

Are reproductive factors indicators of pregnancy-induced hypertension: a cross-sectional analysis

Qiaoli Tong¹, Xiongying Li¹, Jingxia Ying¹, Yinxue Wang^{1*}

¹ Yongkang women and children's health hospital, Jinhua 321300, China;

*Correspondence: Yinxue Wang, email: fubaowyx@163.com

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Abstract: Background: Reproductive factors are important contributors to cardiovascular diseases, but there is limited evidence regarding their relationship with pregnancy-induced hypertension (PIH).

Method: Pregnant patients who underwent physical examinations were enrolled. PIH was determined through medical records and reproductive factors, including age at menarche, menstrual irregularities, menstrual cycle, number of miscarriages or abortions, maternal age at first pregnancy, and history of oral contraceptive use, were collected through telephone follow-up. Statistical analysis included logistic regression and Spearman correlation analysis.

Results: Early menarche age may increase the risk of incidence PIH (Adjusted OR=0.071, (95% CI: 0.029-0.173), $P < 0.001$) and a higher prevalence of cesarean section deliveries (spearman r index =-0.177, $P < 0.001$) and shorter gestational weeks (spearman r index =0.222, $P < 0.001$). However, experiencing miscarriages or abortions, using oral contraceptives, and menstrual indices, after adjusting for cofounders, were not related to PIH.

Conclusion: The age at menarche is associated with pregnancy-induced hypertension (PIH) independently of genetics, age, and lifestyle factors, which emphasizes the potential importance of a woman's menstrual history in evaluating the risk of PIH.

Introduction

Pregnancy-induced hypertension (PIH) affects more than ten percentage of pregnancies and is correlated with heightened mortality and morbidity rates of both gravidas and fetals¹. According to statistics, hypertension-related deaths continue to be a ranking trigger of pregnancy-related mortality. Approximately 42,000 maternal deaths worldwide are associated with hypertension each year². Additionally, pregnancy-induced hypertension also imposes a significant economic burden. Epidemiological results from a study conducted in the United States during 2013-2014 indicated that 10.6% of hospitalized delivery patients had concurrent hypertension-related disorders. Relative to pregnancies characterized by normal blood pressure, hypertension-related pregnancies led to a significant increase in hospitalization duration and incurred substantial hospitali-

zation expenses³. What's more, the impact of PIH does not cease after pregnancy concludes. Women who experience PIH during pregnancy are may suffer more cardiovascular diseases in the future, thus raising their lifetime mortality risk 4-6.

PIH and cardiovascular diseases may share similar underlying mechanisms. Retrospective research on risk factors for PIH has consistently shown certain results, including coagulation disorders (antiphospholipid antibody syndrome), advanced pregnancy, and endocrine abnormalities (polycystic ovarian syndrome) 7. Furthermore, pre-existing cardiovascular risk factors or conditions play a significant role. Pre-pregnancy obesity and excessive weight gain during pregnancy⁸, as well as conditions like diabetes^{9, 10}, significantly increase the incidence of high-risk pregnancies

There exists a complex relationship between reproductive health and the occurrence of diseases like cardiovascular diseases. Previous research suggests that sex hormones play a significant role in cardiovascular health, affecting factors such as lipid metabolism, inflammation, and cardiac remodeling 11. Total testosterone is positively correlated with common carotid artery intima-media thickness, while sex hormone-binding globulin and testosterone levels are linked to the degree of coronary artery calcification¹². Early onset of menstruation is associated with polycystic ovary syndrome (PCOS), while early and premature menopause, as well as significant vasomotor symptoms, are related factors¹³. Higher levels of male sex hormones may increase the likelihood of cardiac remodeling and heart failure¹⁴. Therefore, female reproductive characteristics may be related to the pathophysiological mechanisms of pregnancy-induced hypertension.

Therefore, our study aims to further investigate a comprehensive range of female reproductive factors about the occurrence of pregnancy-induced hypertension and related pregnancy outcomes. This will help enhance our understanding of the pathophysiology of PIH and contribute to the development of strategies for early intervention to mitigate potential risks.

