthplace of the mother (residents or immigrants) and pre-pregnancy BMI ([?] 18.4, 18.5-24.9, or [?] 25 kg/m^2) were included as covariates and to assess the risk factors for the association between maternal blood pressure in early pregnancy and the risks for preeclampsia. For the analysis of the impact of maternal obesity and high TG concentrations on the association of maternal blood pressure and the risks of preeclampsia, women were stratified based on the quartile values of BMI and TG concentrations.

The absolute risk difference compared to normal blood pressure was calculated as the difference between the risk of preeclampsia among women with one or two risk factors. To reduce the bias caused by fewer samples, women were stratified into BMI [?] 25 and $<$ 25 kg/m^2 subgroups; and TG [?] 90$^{\text{th}}$ and $<$ 90$^{\text{th}}$ subgroups. The confidence interval was determined using standard statistical packages. (20) A confidence interval that contained a zero meant that there was no significant difference between the event and the control in terms of risk.

All statistical analyses were performed using SPSS package ver. 16.0 (SPSS Inc., Chicago, IL, USA). A two-tailed P -value $<$ 0.05 was used as the threshold for statistical significance.

Results

Baseline characteristics of the study population

In this cohort, women (n = 78,170) with a mean ($\pm$ SD) age of 30.7 $\pm$ 3.8 years were enrolled. Cases with fetal abnormalities (n = 105), renal disease (n = 24), familial hyperlipidemia (n = 4), or diabetes mellitus (n = 21) were excluded from the study. Finally, 78,016 cases were recruited for further study. Based on the revised criteria for hypertension definition, 11,869 cases were diagnosed as elevated blood pressure, 18,470 cases were diagnosed as stage 1 hypertension, and 6,103 cases as stage 2 hypertension (**Figure 1**). All enrolled women had a median maternal TG concentration of 1.25 mM (quartile 1, 0.98 and quartile 3, 1.60 mM) and a median early pregnancy BMI of 20.70 kg/m^2 (quartile 1, 19.23 and quartile 3, 22.60 kg/m^2). Women with normal blood pressure tended to be slightly younger, less overweight, and multiparous than cases with elevated blood pressure, stage 1 and stage 2 hypertension. Other factors such as educational background, residency status, and ethnicity also contributed to the aberrant blood pressure profile (**Table 1**).

Maternal early pregnancy blood pressure and risks for preeclampsia

Table 2 presents crude ORs and adjusted ORs for this association. While it turned out that 241 women with elevated blood pressure developed preeclampsia (2.03%; OR 1.57; 95% CI: 1.35 to 1.83), 845 women with stage 1 hypertension developed preeclampsia (4.57%; OR 3.24; 95% CI: 3.26 to 4.06) and 577 women with stage 2 hypertension developed preeclampsia (9.45%; OR 7.92; 95% CI: 7.02 to 8.94) compared with 541 women with normal blood pressure who developed preeclampsia (1.30%) (**Table 2**).

After adjusting for maternal age, years of education, parity and birthplace, the adjusted odds ratios (AORs) (95% CI) were 1.45 (1.24 to 1.69) for elevated blood pressure women, 3.16 (2.83 to 3.53) for stage 1 hypertension women and 6.15 (5.42 to 6.98) for stage 2 hypertension women (**Table 2**).

Maternal pre-pregnancy BMI, early pregnancy TG concentration, early pregnancy blood pressure and absolute risks for preeclampsia

We further analyzed the association between maternal pre-pregnancy BMI, early pregnancy blood pressure and the risks for preeclampsia (**Figure 2**). Frequencies represented the absolute risks of preeclampsia (**Figure 2A, C**) and the percentage of participants (**Figure 2B, D**) for the combination of either pre-pregnancy BMI and maternal early pregnancy blood pressure (**Figure 2A, B**) or maternal TG concentrations in early pregnancy and maternal early pregnancy blood pressure (**Figure 2C, D**). The absolute risks of preeclampsia increased across the whole range of maternal pre-pregnancy BMI, early pregnancy TG concentrations, and early pregnancy blood pressure (**Figure 2**). For the combination of pre-pregnancy BMI and maternal blood pressure in early pregnancy, the lowest absolute risk was 1.13% for women with normal blood pressure and a BMI below the 10^{th} quartile, while the highest absolute risk was 14.29% for women with stage 2 hypertension and a BMI above the 90^{th} quartile (**Figure 2A, B**). For the combination of maternal TG concentrations in early pregnancy and maternal early pregnancy blood pressure, the lowest absolute risk was 1.02% for women with normal blood pressure and TG concentrations below the 10^{th} quartile, while the highest absolute risk was 13.59% for women with stage 2 hypertension and TG concentrations above the 90^{th} quartile (**Figure 2C, D**).

