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Impact of gestational hypertension and preeclampsia on preterm birth in China: a large prospective cohort study

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Abstract

Objective: The objective of this study was to investigate the impact of gestational hypertension and preeclampsia on preterm birth.

Design: The data were collected from the China–US Collaborative Project for Neural Tube Defects Prevention, a large population-based cohort study.

Setting and participants: We selected participants who were registered in 2 southern provinces, had exact information on gestational blood pressure and pregnancy outcomes, and were not affected by chronic hypertension and 200,103 participants were finally recruited. The recruitment period was from 1993 to 1995.

Outcome measures: Preterm birth was defined as singleton pregnancy and birth within 37 gestational weeks.

Results: Comparing to the incidences of preterm birth 5.47%, 5.44% for normal group, the incidences were 5.63%, 7.33% for gestational hypertension and preeclampsia group. After adjusting for the potential confounders, gestational hypertension and preeclampsia were associated with preterm birth with risk ratios (RR) of 1.04 [95% confidence interval (CI): 0.98, 1.11] and 1.39 (95% CI: 1.25, 1.55)，respectively. This association was stronger for early onset of gestational hypertension (adjusted RR =2.13, 95% CI: 1.71, 2.65) and preeclampsia (adjusted RR=8.47, 95% CI: 5.59, 12.80).

Conclusions: This study find preeclampsia associated with higher risk of preterm birth. The early-onset gestational hypertension and preeclampsia appear to be more severe than late-onset type.

Strengths and limitations of the study

This study benefits from the large sample size (n=200,103) and homogeneous cohort population which provided enough power to investigate the associations. We

also stratified analysis by disease onset time to have a more comprehensive insight to analyze the impact.

The confounding factors such as smoking or drinking were not obtained as the study was based on existing data. This study only included population from 2 southern provinces in China.

INTRODUCTION

Preterm birth, as a common adverse pregnancy outcome, is one of the leading causes of child death globally, especially in developing countries [1]. It is estimated that global preterm live births reached to 14.84 million, accounting for 10.6% of all births. Asian countries comprised 52.9% of global preterm births, and the proportion of preterm births in China (7.8%) ranked second in the world [2]. Preterm birth is not only at great risk of mortality and morbidity, but also at risk of imposing long-term effects such as respiratory syndrome and infections, which brings heavy medical financial burdens on the families and countries [3, 4]. The mechanism of preterm birth is still uncertain, and some studies suggested that elevated blood pressure levels during pregnancy may play an important role in the development of preterm birth [5, 6].

Pregnancy induced hypertension, including gestational hypertension and preeclampsia, complicates 6-10% of pregnancies [7]. Gestational hypertension and preeclampsia develop novel hypertension after 20 weeks of gestation with/without proteinuria [8]. It still remains uncertain whether gestational hypertension and preeclampsia are separate diseases just sharing common medical manifestations or the same disorders with different severe spectrum [9]. Some studies report pregnancy induced hypertension, especially preeclampsia, may be one of the drivers for preterm birth [10]. On the other hand, researchers pointed that early- or late- onset of

preeclampsia may result from distinct mechanisms [11] and the effect should be observed separately. Women with early-onset preeclampsia characterized by reduced placental blood flow show higher vascular resistance compared with late-onset preeclampsia which has different hemodynamics and origins [12, 13]. The results of association between gestational hypertension and preterm birth are not consistent [14]. Buchbinder [14] found compared with normotensive and mild preeclampsia, severe gestational hypertension had significantly increased rates of preterm delivery. However, other study found gestational hypertension did not associate with preterm birth [15].

Therefore, we used a large prospective cohort study to investigate the impact of gestational hypertension and preeclampsia in China. In addition, we also assessed whether the impact of disease-onset time (early, or late-onset pregnancy induced hypertension) on preterm birth is the same.

MATERIALS AND METHODS

Background and original cohort

The methods of the original study have been described previously [16, 17]. Beginning in 1993, the Chinese Ministry of Health has conducted a public health campaign to prevent neural tube defects in 21 counties among women in 2 southern provinces (Zhejiang and Jiangsu) and 1 northern province (Hebei). During this campaign, all female residents who were planning to get married, or who became pregnant in the project counties, were registered in a pregnancy monitoring system. This system was used as the principal record of antenatal care and the source of demographic information. All women were advised to take a pill solely containing 400 μg of folic acid every day, starting at the time of registration on the pregnancy monitoring system and continuing until completion of the first trimester of pregnancy.

The pills were distributed at the time of registration if the woman agreed to take folic acid. At the end of each month, health care workers recorded the dates of all menstrual periods and how many pills remained in each bottle (if the subject was taking pills). All births at 20 complete gestational weeks, including live births, stillbirths and pregnancy terminations, and all structural congenital anomalies, regardless of gestational week, were recorded. The original cohort included 247,831 women who registered with the pregnancy-monitoring system between f and who delivered by 31 December 1996. The project was approved by the institutional review boards of the U.S. Centers for Disease Control and Prevention and the Peking University Health Science Center. Since rural women in the study area were mostly illiterate in the early 1990s, all women who took pills provided oral informed consent [18].

Selection of study subjects

We selected the participants who were registered in 2 southern provinces (Jiangsu Province and Zhejiang Province). These 2 neighboring provinces had detailed records about pregnancy induced hypertension in their pregnancy monitoring system. Of 215,871 women from the selected provinces, we excluded: 8,749 (4.05%) with multifetal gestation; 5,711 (2.65%) women whose gestational hypertension diagnosis was unknown; and 6,533 (3.03%) for whom who lacked detail of last menstrual period date as well as delivery date records. After these exclusions, 200,103 participants (92.70% of the targeted population) were included in the final analysis. Information regarding formation of the target recruitment population, and derivation of the population used in the final analysis, is shown in **Figure 1.**

Diagnosis of Gestational Hypertension and Preeclampsia

Appropriate cuff bladder size was determined at each visit based on arm circumference. Blood pressure was measured in the right arm with a mercury

sphygmomanometer and was observed on 2 or more consecutive occasions with an interval of ≥6 hours. Gestational hypertension was defined as an absolute blood pressure ≥140/90 mm Hg after 20 weeks of gestation, or as a blood pressure increment of ≥30/15 mm Hg after 20 weeks of gestation as compared with the first trimester [19]. Preeclampsia (including eclampsia) was defined as a blood pressure of ≥140/90 mm Hg or a blood pressure increment of 30/15 mm Hg after 20 weeks of gestation, with concurrent proteinuria (a single random urine specimen containing at least 1+ protein by dipstick test) after 20 weeks of gestation. Considering the different heritability, clinical manifestations, and prognosis of early- and late-onset gestational hypertension and preeclampsia [18, 20], we classified gestational hypertension and preeclampsia into 2 types: early onset (<28th week of gestation at the time of diagnosis) and late onset (onset at ≥28th week of gestation at the time of diagnosis).

