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Impact of gestational hypertension and preeclampsia on fetal gender: A large prospective cohort study in China

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ABSTRACT

Background: Recent studies suggested an association between fetal sex preponderance and hypertensive disorders during pregnancy, but the conclusions were inconsistent. Our objective was to investigate whether the occurrence of gestational hypertensive disorders would affect the possibility of delivering boys.

Methods: Data were obtained from the China-US Collaborative Project for Neural Tube Defects Prevention, a large population-based cohort study. We included participants who were registered in 2 southern Chinese provinces, and whose information of blood pressure and sex delivery were recorded in detailed. Blood pressure was measured during pregnancy by trained health care workers and other health-related information was recorded prospectively. We used log-binomial regression to evaluate the association between gestational hypertension or preeclampsia and the chance of male delivery.

Results: Among 205,605 singleton pregnancy women, the overall incidences of gestational hypertension and preeclampsia were 9.5% and 2.4%, respectively. The prevalence of male delivery was 51.1% and 50.2% in the groups of gestational hypertension and preeclampsia, while in the normotension group was 52.0%. After adjustment for the effects of the main potential confounders, women with gestational hypertension and preeclampsia both showed significantly decreased probability of giving birth to a boy. The adjusted risk ratios (RRs) were 0.98 (95% confidence interval (CI): 0.97–0.99) and 0.96 (95% CI: 0.94–0.99), respectively.

Conclusions: Our results support a slight but significant association between gestational hypertension or preeclampsia and decreased likelihood of male delivery.

1. Introduction

The prediction of baby's sex before birth has been always a hot public topic. A declining proportion of male births in industrialized countries (United States, Canada, Denmark, Netherlands) over the past several decades has been queried as a possible health indicator in the world [1]. With the second largest population and economic growth during the past 20 years, the impact of fetal birth in China played an important role in total population and structural changes thoughtout the world. Since the general implementation of two-child policy carried out recently in China, more and more families would plan to give birth to their second child, with an probable desire for son preference [2]. Some epidemiological studies recognized that sex ratio at birth in human beings typically showed a slight male preponderant state, the determinants of which were not comprehensively understood [3,4]. While numerous researches about genetic factors revealed that the chance of conceiving a boy or girl was equal [5]. Societal stressors, such as disasters, terrorism, economic collapse et al, may reduce the proportion of boys born into a population [6–8]. In recent years, more and more studies focused on the impact of health stressors on the sex ratio, especially the diseases during pregnancy period [9–12].

Hypertensive disorders during pregnancy, including gestational hypertension and preeclampsia, are the most important complications which account about 10% of all pregnancies worldwide [13]. Studies on hormonal factors have found that preeclampsia was associated with a low estrogen level and an increased human chorionic gonadotropin (HCG) level [14–16]. Hormonal imbalances during conception could cause the occurrence of abnormal sex ratios at birth [17–19]. So it is easy to be speculated the potential relations between fetal gender and hypertensive disorders during pregnancy.

Several studies have tried to identify the association of gestational hypertensive disorders with fetal gender, but their results were

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contradictory. Researches from western countries, Japan and China indicated that preeclampsia or hypertensive disorders of pregnancy was associated with a preponderance of female fetuses compared to normotensive pregnancies [20–22], while some other studies have come to an opposite or unrelated conclusions [23,24]. So the aim of this study was to investigate whether the occurrence of gestational hypertension or preeclampsia would affect the possibility of delivering boys.