Method

Study population

As shown in Figure 1, pregnant patients who underwent physical examinations at Yongkang women and children's health hospital between January 2020 to December 2023 were considered. The incidence of pregnancy-induced hypertension among pregnant women was retrospectively collected using the electronic medical records system, and a questionnaire survey regarding lifestyle, family history, and reproductive history was conducted through telephone follow-up. This study was approved by the institutional ethics committee, and all participants were informed and gave their consent to be involved in this study. Inclusion Criteria: (1) Singleton natural pregnancies; (2) Complete clinical data and cooperation with the questionnaire survey. Exclusion Criteria: (1) Mental system

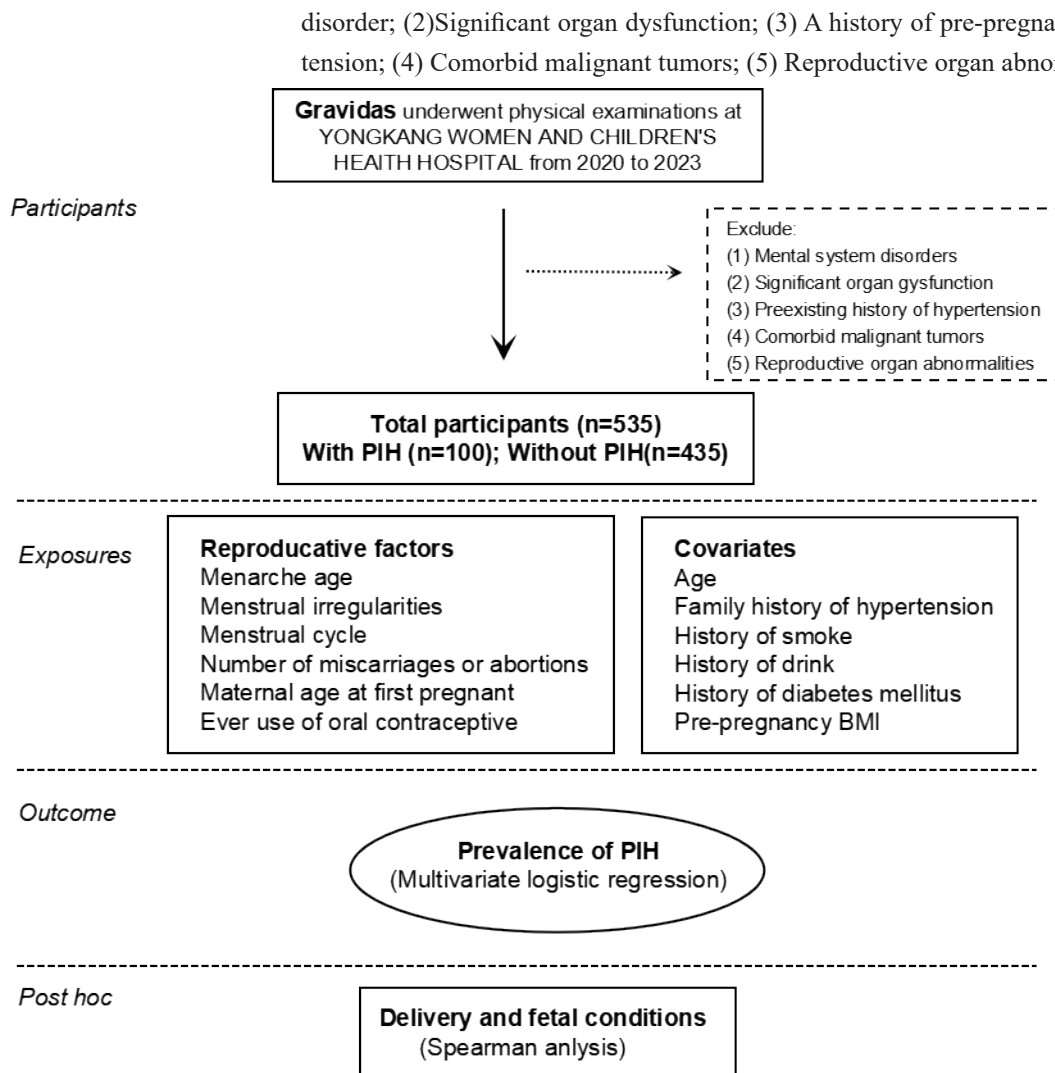


Figure 2. Flow chart

Reproductive factors

The assessment of female reproductive factors was conducted using a survey questionnaire administered through outpatient visits or telephone interviews. The collection of reproductive-related factors, including Menarche age, Menstrual irregularities, Menstrual cycle, Number of miscarriages or abortions, Maternal age at first pregnancy, and Ever use of oral contraceptives, was carried out.

Outcome

The primary outcome was PIH, PIH was defined as systolic blood pressure (SBP) >140 mmHg and diastolic blood pressure (DBP) >90 mmHg¹. The secondary outcomes included pregnancy and fetal conditions, such as the mode of delivery, gestational weeks, Apgar score at birth, and birth weight.