Statistical Analysis

We compared the mean age and body mass index (BMI), and distributions of folic acid use, parity, ethnic origin, education and occupation between gestational hypertension and non-gestational hypertension subjects. For the basic characteristics of different groups, we use Student's *t*-test for quantitative variables and the $\chi 2$ test for categorical variables. We calculated the incidences of preterm birth in gestational hypertension group and non-gestational hypertension group, respectively. Logistic regression models were used to estimate risk ratios (RRs) after adjusting for the main underlying confounders such as maternal age (continuous), BMI (continuous), education, occupation, parity, ethnicity and pill use. We also compared the distribution of preterm birth according to different onset periods of hypertension and preeclampsia. The mean BMI was used if individual data were missing. All data were analyzed using

SPSS for Windows software (ver. 20.0; SPSS Inc, Chicago, IL). Statistical significance was defined as two-sided P <0.05.

Patient and public involvement

No patients were involved in the design of this study, the specific aims or the research questions, nor were they involved in the recruitment and conduct of the study. No patients were involved in the interpretation of study results or write-up of the manuscript. There are no plans to disseminate the results of the research to study participants.

RESULTS

Of the 200,103 women included in this analysis, 19,115 (9.55%) reported gestational hypertension and 4,912 (2.45%) reported preeclampsia, respectively. The baseline characteristics of the participants who had gestational hypertension are shown in **Table 1**. Nearly all participants were of the Han ethnicity. Women who had gestational hypertension were more likely to be older, to have higher BMI level, to be primiparous, less educated, folic acid use and tended to be factory workers.

Table 1. Characteristics of women who enrolled in the pregnancy monitoring system according to gestational hypertension, China, 1993 to 1996

Characteristics	Gestational hypertension group (n=19115)		None-gestational hypertension group (n=180988)		*P*
	n[a]	%[b]	n[a]	%[b]	
Age at pregnancy, (years, mean[SD])	25.04 (3.34)		24.86 (3.21)		<0.001
Body mass index	20.77 (2.25)		20.50 (2.09)		<0.001

(kg/m^2, mean[SD])					
Primiparous	16277	85.15	149967	82.86	<0.001
Han ethnic group	18977	99.28	179670	99.27	0.923
Folic acid use	10245	53.60	94874	52.42	0.002
Education					0.075
High school or higher	2014	10.54	20045	11.08	
Junior high school	11380	59.53	107253	59.26	
Primary school or lower，or unknown	5721	29.93	53690	29.66	
Occupation					<0.001
Farmer	10930	57.18	106992	59.12	
Factory worker	5409	28.30	49257	27.22	
Other or unknown	2776	14.52	24739	13.67	

[a]Values for some characteristics may not be equal to total numbers of gestational hypertension or non-gestational hypertension groups because of missing values.

The incidence of preterm birth in our whole population was 5.49%. The incidence rate of preterm birth for women who had gestational hypertension and preeclampsia were 5.63% and 7.33%, relative to 5.47% and 5.44% for women with normal blood pressure group, respectively. The RRs of preterm birth with gestational hypertension and preeclampsia were 1.03 (95% CI: 0.97, 1.10) and 1.38 (95% CI: 1.23, 1.53). Compared with the term birth group, preterm birth group was more likely to have younger age, lower education, and none folic acid use (**Table 2**). The RR of preterm birth according to gestational hypertension and preeclampsia were 1.04 (95% CI: 0.98, 1.11) and 1.39 (95% CI: 1.25, 1.55), after adjustment for the effects of major

confounding factors (**Table 3**). Furthermore, we compared the incidence rate of preterm birth with regard to early- or late- onset cases. We found that gestational hypertension with early onset only was associated with an increased risk of preterm birth (adjusted RR = 2.13, 95% CI: 1.71, 2.65) and two types of preeclampsia had the similar effects on preterm birth (early onset: adjusted RR = 8.47, 95% CI: 5.59, 12.80); late onset: adjusted RR = 1.30, 95% CI: 1.16, 1.46) (**Table 4**).

Table 2. Incidence and crude RR of preterm birth according to gestational hypertension, preeclampsia, and other women's characteristics, China, 1993 to 1996

Characteristics	No.	Preterm birth		
		Incidence (%)	RR	95% CI
Age, y				
<20	896	10.60	1.92	1.55, 2.38
20-25	115124	5.81	1	…
25-30	59960	5.00	0.85	0.82, 0.89
⩾30	24123	4.90	0.84	0.78, 0.89
Body mass index, kg/m^2				
<18.5	28576	5.54	1.01	0.96, 1.07
18.5-23.9	159985	5.47	1	…
24-27.9	10610	5.45	1.00	0.91, 1.09
⩾28	932	6.33	1.17	0.90, 1.52
Education				
High school or higher	22059	4.71	1	…
Junior high school	118633	5.41	1.16	1.08, 1.24

Primary school or lower，or unknown	59411	5.90	1.27	1.18, 1.36
Occupation				
Farmer	117922	5.60	1	…
Factory worker	54666	5.54	0.99	0.95, 1.03
Other，or unknown	27515	4.86	0.86	0.81, 0.92
Parity				
Multiparous	33859	5.64	1	…
Primiparous	166244	5.45	0.96	0.92, 1.01
Ethnicity				
Han	198647	5.48	1	…
Other	1456	6.46	1.19	0.97, 1.47
Folic acid use				
None	94984	5.90	1	…
Use	105119	5.10	0.86	0.82, 0.89
Gestational Hypertension				
No	180988	5.47	1	…
Yes	19115	5.63	1.03	0.97, 1.10
Preeclampsia				
No	195191	5.44	1	…
Yes	4912	7.33	1.38	1.23, 1.53

CI indicates confidence interval; and RR, risk ratio.

Table 3. The association of gestational hypertension and preeclampsia with preterm birth in multivariate logistic regression, China, 1993 to 1996

	Preterm birth

Risk Factor	Adjusted RR	95% CI
Age (continuous)	1.04	1.03, 1.05
Body mass index (continuous)	1.10	1.02, 1.18
Factory worker	1.00	0.96, 1.05
Other occupation , or unknown	0.93	0.87, 0.99
Junior high school	1.10	1.02, 1.18
Primary school or lower , or unknown	1.22	1.13, 1.32
Folic acid use	0.83	0.80, 0.86
Gestational Hypertension		
No	1	…
Yes	1.04	0.98, 1.11
Preeclampsia		
No	1	…
Yes	1.39	1.25, 1.55

CI indicates confidence interval; and RR, risk ratio.