Impact of the maternal TG concentration in early pregnancy and pre-pregnancy BMI on the association between maternal blood pressure and risks of preeclampsia

We analyzed maternal TG concentrations in early pregnancy and pre-pregnancy BMI on the association between maternal blood pressure and the risk for preeclampsia in the 3 subgroups, categorized based on whether BMI [?] 25 kg/m^2 and/or a TG concentration > the 90^{th} quartile. The absolute risk difference, AOR and 95% CI of each risk factor subgroups among the 4 blood pressure categories are shown in **Figure 3** .

Among all the subgroups, elevated blood pressure was positively correlated with the risk of developing preeclampsia. Among women with a normal weight and TG concentration, the incidence of developing preeclampsia for those combined with stage 1 hypertension was 3.8%, in comparison to 1.2% in the "normal" blood pressure category. Women with stage 1 hypertension were nearly 3 times more likely to develop preeclampsia (AOR, 2.98; 95%CI: 2.63 to 3.39), and the risks rose up to 5.9 times for women with stage 2 hypertension (AOR, 5.91; 95% CI: 5.08 to 6.88).

Among women combined with either a BMI [?] 25 kg/m^2 or a TG concentration [?] the 90th quartile, those with stage 1 hypertension were 5 times more likely to develop preeclampsia (AOR, 5.62; 95% CI: 4.80 to 6.58; risk difference, 5.7%; 95% CI: 3.6% to 7.9%), and the risk increased up to 10 times for women with stage 2 hypertension (AOR, 10.53; 95% CI: 8.87 to 12.50; risk difference, 11.5%; 95% CI: 9.4% to 13.6%) compared to those with "normal" blood pressure, combined with both a BMI < 25 kg/m^2 and a TG concentration < the 90^{th} quartile.

When the two risk factors coexisted, the risk of preeclampsia was significantly increased among all blood pressure ranges. Women with stage 1 hypertension were 6 times more likely to develop preeclampsia(AOR, 6.61; 95% CI: 4.87 to 8.97 with risk difference, 7.0%; 95% CI: 4.9% to 9.1%), and women with stage 2 hypertension had >13-fold increased risks of preeclampsia (AOR, 13.65; 95% CI: 10.31 to 18.08; risk

difference of 15.0%; 95% CI: 13.5% to 16.6%) when compared to normotensive women with normal BMI and TG levels.

Discussion

Main findings

In this cohort study, we found a strong and positive correlation between early-pregnancy blood pressure and risks of preeclampsia. The absolute risks of preeclampsia increased across the whole range of maternal pre-pregnancy BMI, early pregnancy TG concentrations, and early pregnancy blood pressure. Risks of preeclampsia increased significantly within stage 1 or stage 2 hypertension, particularly among women combined with both BMI [?] 25 kg/m^2 and a TG concentration [?] the 90$^{\text{th}}$ quartile. To the best of our knowledge, this is the first study to raise the importance of considering maternal metabolic risk factors such as overweight/obese and high TG in risk prediction of preeclampsia and the necessity of intervention should be conducted among women with stage 1/2 hypertension under those circumstances.

Interpretation

In 2017, the ACC/AHA lowered the diagnostic threshold for hypertension to a blood pressure of 130/80 mmHg based on outcomes data from randomized trials of blood pressure lowering in non-pregnant adults.(16) However, ACOG continues to define hypertension during pregnancy as a blood pressure [?] 140/90 mmHg. Recent studies concluded that lowering the diagnostic threshold for chronic hypertension would not assist clinicians in identifying women at heightened risk for preeclampsia and adverse pregnancy outcomes.(21) Medication for the hypertensive disorder of pregnancy should be considered when the SBP reaches 160 mmHg and/or DBP 110 mmHg. The definition of stage 2 hypertension was beneficial in identifying women with higher risks of adverse outcomes (i.e., preeclampsia), who were advised on how to prevent preeclampsia in advance of pregnancy. (26, 27) Our study provided similar data to a previous study, namely that women with stage 2 hypertension were 6 times more likely to develop preeclampsia.

It has already been reported that women with pre-existing hypertension before pregnancy are more likely to develop preeclampsia than women who are normotensive at conception.(28) In consistent to our work, among women with stage 1 hypertension, 4.6% of them eventually developed preeclampsia. While in the stage 2 hypertension group, 9.45% of the participants develop preeclampsia. In contrast, one recent study reported that raised blood pressure and stage 1 hypertension, diagnosed based on ACC/AHA, did not increase the incidence of preeclampsia in low-resource settings.(29) The major differences between our study and the above-quoted study were the measurement timing of blood pressure and the experimental population. Blood pressure was measured after 20 gestation weeks in that study. While in our present study, we assessed the blood pressure level measured before 20 weeks, which was essential for establishing a diagnosis of chronic hypertension.(18, 30) Additionally, our study was performed in one of the largest obstetrics hospitals in Shanghai, not a low-resource setting and with a much larger sample size for evaluating the risks of developing preeclampsia.