2. Materials and methods

2.1. Background and original cohort

The methods of the original research have been described in the previous literature [25,26]. The Chinese ministry of health launched a public health campaign since 1993, aimed at preventing neural tube defects in one northern province (Hebei) and two southern provinces (Zhejiang and Jiangsu). During this campaign, all women residents living in the project counties that were preparing for marriage or newly pregnant were included in the project and registered on the pregnancy monitoring system, which then served as the demographic information sources and relevant prenatal care principal records. 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. If woman agreed to take folic acid, the pills were distributed on the spot of registration. At the end of each month, health workers recorded the dates of all menstrual periods and how many pills remained in each bottle (if taking pills). To evaluate the effect of folic acid on neural tube defects, we chose women who registered on the monitoring system between October 1993 and September 1995 and who delivered before 31 December 1996, and their fetuses or infants could be confirmed either having a neural tube defect or not (whether stillborn, liveborn, or electively terminated on account of prenatal diagnosis of any severe birth defect). Abortions and elective terminations of pregnancy occurring before the 20th gestational week were not included in this cohort. The original cohort included a total of 247,831 women. The project was approved by the institutional review boards of the US Centers for Disease Control and Prevention and Peking University Health Science Center. Because in the early 1990s, most women in our study areas are uneducated, so all women who participated in the study and took pills provided oral informed consent.

2.2. Subjects for current study

We selected the participants who were registered in 2 southern provinces (Jiangsu Province and Zhejiang Province). These 2 neighboring provinces had detailed records about hypertensive disorders of pregnancy in their pregnancy monitoring system. Of our target population, we excluded: 8749 (4.05%) with multifetal gestation; 611 (0.28%) with unknown or outlier infant sex; and 5711 (2.65%) whose hypertensive disorders of pregnancy diagnosis was unknown. After these exclusions, 205,605 participants (95.24% of the targeted population) were included in the final analysis. Formation of the target recruitment population's relevant information, and derivation of the population used in the final analysis, are shown in Fig. 1.

2.3. Definition of gestational hypertension or preeclampsia during pregnancy and sex of the fetus at delivery

The blood pressure of pregnant woman was measured in the right arm with a mercury sphygmomanometer by trained physicians during each prenatal care, and was observed on 2 or more consecutive occasions with an interval of at least 6 h. Appropriate cuff bladder size was determined according to the pregnant woman's arm circumference in each measurement. Gestational hypertension was defined as absolute blood pressure greater than or equal to 140/90 mm Hg after 20 weeks of gestation, or the increment of blood pressure greater than or equal to 30/15 mm Hg after 20 weeks of gestation compared to the first trimester of pregnancy [27]. Preeclampsia (including eclampsia) was defined as blood pressure greater than or equal to 140/90 mm Hg or the increment of blood pressure greater than or equal to 30/15 mm Hg after 20 weeks of gestation, and with concurrent proteinuria (at least 1 + protein in a single random urine specimen by dipstick test).

Infant sex at birth was confirmed and recorded by the participants' experienced delivery obstetricians.

2.4. Statistical analysis

We conducted analysis of mean age and body mass index (BMI), and distributions of parity, ethnic origin, education, folic acid use and occupation between women who delivering a boy or a girl. The basic characteristics of pregnant women in the different fetal sex groups were compared using Student's *t*-test for quantitative variables, and the chi-square test for categorical variables. We used log-binomial regression models to evaluate the risk ratios (RRs) of male delivery in the women with gestational hypertension or preeclampsia, adjusted for BMI (continuous) and parity (categorized). All data were analyzed using SAS.9.4 (SAS Institute, Cary, NC).

3. Results

Table 1 lists the baseline characteristics of participants according to infant sex. Nearly all the participants were of Han ethnicity. In the 205,605 participants, 106,819 women delivered a boy, accounts for 52.0% of the total population. The average age of women who gave birth to boys was 24.91, a little higher than the average age of women delivering girls ($P < 0.001$). The proportion of being primiparous and folic acid supplements in women who delivered a girl were significantly higher than those who delivered a boy. The proportion of junior high school graduates and above was also higher in girls-born group. More than half of the participants were farmers in both groups, but the proportion of farmers in boys-born group was higher than that in girls-born group, and women who delivered a girl were more likely to be factory workers.