Table 4. The early onset and late onset of gestational hypertension and preeclampsia with risk of preterm birth

Different onset periods	No.	Preterm birth		
		Incidence (%)	Crude RR (95% CI)	Adjusted RR (95% CI)[a]
Gestational hypertension				
No[b]	180988	5.47	1	1
Early onset	849	10.72	2.08 (1.67-2.58)	2.13 (1.71-2.65)
Late onset	18266	5.40	0.99 (0.92-1.06)	1.00 (0.94-1.07)
Preeclampsia				
No[b]	195191	5.44	1	1
Early onset	104	31.73	8.09 (5.35-12.23)	8.47 (5.59-12.80)
Late onset	4808	6.80	1.27 (1.13-1.42)	1.30 (1.16-1.46)

CI indicates confidence interval; and RR, risk ratio.

[a]Adjusted for maternal age (continuous), BMI (continuous), education, occupation, ethnicity and parity.

[b]Reference group.

DISCUSSION

Main findings of this study

This large prospective cohort study investigated whether gestational hypertension, preeclampsia and their different spectrums associated with the risk of preterm birth. We found preeclampsia was associated with an increased risk of preterm birth. A stronger association was observed at early-onset preeclampsia after stratification by the onset time. Meanwhile, gestational hypertension only had a significantly positive association with preterm birth at early-onset time.

The results in our study are consistent with some previous studies [21-23]. Bakke et al [22] used a prospective cohort study conducted in Netherlands to explore the association between blood pressure and preterm birth. They reported an increased risk of preterm birth in preeclampsia group compared with nonhypertensive pregnant group (adjusted odds ratio = 5.89, 95%CI: 2.63, 13.14). But the similar association was not observed in the gestational hypertension group, which was in accordance with our results. However, this study did not distinct the onset time of gestational hypertension and preeclampsia. Previous studies suggested various onset time may impose different effects on preterm birth [11]. Another prospective cohort study showed comparing to the normotensive group, women with pregnancy induced hypertension were associated with an increased risk of preterm delivery (adjusted RR = 5.1, 95%CI: 3.4, 7.8) [23]. Other studies also reported similar results in different population [24, 25]. However, a

study conducted in Zimbabwe showed the risk of preterm delivery did not vary in women with pregnancy induced hypertension and those without (P>0.05) [26]. The discordant findings mainly resulted from the study design, the heterogeneity of population and measurement methods.

It still remains unclear about the differences of mechanism and outcomes in gestational hypertension and preeclampsia. One study used survival curves represented the risk factors imposed on both of them in a similar pattern, but women with preeclampsia had shorter gestational age than those with gestational hypertension [13]. Furthermore, a retrospective case-control study showed severe preeclampsia group was more likely to have preterm labor than gestational hypertension group (OR = 3.18, 95% CI: 2.23, 4.52) [27]. Our study also reported a stronger effect on preterm birth in preeclampsia group than gestational hypertension group. On the contrary, some studies subdivided the gestational hypertension and preeclampsia group and found severe gestational hypertension had higher rates of adverse outcomes than mild preeclampsia [14]. These findings suggest both the high blood pressure and the manifestation of proteinuria may be strong indicators of preterm birth and should be carefully cautioned.

Different disease-onset time of pregnancy induced hypertension were found to have different effects on preterm birth and the early-onset cases seemed more severe than those at late-onset time [28]. One study used population-based data to find that the early-onset (<34 weeks) preeclampsia group had a higher incidence rate of gestational age (34-36 weeks) than late-onset group (60.1% versus 23.4%) [29]. Another retrospective analysis also found the rate of preterm birth was significant higher in early- versus late-onset group [30]. A case series study described the maternal and neonatal outcomes with early-onset preeclampsia before 26 weeks of gestation and found that it may be followed by high maternal complication rates and poor neonatal

survival [31]. These studies were all consistent with our results. One study once used repeated antenatal blood pressure measurements to predict adverse outcomes and validate the result in a survey data [32]. They found the information of blood pressure after 28 weeks may not improve the prediction of preterm birth. Some studies suggested the early-onset pregnancy induced hypertension was related with adverse neonatal outcomes while the late-onset pregnancy induced hypertension may had stronger effect on maternal-related disease [30, 33, 34]. As the earlier the complications appeared, the longer the fetus were affected. Women with early-onset pregnancy induced hypertension were more likely to have preterm birth.

Preterm births nowadays in HDP, especially preeclampsia, are mainly medically induced. So it is more meaningful to focus on gestational hypertension than preeclampsia in recent years. During the 1990's, Chinese women were probably unaware of seeking maternal care, had less prenatal care service attendance, receive delayed or even absent medical intervention to prevent gestational hypertension and preeclampsia due to the shortage of health care resources and poor coverage of health insurance. Especially among Chinese pregnant women in rural regions, they might miss good opportunity for supplemental calcium, low-dose aspirin and magnesium sulfate therapy and lifestyle modification, etc [35, 36]. The data in our cohort indicated that the rates of caesarean sections and induced deliveries were 30.76%, 5.77% in early-onset of preeclampsia women, and 48.92%, 0.54% in late-onset of preeclampsia women, respectively. Those rates were much lower than nowadays, so the medical behavior in the 1990's of China was to "let do nature". Poorly-controlled hypertension during pregnancy significantly increases maternal and fetal morbidity and mortality. Our study mainly analyzed differences about the effects of gestational hypertension and preeclampsia on preterm birth without active medical decisions. From the perspective

of epidemiological laboratory test, our relevant results about preeclampsia would provide the theoretical reference of obstetric and paediatric guidelines in some way [37].

Possible mechanisms of this study

The pathophysiological mechanisms linking pregnancy induced hypertension to preterm birth include inflammation, oxidative stress and endocrine disruption [38-40]. The biomarkers of hypertensive disorders like inflammatory Interleukin-6 (IL-6)[38] and reactive oxygen species [39] also play an important role in the development of preterm birth [41, 42]. A recent study showed that hypertensive disorders may influence the fetal growth by dysregulating the release of hormones such like adipolines, thus leading to preterm birth [40]. In particular, placental hypoperfusion induced by impaired development of placental blood vessels and endothelial dysfunction are treated as the most common manifestations of higher blood pressure, which are also associated with reduced fetal growth [43, 44].

