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*Original Research*

# Interaction Between Preeclampsia and Previous Preterm Birth Increases the Risk of Subsequent Preterm Delivery: A Prospective Cohort Study

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**Abstract**

**Background:** This study aimed to investigate whether a positive additive interaction exists between previous preterm birth (PTB) and preeclampsia, which could increase the risk of subsequent PTB. PTBs can be classified into two categories: iatrogenic preterm births (iPTBs) and spontaneous preterm births (sPTBs). **Methods:** We conducted a prospective cohort study across 15 hospitals in China in 2018. The case group included parturients who delivered live-born singleton preterm infants. The control group consisted of parturients who delivered live-born singleton term infants of the same sex, paired with the corresponding preterm case within a two-day interval. Exclusion criteria included women with a history of preeclampsia in previous pregnancies or with chronic or gestational hypertension. Logistic regression was used to compare the PTB group with the term birth group. The interaction between the two risk factors was assessed using the synergy index (S) and the relative excess risk due to interaction (RERI). **Results:** A total of 2533 mothers with PTB and 2533 mothers with term live birth were included. After adjusting for confounding variables through logistic regression, the presence of both exposures—preeclampsia and a history of previous PTB—was significantly associated with all PTBs (adjusted odds ratio [aOR11] = 25.577; 95% confidence interval [CI] 3.445–189.919). The interaction between these two factors was positive (S = 2.072), contributing to a 12.707-fold increase in the risk of all PTBs (RERI = 12.707). Similar patterns were observed for iPTBs (aOR11 = 80.273; 95% CI 10.712–601.512; S = 2.402; RERI = 46.205). **Conclusions:** Our multicenter study provides novel evidence of a positive additive interaction effect between preeclampsia and a history of previous PTB, which significantly heightens the overall risk of PTBs, particularly in cases of iPTBs. For pregnant women with a history of PTB, the prevention of preeclampsia should be prioritized to reduce the incidence of premature birth. **Clinical Trial Registration:** This study is registered on the https://clinicaltrials.gov/ (registration number: NCT03602625; registration link: https://clinicaltrials.gov/study/NCT03602625;registration time: July 2018).

**Keywords:** preeclampsia; preterm birth; previous preterm birth history; interaction; risk factor

## 1. Introduction

Preterm birth (PTB) is characterized as a delivery occurring before 37 weeks of gestation [1,2]. The prevalence of preterm birth in China was 6.9% [3]. Because of the large population, China has the fourth largest number of preterm infants in the world [2]. Premature birth is an unsolved social and public problem. Research has indicated that PTB is a leading contributor to mortality among neonates and children under the age of five [4,5]. PTBs can be classified into two categories: iatrogenic PTB and spontaneous PTB, which arise from clinical interventions [1].

The underlying causes of PTB are believed to be multifaceted and remain largely elusive. Numerous studies have demonstrated a strong correlation between preeclampsia and the incidence of PTB [1,6,7]. Between the years 2002 and 2010, the worldwide incidence of preeclampsia was approximated to be 4.6% of all deliveries; however, the reported rates across different regions ranged from 1% to 5.6% [8]. The overall incidence rate of preeclampsia in the Chinese population is about 2.3% to 3.3% [9,10]. Preeclampsia is currently defined as a pregnancy-specific, multisystemic inflammatory disorder that occurs after 20 weeks of gestation, based on hypertension and accompanied by evidence of terminal organ dysfunction [11].

Furthermore, a history of previous PTB has been shown to significantly increase the risk of subsequent PTB [12,13]. Among pregnant women in the United States, the incidence of those with a history of preterm birth is 3.3% [14]. The previous premature birth rate among multiparous women in China was 1.89% [15]. Preterm labor is currently understood as a syndrome that arises from various mechanisms, such as infection or inflammation, uteroplacental ischemia or hemorrhage, stress, and other processes mediated by the immune system. Given that numerous risk factors contribute to heightened systemic inflammation, it is plausible that the augmented activation of the infection or inflammation pathway may account for the observed rise in preterm births linked to multiple risk factors [1].

A recent study showed that there was a significant interaction between gestational hypertension and the history of preterm birth on preterm birth risk [16]. Preeclampsia and a history of preterm birth share the same pathophysiological mechanisms-systemic inflammatory disorder [16]. When these two factors co-exist, the effect on preterm birth may be increased. However, research on the interaction between preeclampsia and prior preterm birth history in relation to PTB and the prevalence of women with these two factors is scarce.