Static analysis

All analysis and figures were conducted in R 4.2.2, Graphpad Pism9.5, and

Adobe Illustrator 2021. Count data were expressed as proportions or percentages (%), and comparisons were conducted using the chi-square test. Measurement data were presented as mean $\pm$ standard deviation (SD), and comparisons were performed using the t-test or analysis of variance (ANOVA). Multivariate logistic regression model analysis was employed to examine factors related to pregnancy-induced hypertension. Correlation analysis was conducted using the Spearman method.

Results

Baseline characteristics

A total of 535 pregnant women were included in the study, with an average age of 29.64 years. Among them, 100 individuals experienced pregnancy-induced hypertension, resulting in an incidence rate of 18.7%. **Table 1** reveals that, in comparison to pregnant women who did not develop pregnancy-induced hypertension, those who did had a higher prevalence of a family history of hypertension (50.0% vs. 24.6%, $P < 0.001$), possibly had an advanced menarche age (11.05 years vs. 13.43 years, $P < 0.001$), and may have had a higher proportion of menstrual irregularities (27.0% vs. 17.0%, $P = 0.031$).

Furthermore, it can also be observed that pregnant women with pregnancy-induced hypertension had a higher rate of cesarean section delivery, longer gestational periods, and heavier birthweight babies. However, there were no significant differences in Apgar at birth.

Table 1. Baseline characteristics of the study population.

	Overall (n=535)	non-PIH (n=435)	PIH (n=100)	P value
Sociodemographic factors				
Age, years, mean (SD)	29.64 (6.12)	29.70 (6.04)	29.36 (6.48)	0.615
Family history of hypertension, n (%)	157 (29.3)	107 (24.6)	50 (50.0)	<0.001
History of smoke, n (%)	46 (8.6)	34 (7.8)	12 (12.0)	0.251
History of drink, n (%)	94 (17.6)	70 (16.1)	24 (24.0)	0.084
History of diabetes mellitus, n (%)	96 (17.9)	75 (17.2)	21 (21.0)	0.460
Pre-pregnancy BMI, kg /m2, (mean (SD))	24.89 (3.93)	24.65 (3.82)	25.34 (4.03)	0.393
Reproductive Factors				
Menarche age, years, (mean (SD))	12.98 (6.42)	13.43 (7.05)	11.05 (0.58)	0.001
Menstrual irregularities, n (%)	101 (18.9)	74 (17.0)	27 (27)	0.031
Menstrual cycle, days, mean (SD)	31.05 (12.32)	30.98 (12.78)	32.13 (10.67)	0.056
Number of miscarriages or abortions, mean (SD)	1.16 (0.13)	1.12(0.10)	1.25(0.23)	0.051
Maternal age at first pregnant, years, mean (SD)	26.12 (5.77)	24.56 (6.43)	27.67 (5.90)	0.784
Ever use of oral contraceptive, n (%)	370 (69.2)	300 (69.0)	70 (70.0)	0.935
Delivery and fetal factors				
Cesarean section, n (%)	298 (56.0)	224 (51.9)	74 (74.0)	<0.001
Gestational weeks, mean (SD)	37.94 (2.92)	38.17 (2.68)	36.91 (3.62)	<0.001
Birth weight, kg, mean (SD)	3.00 (7.45)	3.05 (7.26)	2.75 (7.80)	<0.001
Apgar score, mean (SD)	9.61 (1.69)	9.59 (1.75)	9.71 (1.44)	0.523

Abbreviations: PIH, Pregnancy-Induced Hypertension; BMI, Body mass index.

Reproductive factors and prevalence of PIH

As shown in Table 2 and Figure 2, after adjusting for age, age at menarche and PIH had a significant association (OR=0.075, (0.032-0.176), $P < 0.001$). Additionally, no significant associations were found between menstrual irregularities (OR=3.737, (0.898-15.551), $P=0.070$), menstrual cycle (OR=1.023 (0.898-1.167), $P=0.729$), history of miscarriages or abortions (OR=1.056, (0.836-1.334), $P=0.647$), age at first pregnancy (OR=0.922, (0.756-1.126), $P=0.427$), prior use of oral contraceptives (OR=0.802, (0.580-1.109), $P=0.182$), and PIH. Even after further adjusting for factors such as age, family history of hypertension, smoking, drinking, previous diabetes mellitus, and pre-pregnancy BMI, the result between age at menarche and PIH remained significant (OR=0.071, (0.029-0.173), $P < 0.001$).