Strengths of this study

Our study had several strengths. First, we conducted a large population-based prospective cohort study to explore the association where hypertensive information during pregnancy was collected before the outcomes. It avoided the risk of selection and recall biases to a large extent. Meanwhile, the large sample size supported us to investigate the association with enough power. Second, our study divided gestational hypertension and preeclampsia into different onset time, which provided a more comprehensive insight to analyze their impact. Finally, most of our participants were Han ethnicity living in similar regions, which ensured the comparability.

Limitations of this study

However, there are some limitations should be considered in the interpretation of our findings. Some confounding factors, such as the maternal smoking or drinking were

unavailable as the study was based on existing data. However, smoking and drinking were both rare in Chinese women at the time of our study, especially among reproductive-age women living in rural regions. A survey conducted in 1996 on the national prevalence of smoking in China showed that the smoking prevalence among women aged 20-29 years was less than 2% [45]. Another limitation in our study pertained the population selection. The original cohort included 2 southern provinces and 1 northern province. We excluded the northern province in our current analysis as detailed clinical records about hypertensive diagnosis during pregnancy were unavailable.

This study investigated the impact of different conditions of hypertension in pregnancy (gestational hypertension and preeclampsia, respectively) on preterm birth, and compared whether the effects vary on different disease-onset time. Our findings indicate that women with preeclampsia had significantly higher risk of delivering preterm infants. Early-onset of hypertensive disorders of pregnancy has a greater influence than late-onset on the etiology of preterm birth.

CONCLUSION

In this large prospective cohort study conducted in Chinese women, we found that early-onset of gestational hypertension and preeclampsia could both significantly increase the risks of preterm birth. Preeclampsia may impose more detrimental than gestational hypertension in the etiology of preterm infants. Further measures should be taken to increase awareness of the health risks associated hypertensive disorders of pregnancy with respect to the prevention of preterm birth.

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Contributors

HA, MJ and NL proposed study concept and designed the analysis. HA performed the analyses and authored the first draft of the article. MJ, NL, LZ, ZL, HL and YZ provided advice on the first draft. RY and Nan Li accept responsibility for the final content of the article. All of the authors reviewed the manuscript approved the study before submission.

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Competing interests

The authors declare that they have no competing interests.

Patient consent for publication

Not required.

Ethics approval

The project was approved by the institutional review boards of the U.S. Centers for Disease Control and Prevention and the Peking University Health Science Center and was conducted in accordance with the guidelines laid down in the Declaration of Helsinki. Since rural women in the study area were mostly illiterate in the early 1990s, all women who took pills provided oral informed consent. The informed consent was

obtained from a parent and/or legal guardian of the study participants as some of the participants are illiterate.

Provenance and peer review

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Date sharing statement

Original data is available on request. Please contact the corresponding author for further information (linan01@pku.edu.cn).

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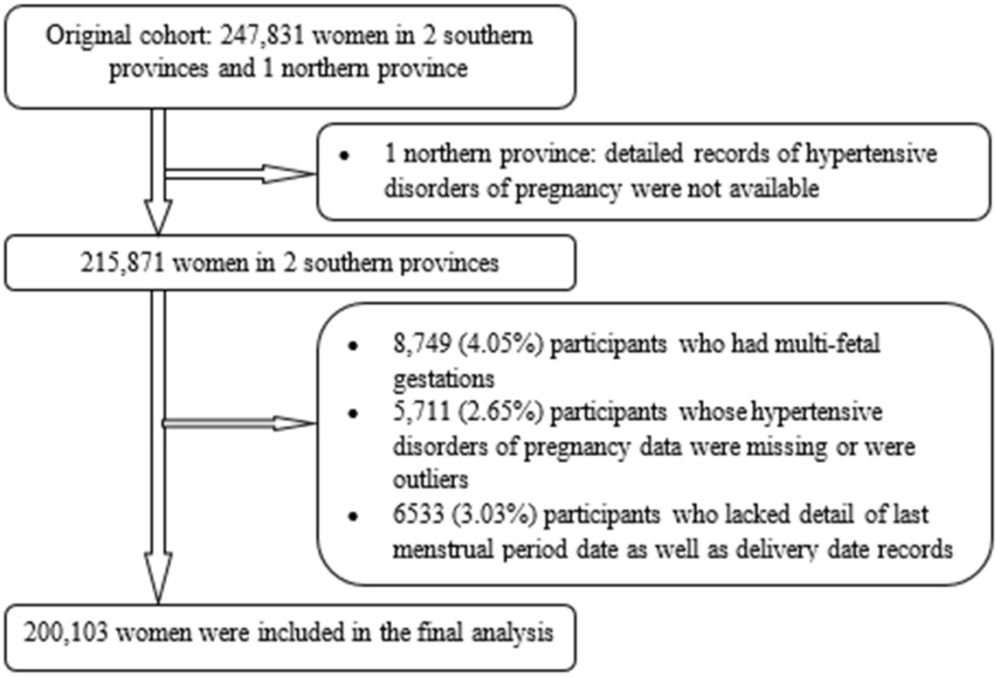

Figure 1: Flowchart of participants

96x71mm (600 x 600 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	16
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9 8 9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Impact of gestational hypertension and preeclampsia on preterm birth in China: a large prospective cohort study

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Abstract

Objective: To investigate the impact of gestational hypertension and preeclampsia on preterm birth.

Design: The data were collected from the China–US Collaborative Project for Neural Tube Defect Prevention; this was a large population-based cohort study.

Setting and participants: We selected participants registered in two southern provinces, for whom we had exact information on gestational blood pressure and pregnancy outcomes, and who were not affected by chronic hypertension. In total, 200,103 participants were recruited from 1993 to 1995.

Outcome measures: Preterm birth was defined as a singleton pregnancy and birth before 37 gestational weeks.

Results: The incidences of gestational hypertension and preeclampsia were 5.47% and 5.44%, respectively, for women who gave birth at full term, and 5.63% and 7.33%, respectively, for those who gave birth pre-term. After adjusting for potential confounders, the risk ratios (RRs) of preterm birth in women with gestational hypertension and preeclampsia were (95% confidence interval [CI] 0.98, 1.11) and 1.39 (95% CI 1.25, 1.55), respectively. The associations were stronger for early-onset (< 28 weeks of gestation) gestational hypertension (adjusted RR = 2.13, 95% CI 1.71, 2.65) and preeclampsia (adjusted RR = 8.47, 95% CI 5.59, 12.80).

Conclusions: Preeclampsia was associated with a higher risk of preterm birth. The early-onset gestational hypertension and preeclampsia were associated with more severe risks than late-onset conditions.