The prevalence of male delivery and associations with different characteristics are shown in Table 2. The prevalence of women who delivered a boy was 51.1% and 50.2% for women with gestational hypertension and preeclampsia, and 52.0% for women with normal blood pressure group. Compared as women with normal blood pressure group, the RRs of male delivery for those with gestational hypertension and preeclampsia were 0.98 (95% CI: 0.97, 0.99) and 0.96 (95% CI: 0.94, 0.99). While in the pregnant women with preterm birth outcomes, the risk ratio of male delivery was 1.02 (0.92, 1.12) for preterm preeclampsia. Older age, greater body mass index, lower education, being primiparous, and non-folic acid use were associated with elevated risk of women who give birth to a boy. After further controlling for the confounding factors including BMI and parity status, gestational hypertension and preeclampsia were still associated with lower relative probability of delivering a boy with the RRs were 0.98 (95% CI: 0.97, 0.99) and 0.96 (95% CI: 0.94, 0.99), respectively (Table 3).

4. Discussion

In this large population-based cohort study that included 205,605 pregnant women in China, we examined the association between gestational hypertension or preeclampsia and the possibility of delivering a boy. Our research revealed that compared to women with normotension, the occurrence of gestational hypertension or preeclampsia could significantly reduce the probability of giving birth to a boy.

Many studies have been done to find a link between pregnancy hypertensive disorders and sex ratio, while the results were not consistent. Two case-control studies in Pakistani and Denmark both showed

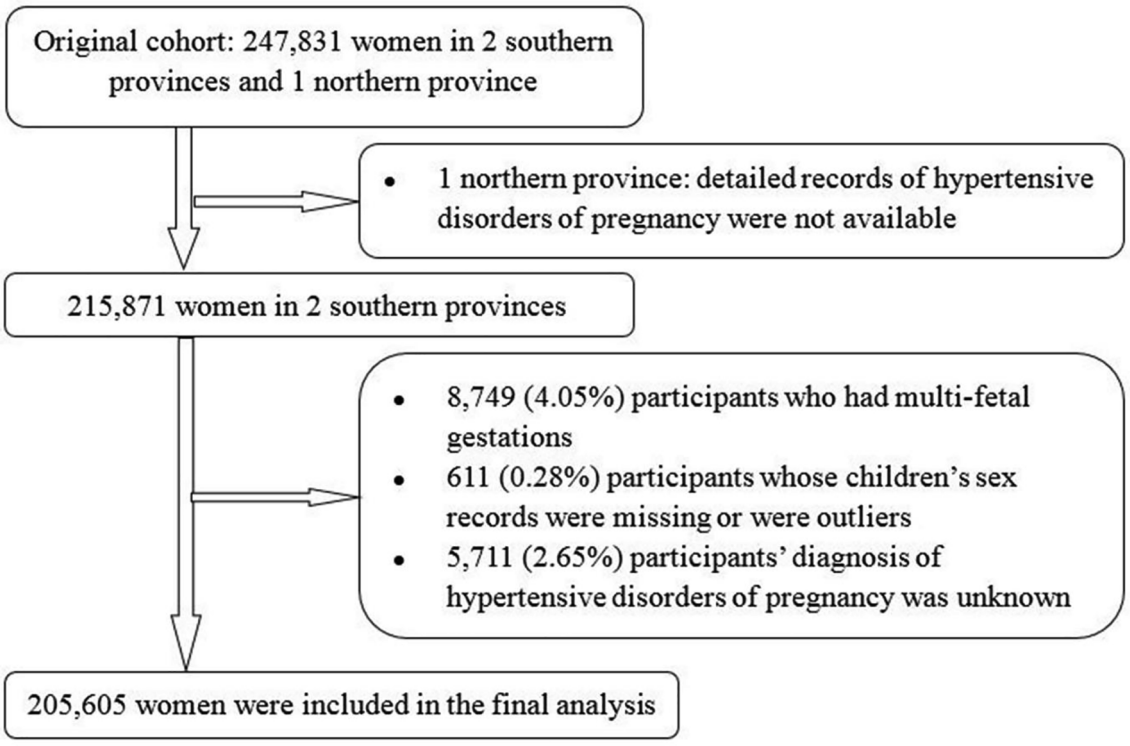

Fig. 1. Flowchart of participants.