When two risk factors are present concurrently, the cumulative risk is often amplified, exceeding the individual risks associated with each factor, thereby indicating a positive interaction between them. The Relative Excess Risk due to Interaction (RERI), Proportion Attributable to Interaction (AP), and Synergy Index (S) are three commonly used measures to quantify biological interaction between two exposures. The relative excess risk due to interaction (RERI) serves as an indicator to evaluate the comparative magnitude of the effect generated by the interplay between these two risk factors. AP represents the proportion of the total risk in the joint exposure group that is attributable to the interaction between the two exposures. The Synergy Index quantifies interaction relative to the additive model by comparing the observed combined risk to the expected combined risk under additivity. If S >1, there is a positive additive interaction between the two factors [17,18].

In this investigation, we posited that a positive additive interaction exists between preeclampsia and previous PTB, thereby increasing the likelihood of PTB. The results of this investigation offer novel perspectives on the relationships among various risk factors associated with PTB and provide clinical evidence to make the strategy for preventing PTB.

## 2. Materials and Methods

### *2.1 Study Design and Population*

This investigation employed a multicentre prospective cohort study. In this study, all pregnant women hospitalized in the 15 hospitals from January to December 2018 in China were selected as the study population [19]. During the study period, all pregnant women who gave birth to single premature infants were included in the case group, while those who gave birth to full-term infants of the same sex within two days after the preterm delivery were included in the control group. The institutions involved in the study included four hospitals at the county level, six hospitals at the prefecture level, and five hospitals at the provincial level, all of which were situated across the south-central, eastern, and north-western areas of the nation. The research centre was identified as the Children's Hospital of Fudan University, which facilitated data coordination and information integration.

The study participants included mothers who gave birth to live-born singleton preterm infants, specifically those who delivered between 24 and 36 weeks of gestation. Conversely, the control group consisted of mothers who delivered live-born singleton term infants, defined as those born between 37 and 41 weeks of gestation with birth weights between 2500 g and 4000 g. Each eligible control was collected with a corresponding case based on several criteria: the delivery date (within a two-day interval), the place of delivery (same hospital), and the sex of the newborn. The exclusion criteria included the following: (1) pregnant women lacking complete information; (2) those who experienced gestational hypertension, chronic hypertension, or preeclampsia in prior pregnancies; and (3) pregnant women who declined participation.

Assessment of gestational age was conducted by calculating the last menstrual period, considering irregular menstrual cycles alongside ultrasonic examinations. The identification of maternal diseases was performed in accordance with the textbook "Obstetrics and Gynecology" (9th Edition) under the editorial guidance of Xie X [20] and colleagues, published by the People's Medical Publishing House in 2018. The identification of gestational diabetes and preeclampsia during pregnancy was conducted in accordance with established national protocols [21,22,23]. Prepregnancy body mass index (BMI) was categorized into two distinct groups, those with a BMI of less than 24 $kg/m^2$ and those with a BMI of 24 $kg/m^2$ or greater, in line with Chinese standards [24,25]. Because scientific evidence suggests that Asian populations have different associations between BMI, percentage of body fat, and health risks than do European populations. The consultation concluded that the proportion of Asian people with a high risk of type 2 diabetes and cardiovascular disease is substantial at BMIs lower than the existing World Health Organization (WHO) cut-off point for overweight ($\geq$25 $kg/m^2$) [26]. Furthermore, smoking status included both passive and active smoking, as defined by the WHO [27].

### *2.2 Data Collection*

When the parturients were hospitalized in the hospitals, we gathered an extensive array of data concerning both maternal and foetal attributes. These included maternal age, the number of previous births (parity), educational background of the mother, race, residential status during pregnancy, household income, history of prior preterm deliveries, instances of preeclampsia, maternal smoking habits during pregnancy, gestational diabetes, chronic kidney disease, hypothyroidism, complications related to the placenta, BMI prior to conception, utilization of assisted reproductive technologies, frequency of prenatal care visits, folic acid supplementation before and during the early stages of pregnancy, and a family history of hypertension. After childbirth, we collect information about the newborn's age, sex, and birth weight.

**Table 1. The exposure categories and odds ratios (ORs) for two exposures.**

| Exposure category | Exposure A | Exposure B | Odds ratio (OR) | Notation |
|---|---|---|---|---|
| 1 | 0 | 0 | Reference (OR = 1) | $OR_{00}$ |
| 2 | 1 | 0 | OR for A only | $OR_{10}$ |
| 3 | 0 | 1 | OR for B only | $OR_{01}$ |
| 4 | 1 | 1 | OR for A+B (joint exposure) | $OR_{11}$ |

0 = unexposed, 1 = exposed.