Table 2. Association of reproductive factors with pregnancy-induced hypertension.

Reproductive Factors	Age-adjusted model			Multivariable model#		
	OR	95%CI	P value	OR	95%CI	P value
Menarche age	0.075	(0.032-0.176)	<0.001	0.071	(0.029-0.173)	<0.001
Menstrual irregularities	3.737	(0.898-15.551)	0.070	1.158	(0.753-1.782)	0.504
Menstrual cycle	1.023	(0.898-1.167)	0.729	1.190	(0.782-1.810)	0.417
Number of miscarriages or abortions	1.056	(0.836-1.334)	0.647	1.000	(1.000-1.000)	0.987
Maternal age at first pregnant	0.922	(0.756-1.126)	0.427	0.794	(0.494-1.279)	0.344
Ever use of oral contraceptive	0.802	(0.580-1.109)	0.182	0.996	(0.958-1.035)	0.829

#Multivariable models were adjusted for Age, Family history of hypertension, History of smoke, History of drink, History of diabetes mellitus, Pre-pregnancy BMI.

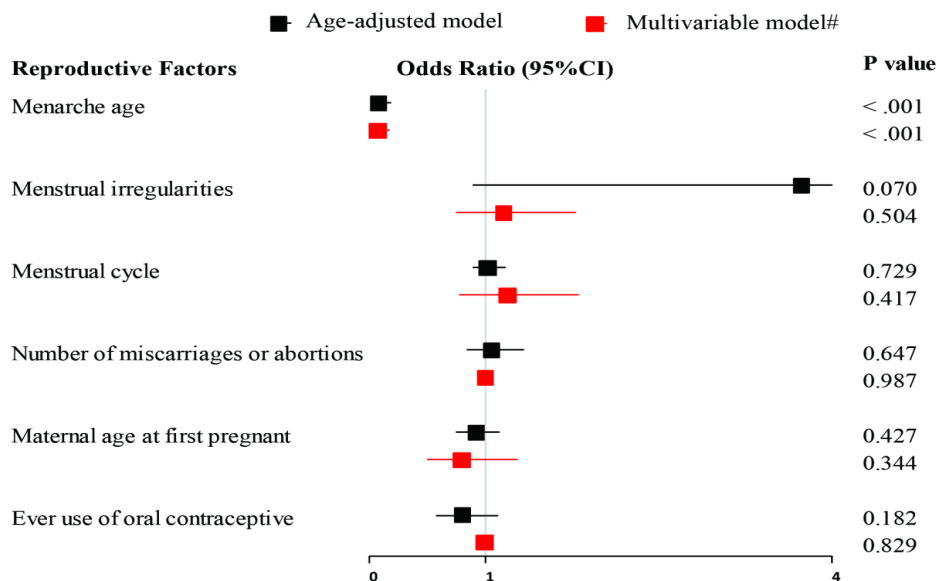


Figure 2. Association of reproductive factors with pregnancy-induced hypertension.

#Multivariable models were adjusted for Age, Family history of hypertension, History of smoke, History of drink, History of diabetes mellitus, Pre-pregnancy BMI.

Reproductive index and delivery and fetal factors

We also conducted a correlation analysis between the aforementioned reproductive factors and delivery as well as fetal outcomes, as shown in Table 3 and **Figure 3**, age at menarche showed a negative relationship with cesarean section delivery (spearman r index = -0.177, $P < 0.001$) and a positive relationship with gestational weeks (spearman r index = 0.222, $P < 0.001$). It also exhibited a positive relationship with the birth weight of the fetus (spearman r index = -0.143, $P = 0.031$). Additionally, irregular menstrual cycles were positively correlated with cesarean section delivery (spearman r index = 0.092, $P = 0.033$). However, no significant relationships were observed between other reproductive parameters and delivery or fetal factors.

Table 3. Correlation analysis between reproductive index and delivery and fetal factors.

	Cesarean section		Gestational weeks		Birth weight		Apgar	
	r index	P value	r index	P value	r index	P value	r index	P value
Menarche age	-0.177	<0.001	0.222	<0.001	0.203	<0.001	0.031	0.483
Menstrual irregularities	0.092	0.033	-0.08	0.067	-0.034	0.436	-0.04	0.356
Menstrual cycle	0.019	0.657	-0.063	0.152	0.037	0.402	1	NA
Number of miscarriages or abortions	0.214	0.343	0.056	0.062	0.089	0.163	-0.044	0.267
Maternal age at first pregnant	-0.23	0.546	0.024	0.575	0.126	0.078	0.054	0.354
Ever use of oral contraceptive	0.034	0.346	-0.128	0.77	-0.143	0.36	-0.013	0.752