Strengths and limitations of this study

- Strengths of the study are the large sample size, prospective study design and detailed subtypes of hypertensive disorders of pregnancy.
- Limitation of this study is our inability to control for certain confounding factors including smoking and alcohol consumption.
- Although this study reported the effect of hypertensive disorders of pregnancy and subtypes thereof on preterm birth, further researches are needed to explore the mechanisms results.

INTRODUCTION

Preterm birth, a common adverse pregnancy outcome, is one of the leading causes of child death globally, especially in developing countries [1]. It is estimated that, globally, annual preterm live births number 14.84 million, thus 10.6% of all births. Asian countries account for 52.9% of global preterm births; the proportion in China (7.8%) is the second highest worldwide [2]. Preterm birth greatly increases the risks of infant mortality and morbidity, and the risks of long-term effects including respiratory syndrome and infections, which brings heavy medical financial burdens on the families and countries [3, 4]. The mechanism of preterm birth is still uncertain, and some studies suggested that elevated blood pressure levels during pregnancy may play an important role in the development of preterm birth [5, 6].

Pregnancy induced hypertension, including gestational hypertension and preeclampsia, complicates 6–10% of pregnancies [7]. Gestational hypertension and preeclampsia trigger new-onset hypertension after 20 weeks of gestation, with or without proteinuria [8]. It remains uncertain whether gestational hypertension and preeclampsia are separate diseases sharing common medical manifestations or the same disorder differing only in terms of spectral position [9]. Some studies have reported that

pregnancy induced hypertension, especially preeclampsia, may be a driver of preterm birth [10]. However, researchers have observed that early- and late-onset of preeclampsia may have different triggers [11], and should be viewed as distinct conditions. Women with early-onset preeclampsia (characterized by reduced placental blood flow) exhibit a higher level of vascular resistance than do those with late-onset preeclampsia (which differs in terms of both origin and the hemodynamics) [12, 13]. The reported associations between gestational hypertension and preterm birth are not consistent [14]. Buchbinder [14] found that (compared to subjects with normotensive and mild preeclampsia) women with severe gestational hypertension exhibited a significantly higher rate of preterm delivery. However, another study found that gestational hypertension was not associated with preterm birth [15].

Therefore, we performed a large prospective cohort study to investigate the impacts of gestational hypertension and preeclampsia on preterm birth in China. In addition, we also assessed whether the time of disease onset (early-, or late-onset pregnancy induced hypertension) affected the preterm birth rate.

MATERIALS AND METHODS

Background and original cohort

The methodshave been described previously [16, 17]. Commencing in 1993, the Chinese Ministry of Health conducted a public health campaign to prevent neural tube defects in 21 counties of two southern provinces (Zhejiang and Jiangsu) and one northern province (Hebei). During this campaign, all females who planned to get married, or who became pregnant, were registered in a pregnancy monitoring system. This served as the principal record of antenatal care and the prime source of demographic information. All women were advised to take 400 μg of folic acid daily,

commencing at the time of registration and continuing until completion of the first trimester of pregnancy. Pills were distributed at the time of registration. At the end of each month, healthcare workers recorded the dates of all menstrual periods and how many pills remained in each bottle. All reproductive events that occurred after 20 complete gestational weeks (live births, stillbirths, and pregnancy terminations) were recorded, as were all structural congenital anomalies (regardless of the gestational week). The original cohort included 247,831 women registered between October 1993 and September 1995 who delivered infants by 31 December 1996. The project was approved by the institutional review boards of the U.S. Centres for Disease Control and Prevention and the Peking University Health Science Centre. As most women in the (rural) study area were illiterate in the early 1990s, all women who took pills provided oral informed consent [18].

Selection of study subjects

We selected participants registered in two southern provinces (Jiangsu Province and Zhejiang Province). Both provinces kept detailed records on pregnancy induced hypertension. Of 215,871 women, we excluded 8,749 (4.05%) with multifetal gestation, 5,711 (2.65%) women with chronic hypertension or whose gestational hypertension diagnosis was unknown, and 6,533 (3.03%) for whom details of the last menstrual periods and/or delivery dates were lacking. Ultimately, 200,103 women (92.70% of the target population) were included in the final analysis. Recruitment and derivation of the population used in the final analysis, are shown in **Figure 1.**

Diagnosis of Gestational Hypertension and Preeclampsia

An appropriate cuff bladder size was determined at each visit (based on arm circumference). Blood pressure was measured in the right arm using a mercury sphygmomanometer on at least two occasions separated by ≥ 6 h. Gestational

hypertension was defined as an absolute blood pressure ≥ 140/90 mm Hg after 20 weeks of gestation, or a blood pressure increment ≥ 30/15 mm Hg after 20 weeks of gestation compared to that of the first trimester [19]. Preeclampsia (including eclampsia) was defined as a blood pressure of ≥ 140/90 mm Hg or a blood pressure increment 30/15 mm Hg after 20 weeks of gestation, with concurrent proteinuria (score 1+ as revealed by a dipstick test of a single random urine specimen collected after 20 weeks of gestation). Given the different heritabilities, clinical manifestations, and prognoses of early- and late-onset gestational hypertension and preeclampsia [18, 20], we divided gestational hypertension and preeclampsia into two types: early-onset (< week 28 of gestation at diagnosis) and late-onset (at ≥ week 28 of gestation sis).

Statistical Analysis

We compared the mean age and body mass index (BMI), folic acid use, parity, ethnicity, educational level, and occupation between women with and without gestational hypertension. We used Student's *t*-test to compare quantitative variables and the $\chi 2$ test to compare categorical variables. We calculated the incidences of preterm birth in women with and without gestational hypertension. Logistic regression models were used to estimate risk ratios (RRs) after adjusting for the principal underlying confounders including maternal age (continuous), BMI (continuous), educational level, occupation, parity, ethnicity, and folic acid use. We compared the preterm birth incidences by the onset times of hypertension and preeclampsia. The mean BMI was used if individual BMI data were lacking. All data were analysed using SPSS for Windows software (ver. 20.0; SPSS Inc, Chicago, IL, USA). Statistical significance was defined as two-sided $P < 0.05$.

Patient and public involvement

No patient was involved in the study design, in formulation of the study aims or the research questions, or in subject recruitment or study conduct. No patient was involved in the interpretation of results or manuscript preparation. We do not plan to disseminate the results to the study participants.