### *2.3 Sample Size*

We employed PASS 15.0 software (NCSS, LLC. Kaysville, Utah, USA) to determine the necessary sample sizes for the primary risk factors in this study. The parameters were established based on the odds ratio (OR) values from earlier research and the incidence rate observed in the control group, with α set at 0.05 and β at 0.20. With respect to the risk factor for preeclampsia, which was characterized by an OR of 9 and an incidence of 1.5% in the control group, the required sample size was determined to be 26 cases. Conversely, for a previous history of PTB, with an OR of 4.2 and an incidence of 1.3% in the control group, the required sample size was determined to be 770 cases [12]. For the interaction of preeclampsia and previous preterm birth, with an OR of 6 and an incidence of 0.2% in the control group, the required sample size was determined to be 2450 cases [16].

### *2.4 Statistical Analyses*

EpiData version 3.4, developed by the EpiData Association based in Odense, Denmark, facilitated the creation of the database, execution of logical consistency assessments, and data validation. For statistical analysis, we employed Stata version 15.0 from StataCorp, which is located in College Station, TX, USA. The univariate analyses included the chi-square test, paired Wilcoxon signed-rank test, two-sample independent *t*-tests, and the rank-sum test. Normality was assessed using normality tests. We applied stepwise multivariate logistic regression analysis to determine both the combined and individual adjusted odds ratios (aORs) associated with two exposure factors, namely, preeclampsia and prior PTB, in relation to the likelihood of PTB. Furthermore, we stratified the analysis to evaluate the combined and individual aORs of these two exposures on the risks of iatrogenic PTB and spontaneous PTB, while controlling for confounding variables. We defined the exposure categories and ORs for the two exposures (A and B, where 0 = unexposed, 1 = exposed) (Table 1). The interaction effect between the two exposures was quantified using the RERI, the AP, and the S. The calculated values for RERI ($RERI = OR_{11} - OR_{10} - OR_{01} + 1$), S [$S = (OR_{11} - 1)/(OR_{10} + OR_{01} - 2)$], and AP ($AP = RERI/OR_{11}$) were derived from the combined and individual aORs. A $p < 0.05$ was considered to indicate statistical significance. Instances of missing data were excluded from the analysis.

## 3. Results

### *3.1 Demographic Characteristics of the Study Participants*

A flowchart depicting the participant recruitment process is shown in Fig. 1. Initially, 2774 PTBs were included. However, 20 individuals declined to participate in the survey, 73 cases were omitted because of incomplete data, and 148 cases were excluded due to a history of gestational hypertension, chronic hypertension, or preeclampsia in previous pregnancies. As a result, the case group comprised 2533 preterm cases, of which 1491 (58.9%) resulted in male infants. Ultimately, the control group consisted of 2533 term controls who satisfied the specified inclusion and exclusion criteria.

The demographic features of the two groups are listed in Table 2. The median age of all the participants was 30 years. Among the participants, 1547 individuals (30.5%) had an educational attainment of middle school or lower, 1032 participants (20.4%) had completed high school, and 2487 participants (49.1%) had a university degree or higher. During their pregnancies, 777 participants (15.3%) lived in rural areas, 1965 participants (38.8%) resided in small towns, and 2324 participants (45.9%) lived in urban settings. Statistical analysis revealed significant differences ($p < 0.05$) between the two cohorts in terms of level of maternal education, maternal age, parity, monthly family income per capita, and place of residence during pregnancy.

### *3.2 Univariate and Multivariate Conditional Logistic Analyses of Risk Factors for PTB*

We performed univariate analyses to assess the prevalence of prenatal conditions, maternal age, folic acid (FA) supplementation, and prepregnancy BMI between the term and preterm groups (refer to Table 3). Among the term group, 1.7% of the women experienced preeclampsia, in contrast to 14.5% in the preterm group. Additionally, the incidence of a previous PTB was 1.4% in the term group, while it was notably higher at 6.1% among the preterm participants.