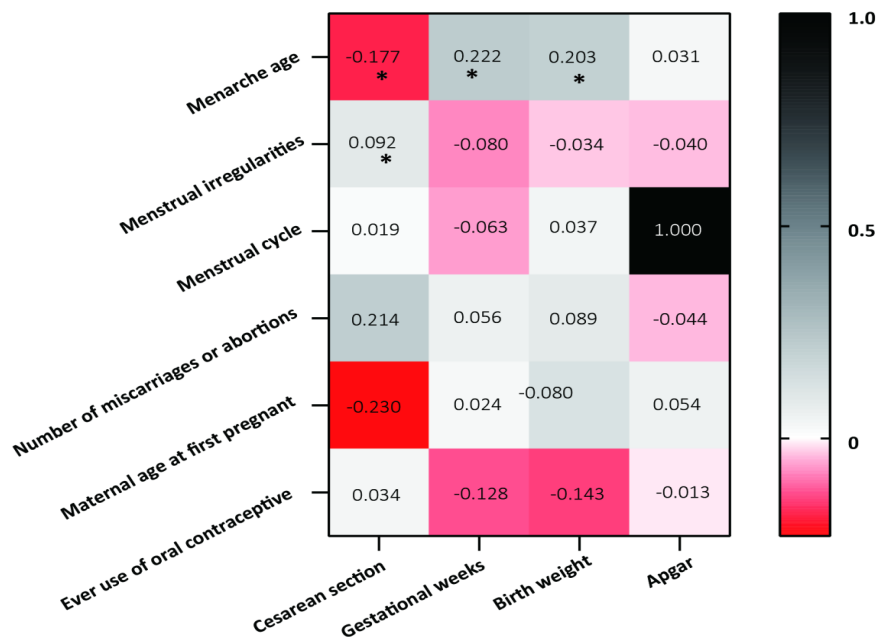


Figure 3. Correlation analysis between reproductive index and delivery and fetal Factors.

The spearman r index was summarized in each box; * $P < 0.05$.

Discussion

Our study utilized hospital medical records data to retrospectively comprehensively collect information, including menarche age, menstrual irregularities, menstrual cycle, number of miscarriages or abortions, maternal age at first pregnancy, and ever use of oral contraceptives. We investigated the relationship between early reproductive factors with pregnancy-induced hypertension. We found that age at menarche may be a meaningful factor independent of genetics, age, and lifestyle habits about pregnancy-induced hypertension. The earlier the age at menarche, the higher the risk of developing pregnancy-induced hypertension (Adjusted OR=0.071, 95%CI: (0.029-0.173), $P < 0.001$). The results may underscore the potential significance of a woman's menstrual history in assessing the risk of pregnancy-induced hypertension. Healthcare professionals should consider screening for menstrual history when collecting medical histories to identify individuals at higher risk for pregnancy-induced hypertension, enabling more proactive blood pressure monitoring and appropriate interventions.

Mechanisms of the association between age at menarche and the risk of PIH are still unclearly understood. Previous research has suggested that early menarche may be a risk factor for cardiovascular diseases and related mortality^{15, 16}. Early menarche is more common in childhood obesity¹⁷ and is often accompanied by hyperinsulinemia¹⁸. Insulin can increase the bioavailability of sex steroids¹⁹, leading to the development of a series of metabolic syndromes, including insulin resistance²⁰. Therefore, the link between menarche age and PIH may be partially explained by the interactions of childhood obesity and its corresponding metabolic disturbances. In our study, factors related to adult obesity were considered (we adjusted for pre-pregnancy BMI in our multivariate analysis), but we did not have data on childhood BMI for further analysis. This may require additional research in the future to further confirm this relationship.

Our study has some limitations. Firstly, the study participants were from a single center in China, and although the sample size was reasonable, further investigations are needed to establish the generalizability of our research findings. Secondly, the data concerning reproductive factors were obtained through self-report questionnaires, which may introduce subjectivity and recall bias. Thirdly, while we adjusted for factors such as family history, lifestyle, BMI, etc., they were single measurements at the baseline of the study, and we cannot rule out the possibility of confounding by these factors changing over time. We were unable to define PIH subtypes as the data in this part of the medical records did not support it, limiting the depth of our study.

Conclusion

The age at menarche is associated with PIH independently of genetics, age, and lifestyle factors. This emphasizes the potential importance of a woman's

menstrual history in evaluating the risk of pregnancy-induced hypertension.

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