RESULTS

Of the 200,103 women included in analysis, 19,115 (9.55%) evidenced gestational hypertension and 4,912 (2.45%) preeclampsia. The baseline characteristics of the participants with gestational hypertension are shown in **Table 1**. Nearly all were ethnically Han. Women with gestational hypertension were more likely to be older than others, to have a higher BMI, to be primiparous, to take folic acid, and to be factory workers. The characteristics of women with and without preeclampsia are showed in **Supplementary Table 1**.Women with preeclampsia were more likely to be older than others, to have a higher BMI, to be primiparous, to take folic acid, and to have a lower education level.

Table 1. Characteristics of women enrolled in the pregnancy monitoring system by gestational hypertension status; China, 1993 to 1996.

Characteristic	Gestational hypertension group (n=19,115)		Non-gestational hypertension group (n=180,988)		*P*
	n[a]	%	n[a]	%	
Age at pregnancy, (years, mean[SD])	25.04 (3.34)		24.86 (3.21)		<0.001
Body mass index at first visit (kg/m^2, mean[SD])	20.77 (2.25)		20.50 (2.09)		<0.001

Primiparous	16,277	85.15	149,967	82.86	<0.001
Han ethnicity	18,977	99.28	179,670	99.27	0.923
Folic acid use	10,245	53.60	94,874	52.42	0.002
Education level					0.123
High school or higher	2,014	10.54	20,045	11.08	
Junior high school	11,380	59.53	107,253	59.26	
Primary school or lower	5,672	29.67	53,175	29.38	
Unknown	49	0.26	515	0.28	
Occupation					<0.001
Farmer	10,930	57.18	106,992	59.12	
Factory worker	5,409	28.30	49,257	27.22	
Other[b]	2,754	14.41	24,480	13.53	
Unknown	22	0.12	259	0.14	

[a]Values for certain characteristics may be lower than the total numbers of subjects with or without gestational hypertension because some data were missing.

[b]Other includes businessman, teacher, day laborer and civil servant.

The overall incidence of preterm birth was 5.49%. The incidences for women with gestational hypertension and preeclampsia were 5.63% and 7.33%, respectively, and 5.47% and 5.44% for women with normal blood pressure. The RRs of preterm birth in women with gestational hypertension and preeclampsia were 1.03 (95% confidence interval [CI] 0.97, 1.10) and 1.38 (95% CI 1.23, 1.53), respectively. Compared to the term birth group, the preterm birth group was more likely to be younger, of lower educational level, and to not take folic acid (**Table 2**). The RRs of preterm birth in women with gestational hypertension and preeclampsia were 1.04 (95% CI 0.98, 1.11) and 1.39 (95% CI 1.25, 1.55), respectively, after adjusting for the effects of major

confounding factors (**Table 3**). Sensitivity analysis was conducted after excluding newborns with major external birth defects (**Supplementary Table 2**). The results were consistent with those described above. The results were consistent with those described above. We also compared the preterm birth rates by early- or late-onset gestational hypertension. Early-onset hypertension was associated with an increased risk of preterm birth (adjusted RR = 2.13, 95% CI 1.71, 2.65), but the two types of preeclampsia exerted similar effects on preterm birth (early-onset: adjusted RR = 8.47, 95% CI 5.59, 12.80; late-onset: adjusted RR = 1.30, 95% CI 1.16, 1.46) (**Table 4**).

Table 2. Incidences and crude RRs of preterm birth by gestational hypertension and preeclampsia status, and other characteristics; China, 1993 to 1996.

Characteristic	No.	Preterm birth		
		Incidence (%)	RR	95% CI
Age (years)				
< 20	896	10.60	1.92	1.55, 2.38
≥ 20–< 25	115,124	5.81	1	…
≥ 25–< 30	59,960	5.00	0.85	0.82, 0.89
≥ 30	24,123	4.90	0.84	0.78, 0.89
Body mass index (kg/m^2)				
< 18.5	28,576	5.54	1.01	0.96, 1.07
≥ 18.5–< 24	159,985	5.47	1	…
≥ 24–< 28	10,610	5.45	1.00	0.91, 1.09
≥ 28	932	6.33	1.17	0.90, 1.52
Education level				
High school or higher	22,059	4.71	1	…

Junior high school	118,633	5.41	1.16	1.08, 1.24
Primary school or lower	58,847	5.91	1.27	1.18, 1.36
Unknown	564	5.85	1.26	0.88, 1.80
Occupation				
Farmer	117,922	5.60	1	…
Factory worker	54,666	5.54	0.99	0.95, 1.03
Other[b]	27,234	4.89	0.87	0.82, 0.92
Unknown	281	2.49	0.43	0.20, 0.91
Parity				
Multiparous	33,859	5.64	1	…
Primiparous	166,244	5.45	0.96	0.92, 1.01
Ethnicity				
Han	198,647	5.48	1	…
Other	1,456	6.46	1.19	0.97, 1.47
Folic acid use				
No	94,984	5.90	1	…
Yes	105,119	5.10	0.86	0.82, 0.89
Gestational hypertension				
No	180,988	5.47	1	…
Yes	19,115	5.63	1.03	0.97, 1.10
Preeclampsia				
No	195,191	5.44	1	…
Yes	4,912	7.33	1.38	1.23, 1.53

CI: confidence interval; RR: risk ratio.

[b]Other includes businessman, teacher, day laborer and civil servant.

Table 3. The associations between gestational hypertension and preeclampsia and preterm birth as revealed by multivariate logistic regression; China, 1993 to 1996

Risk factor	Preterm birth	
	Adjusted RR	95% CI
Age (continuous)	1.04	1.03, 1.05
Factory worker	1.00	0.96, 1.05
Other[b]	0.93	0.87, 1.00
Unknown occupation	0.40	0.19, 0.87
Junior high school	1.10	1.02, 1.18
Primary school or lower	1.22	1.13, 1.32
Unknown education	1.38	0.95, 1.99
Folic acid use	0.83	0.80, 0.86
Gestational hypertension		
No	1	…
Yes	1.04	0.98, 1.11
Preeclampsia		
No	1	…
Yes	1.39	1.25, 1.55

CI: confidence interval; RR: risk ratio.

[b]Other includes businessman, teacher, day laborer and civil servant.

Table 4. Associations between early- and late-onset gestational hypertension and preeclampsia and the risk of preterm birth.

Onset period		Preterm birth		
	No.	Incidence (%)	Crude RR (95% CI)	Adjusted RR (95% CI)[a]
Gestational hypertension				
None[b]	180,988	5.47	1	1
Early-onset	849	10.72	2.08 (1.67-2.58)	2.13 (1.71-2.65)
Late-onset	18,266	5.40	0.99 (0.92-1.06)	1.00 (0.94-1.07)
Preeclampsia				
None[b]	195,191	5.44	1	1
Early-onset	104	31.73	8.09 (5.35-12.23)	8.47 (5.59-12.80)

Late-onset	4,808	6.80	1.27 (1.13-1.42)	1.30 (1.16-1.46)

CI: confidence interval; RR: risk ratio.