Table 1
Baseline Characteristics of Participants by Infant Sex in China, 1993–1996.

Characteristics	Women who delivered a boy (n = 106819)		Women who delivered a girl (n = 98786)		*P*
	n	%	n	%	
Age (years, mean [SD])	24.91 (3.26)		24.85 (3.19)		< 0.001
Body mass index (kg/m^2, mean [SD])	20.54 (2.10)		20.51 (2.11)		0.111
Primiparous	87,700	82.1	82,235	83.2	< 0.001
Han ethnic group	106,013	99.2	98,085	99.3	0.233
Folic acid use	55,340	51.8	51,877	52.5	0.001
Education					0.019
High school or higher	11,517	10.8	10,899	11.1	
Junior high school	63,072	59.2	58,568	59.5	
Primary school or lower, or unknown	31,937	30.0	29,037	29.5	
Occupation					0.048
Farmer	63,411	59.4	58,142	58.9	
Factory worker	28,911	27.1	27,174	27.5	
Other or known	14,497	13.6	13,470	13.6	

SD, standard deviation.

a higher male to female sex ratio in births complicated with maternal pregnancy hypertensive disorders [24,28]. The research conducted by Makhseed in Kuwaiti population did not elicit any relationship between fetal gender and pregnancy-induced hypertension or preeclampsia [23]. While studies from China, Japan and western countries indicated apparent female preponderance in women with preeclampsia or hypertensive disorders [20–22], whose findings were similar with our study. Different results of previous researches may due to demographic differences, case selection bias, diagnostic inconsistencies, and mixture of parities.

Although several epidemiological studies have identified the association of pregnancy hypertensive disorders with fetal gender, but the mechanism of this relationship remains unclear. There is growing evidence that gender-specific adaptation to the placenta may be of great importance in the differences during fetal growth and survival [21,29,30]. Clifton [30] has suggested that there are sex differences in insulin-like growth factor pathway, placental cytokine expression and placental function alterations. Myatt and his colleagues [31] found that female fetus could affect the expression of miR-210 which was mediated by the NF-κB pathway, increasing placental miR-210 levels, and then causing placental mitochondrial dysfunction with severe preeclampsia. Furthermore, in the past few decades, abnormal changes in human chorionic gonadotropin (HCG) levels in pregnancy have been considered reliable markers of preeclampsia [15,16]. Several published researches have also found that women with female fetuses have higher circulating HCG levels than women with male fetuses, especially during the first and third trimester of pregnancy [18,19,32], which may reflect a compensatory angiogenic response to fetal placental hypoxia or down-regulated luteinizing hormone/HCG receptors [20]. These findings and hypotheses may provide an explanation for the association between hypertensive disorders of pregnancy and sex ratio, and provide a direction for further studies.

Our study had several strengths. First, the study was population based, with nearly complete ascertainment of gestational hypertension and preeclampsia among large numbers of women whose pregnancies lasted at least 20 weeks. The data were collected on both exposure and outcome, which could minimize the risk of selection and recall bias. Hypertension was diagnosed by trained professionals using mercury sphygmomanometer to measure blood pressure directly, thus, reducing the possibility of misclassification bias. Secondly, the two provinces we selected (Jiangsu and Zhejiang) are located on the east coast of China. The environment, climate and living habits are similar in both regions, and the population is ethnically homogenous with more than 99% of our population being Han Chinese. Thirdly, the sample size was large enough and there were detailed prenatal health data and clinical records for us to detect the relationship between gestational hypertension

Table 2
Prevalence of Male Delivery and Association with Gestational Hypertension and Preeclampsia in China, 1993–1996.