Usually, preeclampsia manifests clinical symptoms after 20 weeks of gestation. Until now, physical or biochemical tests that can predict the onset of preeclampsia during pregnancy remain limited studied.(31) Hence, identification of the high-risk population for preeclampsia in early pregnancy would be of great significance for the prevention and reduction of maternal deaths that are often associated with a missed or delayed diagnosis.(32) Being overweight/obese increases the risk of developing preeclampsia by up to 2.48 times,(33) which has been mainly attributed to inflammatory changes in adipose tissue and impaired placental development. (34, 35) Serum TGs are critical sources of energy. Elevated serum concentrations of TGs have been associated with the risk of developing pregnancy-associated hypertension.(36-38) Therefore, it is reasonable to suspect that measurements of maternal metabolic factors may be beneficial in predicting women who are more likely to develop preeclampsia.

Strengths and Limitations

Our study has several strengths, including a large study population and the advanced timing of blood

parameters measurements, while conventional obstetric examinations were generally taken place before 20 weeks of gestation. The results of our work may provide clinical evidence for considering maternal risk factors when setting hypertension diagnostic thresholds and conducting possible preventive therapies. Nevertheless, this study had several limitations. A major limitation of our study is the use of blood pressure measurements during pregnancy for classification of stage 1 hypertension, since pre-pregnancy blood pressure measurements are ideal for chronic hypertension diagnoses. Second, we did a retrospective and single-center cohort study, and the study didn't include the low-resource settings, which would prevent its extrapolation to nationwide. Third, personal information such as social status and family income were not available in this study, and therefore, the residents/immigrants' status was used instead.

Conclusion

In summary, our study found that elevated blood pressure, stage 1 and stage 2 hypertension diagnosed based on 2017 ACC/AHA criteria increase the risks of preeclampsia, especially the latter two. Obesity and elevated TG serum concentrations were two independent risk factors for developing preeclampsia (data not shown), and they tended to strengthen the association between the new BP categories and the risk of developing preeclampsia, especially in stage 1 and stage 2 hypertension. The results would add value to the clinical practice that clinicians should pay more attention and raise the necessity of intervention to women with stage 1/2 hypertension at <20 weeks gestation under the condition of overweight/obesity and high TG in identifying women at heightened risk for preeclampsia.

Author contributions: Drs Lin and Wu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of its analysis.

Concept and design: Huang, Lin and Wu.

Acquisition, analysis and interpretation of data: All authors.

Drafting of the manuscript: Wu, Lin.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Wu, Lin and Wei.

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Administrative, technical, or material support: Wu, Lin, Huang.

Supervision: Lin, Huang.

Conflict of interest disclosures: No disclosures to report.

Data sharing statement: The dataset generated from the study is available on request to the corresponding author.

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Table and Figure Legends Table 1 Characteristics of study population [a] Calculated as weight in kilograms divide

Data are presented as median (interquartile range) or number/total number (percentage), unless otherwise indicated. **Tabl**

Abbreviations: AOR, adjusted odds ratio.CI,confidence interval.

Data are shown as adjusted OR (95% CI), adjusted for maternal age, years of education, parity, birth place, pre-pregnancy

Figure 1

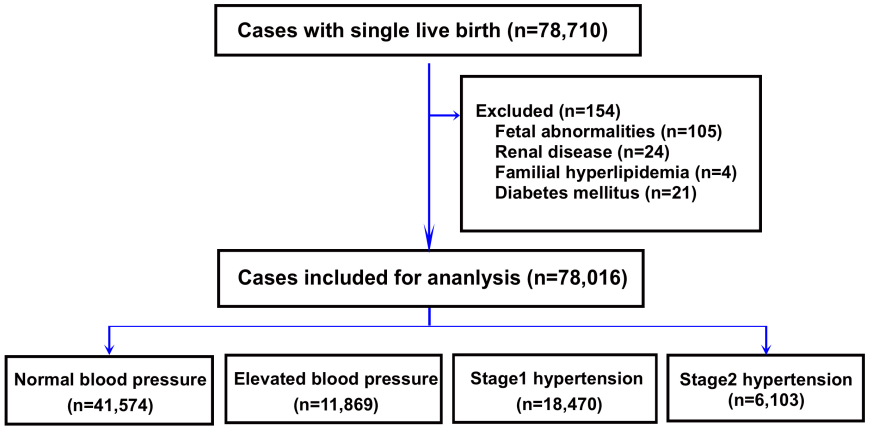

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Table 1 Characteristics of study population.docx available at https://authorea.com/users/659752/articles/663588-impact-of-metabolic-risks-on-preeclampsia-among-women-with-different-early-pregnancy-blood-pressures-based-on-2017-aha-guidelines-a-retrospective-study

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Table 2 .docx available at https://authorea.com/users/659752/articles/663588-impact-of-metabolic-risks-on-preeclampsia-among-women-with-different-early-pregnancy-blood-pressures-based-on-2017-aha-guidelines-a-retrospective-study