[a]Adjusted for maternal age (continuous), BMI (continuous), education level, occupation, ethnicity, parity, and folic acid use.

[b]Reference group.

DISCUSSION

Main findings of this study

This large prospective cohort study investigated whether gestational hypertension, preeclampsia and the times of onset thereof were associated with the risk of preterm birth. We found that preeclampsia (particularly early-onset preeclampsia) was associated with an increased risk of preterm birth. Only early-onset gestational hypertension was significantly positively associated with preterm birth.

Our results are consistent with those of some previous studies [21-23]. Bakke et al [22] performed a prospective cohort study in the Netherlands to explore the association between blood pressure and preterm birth and reported an increased risk of preterm birth in a preeclampsia group compared to a nonhypertensive pregnant group (adjusted odds ratio = 5.89, 95% CI 2.63, 13.14). However, no such association was observed in a gestational hypertension group, in agreement with our results. However, the cited work did not describe the onset times of gestational hypertension or preeclampsia. A previous study suggested that onset time may affect the preterm birth rate [11]. Another prospective cohort study showed that, compared to a normotensive group, women with pregnancy-induced hypertension were at an increased risk of preterm delivery (adjusted RR = 5.1, 95% CI 3.4, 7.8) [23]. Other studies reported similar results in different population [24, 25]. However, a study in Zimbabwe found that the risk of preterm delivery did not vary between women with and without pregnancy-induced

hypertension ($P > 0.05$) [26]. The different findings may reflect differences in study design, population heterogeneities, and the measurement methods.

Both the causes and outcomes of gestational hypertension and preeclampsia remain unclear. One study used survival curves to show that the risk factors imposed by both conditions were similar, but women with preeclampsia gave birth at a lower gestational age than did those with gestational hypertension [13]. One retrospective case-control study showed that severe preeclampsia was more likely to be associated with preterm labour than gestational hypertension (OR = 3.18, 95% CI 2.23, 4.52) [27]. We also found that preeclampsia was associated with a higher risk of preterm birth than gestational hypertension. By contrast, one study subdivided the gestational hypertension and preeclampsia groups and found that severe gestational hypertension was associated with higher rates of adverse outcomes than was mild preeclampsia [14]. These findings suggest that both high blood pressure and proteinuria may be strong indicators of preterm birth and should thus be carefully monitored.

The onset times of pregnancy-induced hypertension exerted different effects on preterm birth; early-onset subjects seemed to be at greater risk than late-onset cases [28]. One study using population-based data found that an early-onset (< 34 weeks) preeclampsia group exhibited a higher incidence of gestational age (34–36 weeks) than did a late-onset group (60.1% versus 23.4%) [29]. Another retrospective analysis also found that the rate of preterm birth was significantly higher in an early- than a late-onset group [30]. One case series explored the maternal and neonatal outcomes of early-onset preeclampsia (before 26 weeks of gestation) and found high maternal complication rates and poor neonatal survival [31]. All these findings are consistent with our results. One study used repeated antenatal blood pressure measurements to predict adverse outcomes and validated the results by performing a survey [32]. The

cited authors found that blood pressure data obtained after 28 weeks of gestation did not aid prediction of preterm birth. Some studies suggested that early-onset pregnancy-induced hypertension was associated with adverse neonatal outcomes whereas late-onset hypertension exerted stronger effects on maternal disease [30, 33, 34]. The earlier the complications, the longer the foetus was affected. Women with early-onset pregnancy-induced hypertension were more likely to give birth preterm.

Today, most preterm births in women with hypertensive disorders during pregnancy (especially preeclampsia) are medically induced. It is thus more meaningful to focus on gestational hypertension rather than preeclampsia. During the 1990s, many Chinese women did not seek maternal care, received little prenatal attention, and medical interventions seeking to prevent gestational hypertension and preeclampsia were delayed (or even absent) given a shortage of healthcare resources and poor insurance coverage. Especially in rural regions, Chinese women often lacked access to supplemental calcium, low-dose aspirin, and magnesium sulphate; and were not educated in terms of lifestyle modification [35, 36]. In our cohort, the rates of caesarean section and induced delivery were 30.76% and 5.77%, respectively, in those with early-onset preeclampsia and 48.92% and 0.54%, respectively, in those with late-onset preeclampsia, thus much lower than today. In the 1990s in China, the medical philosophy was “let nature take its course”. Poorly controlled hypertension during pregnancy significantly increases maternal and foetal morbidity and mortality. The differences in the effects of gestational hypertension and preeclampsia on preterm birth that we found are those in (principally) women lacking active medical attention. This was thus an “epidemiological laboratory” test; our preeclampsia data provide the theoretical baseline that will inform modern obstetric and paediatric guidelines [37].

Possible mechanisms of this study

The pathophysiological mechanisms linking pregnancy-induced hypertension to preterm birth include inflammation, oxidative stress, and endocrine disruption [38-40]. Biomarkers of hypertensive disorders (including inflammatory Interleukin-6 [IL-6] [38] and reactive oxygen species [39]) play important roles in preterm birth [41, 42]. A recent study showed that hypertensive disorders may influence foetal growth by dysregulating the release of hormones including adipolines, triggering preterm birth [40]. In particular, placental hypoperfusion induced by impaired development of placental blood vessels, and endothelial dysfunction, are the most common manifestations of high blood pressure, and are also associated with reduced foetal growth [43, 44].

Strengths of this study

Our study had several strengths. First, this was a large, population-based, prospective cohort study; hypertensive data were collected during pregnancy (thus before birth). Selection and recall biases are minimal. The large sample size afforded excellent statistical power. Also, we considered the onset times of gestational hypertension and preeclampsia; this afforded more comprehensive insights. Finally, most participants were Han ethnics living in similar regions, ensuring comparability.

Limitations of this study

Our work had certain limitations. Although we report the impacts of early-onset gestational hypertension and preeclampsia on preterm birth, we cannot discuss possible causal relationships; additional research is needed. Some confounding factors (e.g. maternal smoking and alcohol consumption data) were unavailable. However, during the time of the study, few (especially rural, reproductive-age) Chinese women smoked or drank. A 1996 survey revealed that the smoking rate among Chinese women aged 20–29 years was less than 2% [45]. Other maternal lifestyles such as physical activity,

diet quality, and factors such as family income and gestational diabetes were also unavailable in this study. Further studies are needed to collect these information and test their possible modification effect. Another limitation is population-based. The original cohort included two southern provinces and one northern province; we excluded the latter because detailed clinical data on hypertension during pregnancy were unavailable.