	Boy delivery (n = 106819)		Girl delivery (n = 98786)			
Characteristics	No.	Prevalence (%)	No.	Prevalence (%)	RR	95% CI
Age, y						
< 20	516	53.1	456	46.9	1.03	0.97, 1.09
20–25	61,141	51.7	57,158	48.3	1	…
25–30	31,995	52.0	29,520	48.0	1.01	0.99, 1.02
≥30	13,167	53.1	11,652	46.9	1.03	1.01, 1.04
Body mass index, kg/m^2						
< 18.5	14,863	51.0	14,260	49.0	0.98	0.97, 0.99
18.5–23.9	85,634	52.0	78,898	48.0	1	…
24–27.9	5811	53.0	5163	47.0	1.02	0.99, 1.04
≥28	511	52.4	465	47.6	1.01	0.95, 1.07
Education						
High school or higher	11,517	51.4	10,899	48.6	1	…
Junior high school	63,072	51.9	58,568	48.1	1.01	1.00, 1.02
Primary school or lower, or unknown	32,230	52.4	29,319	47.6	1.02	1.00, 1.03
Occupation						
Farmer	63,411	52.2	58,142	47.8	1	…
Factory worker	28,911	51.5	27,174	48.5	0.99	0.98, 0.99
Other or unknown	14,497	51.8	13,470	48.2	0.99	0.98, 1.01
Parity						
Multiparous	19,119	53.6	16,551	46.4	1	…
Primiparous	87,700	51.6	82,235	48.4	0.96	0.95, 0.97
Ethnicity						
Han	106,013	51.9	98,085	48.1	0.97	0.93, 1.02
Other	806	53.5	701	46.5	1	…
Folic acid use						
None	51,479	52.3	46,909	47.7	1	…
Use	55,340	51.6	51,877	48.4	0.99	0.98, 0.99
Gestational Hypertension						
No	96,782	52.0	89,196	48.0	1	…
Yes	10,037	51.1	9590	48.9	0.98	0.97, 0.99
Preeclampsia						
No	104,297	52.0	96,281	48.0	1	…
Yes	2522	50.2	2505	49.8	0.96	0.94, 0.99
Preterm preeclampsia						
No	5700	54.1	4833	45.9	1	…
Yes	197	55.0	161	45.0	1.02	0.92, 1.12

Table 3
The Association of Gestational Hypertension and Preeclampsia with Sex Ratio in Multivariate Logistic Regression, China, 1993–1996.

	Delivering a boy	
Characteristics	Adjusted RR	95% CI
Gestational Hypertension		
Body mass index (continuous)	0.99	0.99, 0.99
Primiparous	0.96	0.95, 0.98
Gestational Hypertension		
No	1	…
Yes	0.98	0.97, 0.99
Preeclampsia		
Body mass index (continuous)	0.99	0.99, 0.99
Primiparous	0.96	0.95, 0.97
Preeclampsia		
No	1	…
Yes	0.96	0.94, 0.99

CI indicates confidence interval; and RR, risk ratio.

or preeclampsia and the possibility of delivering boys under the premise of controlling the confounding factors.

Limitations should also be acknowledged in our research. Because our research participants were almost all Han (China's predominant ethnic group), so our findings may not be generalizable to other populations. In the same way, our study participants were collected in two southern provinces, so there may be some limitations in the generalization to the northern population. Additionally, because the study relies on existing data, there were some certain confounding factors that had not been collected, such as maternal smoking and alcohol using, certain environmental toxins exposures, air pollution and so on. However, smoking and alcohol use were both rare among women in China at the time of our study, especially among reproductive-age women living in rural areas. Results of the 1996 national smoking prevalence survey in China reported that smoking prevalence among women aged 20–29 years was < 2% [33].

Overall, this study provides unique insight into the impact of gestational hypertension and preeclampsia on male delivery. Our findings indicate that women with gestational hypertension or preeclampsia had significantly lower probability of delivering a boy. Further research is needed to clarify the pathogenetic effect of gestational hypertension and preeclampsia on sex ratio in the aspect of immunology.

5. Conclusions

In this large population-based cohort study conducted in Chinese women, we found that compared to normotensive pregnancies, women with gestational hypertension or preeclampsia showed significantly decreased probability of giving birth to a boy.

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