We investigated the impacts of gestational hypertension and preeclampsia on preterm birth, and the effects of disease onset times. Women with preeclampsia were at a significantly higher risk of preterm birth. Early-onset hypertensive disorders of pregnancy affected the preterm birth rate more than did late-onset disorders.

CONCLUSION

In this large, prospective cohort study on Chinese women, early-onset gestational hypertension and preeclampsia both significantly increased the risk of preterm birth. Preeclampsia may be more detrimental than gestational hypertension. It is important to increase awareness of the health risks associated with hypertensive disorders of pregnancy, particularly the risk of preterm birth.

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Contributors

HA, MJ and NL proposed study concept and designed the analysis. HA performed the analyses and authored the first draft of the article. MJ, NL, LZ, ZL, HL and YZ provided advice on the first draft. RY and Nan Li accept responsibility for the final

content of the article. All of the authors reviewed the manuscript approved the study before submission.

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Competing interests

The authors declare that they have no competing interests.

Patient consent for publication

Not required.

Ethics approval

The project was approved by the institutional review boards of the U.S. Centers for Disease Control and Prevention and the Peking University Health Science Center and was conducted in accordance with the guidelines laid down in the Declaration of Helsinki. Since rural women in the study area were mostly illiterate in the early 1990s, all women who took pills provided oral informed consent. The informed consent was obtained from a parent and/or legal guardian of the study participants as some of the participants are illiterate.

Provenance and peer review

Not commissioned; externally peer reviewed.

Date sharing statement

Original data is available on request. Please contact the corresponding author for further information (linan01@pku.edu.cn).

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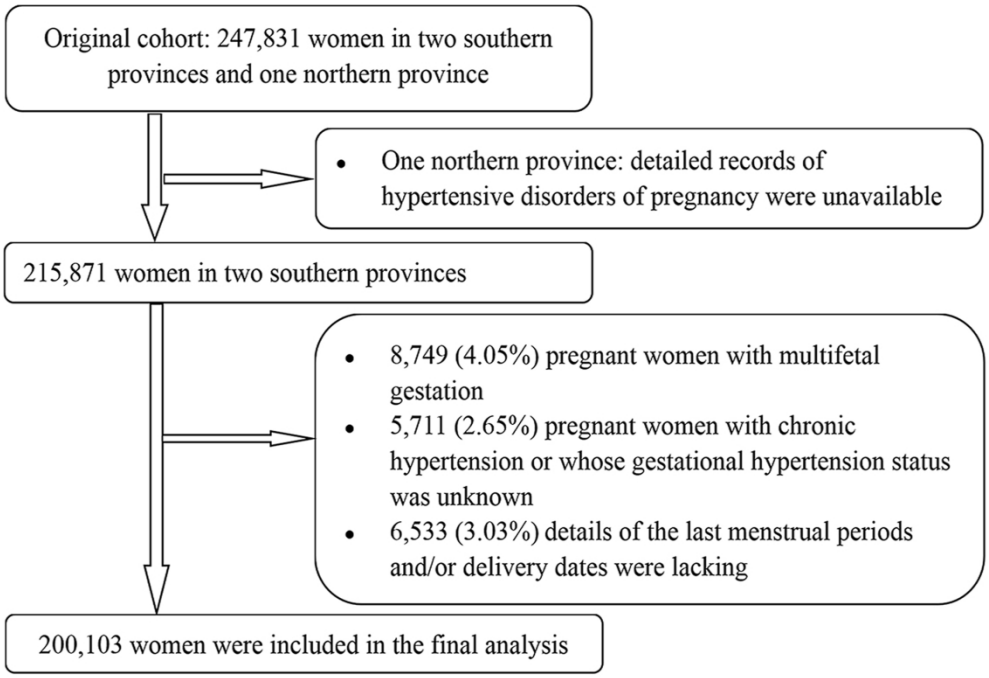

Figure 1: Flowchart of participants

1166x874mm (72 x 72 DPI)

Impact of gestational hypertension and preeclampsia on preterm birth in China: a large prospective cohort study

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Supplementary Table 1. Characteristics of women enrolled in the pregnancy monitoring system by pre-eclampsia status; China, 1993 to 1996.

Characteristic	Pre-eclampsia group (n=4,912)		Non-pre-eclampsia group (n=195,191)		*P*
	n[a]	%	n[a]	%	
Age at pregnancy, (years, mean[SD])	25.14 (3.44)		24.87 (3.21)		<0.001
Body mass index at first visit (kg/m^2, mean[SD])	20.90 (2.40)		20.51 (2.10)		<0.001
Primiparous	4,232	86.16	162,012	83.00	<0.001
Han ethnicity	4,872	99.19	193,775	99.27	0.449
Folic acid use	2,711	55.19	102,408	52.47	<0.001
Education level					<0.001
High school or higher	469	9.55	21,590	11.06	
Junior high school	2,873	58.49	115,760	59.31	
Primary school or lower	1,557	31.70	57,290	29.35	
Unknown	13	0.26	551	0.28	
Occupation					0.128
Farmer	2,834	57.18	115,088	58.96	
Factory worker	1,386	28.30	53,280	27.30	
Other[b]	689	14.03	26,545	13.60	

Unknown	3	0.06	278	0.14

[a]Values for some characteristics may not be equal to total numbers of preeclampsia or non-preeclampsia groups because of missing values.

[b]Other includes businessman, teacher, day laborer and civil servant.

Supplementary Table 2. The associations between gestational hypertension and pre-eclampsia and preterm birth as revealed by multivariate logistic regression after excluding major external birth defects; China, 1993 to 1996.

	Preterm birth	
Risk factor	Adjusted RR	95% CI
Age (continuous)	1.04	1.03, 1.05
Factory worker	1.00	0.96, 1.05
Other[b]	0.93	0.87, 1.00
Unknown occupation	0.43	0.20, 0.93
Junior high school	1.11	1.03, 1.20
Primary school or lower	1.23	1.14, 1.34
Unknown education	1.40	0.97, 2.04
Folic acid use	0.83	0.80, 0.86
Gestational hypertension		
No	1	…
Yes	1.05	0.98, 1.12
Preeclampsia		
No	1	…
Yes	1.37	1.22, 1.53

CI: confidence interval; RR: risk ratio.
[b]Other includes businessman, teacher, day laborer and civil servant.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	16
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9 8 9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.