The findings from the multivariate analysis are presented in Table 4, which encompasses all statistically significant variables identified through univariate analyses, in addition to assisted reproductive technologies, for a comprehensive comparison between preterm and term births. After controlling for potential confounding variables, the analysis revealed significant associations with preeclampsia (aOR = 9.509; 95% confidence interval [CI]: 6.838–13.224) and

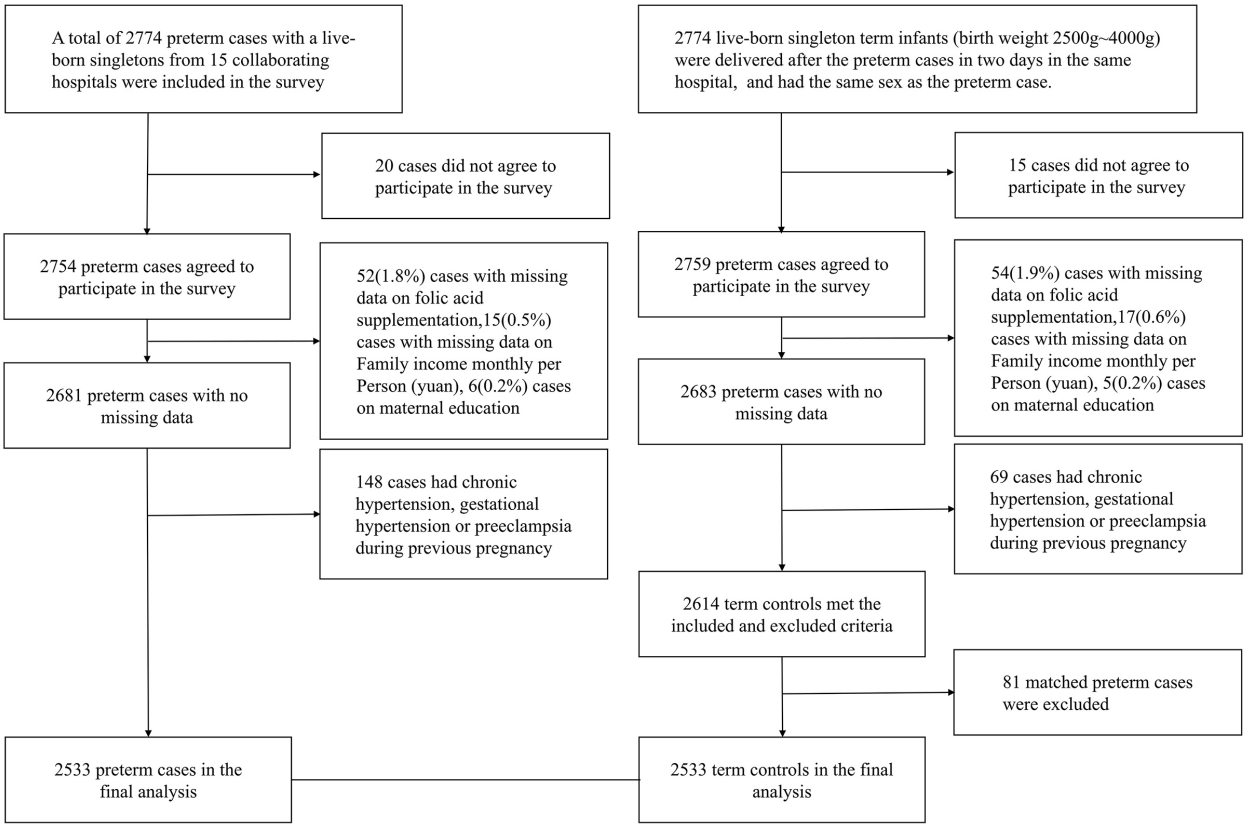


**Fig. 1. Flowchart showing the recruitment process for participants**.

**Table 2. Demographic characteristics of the study participants (n, %)**.

| Characteristics | Categories | Total n = 5066 | Preterm n = 2533 | Term n = 2533 | *p* value |
|---|---|---|---|---|---|
| Maternal age* (years) | Median | 30 (27, 34) | 30 (27, 34) | 29 (27, 33) | <0.001 |
| | <20 | 70 (1.4) | 49 (1.9) | 21 (0.8) | <0.001 |
| | 20–34 | 3955 (78.1) | 1906 (75.2) | 2049 (80.9) | |
| | ≥35 | 1041 (20.5) | 578 (22.8) | 463 (18.3) | |
| Parity | Unipara | 2325 (45.9) | 1069 (42.2) | 1256 (49.6) | <0.001 |
| | Multipara | 2741 (54.1) | 1464 (57.8) | 1277 (50.4) | |
| Race | Han | 4847 (95.7) | 2411 (95.2) | 2436 (96.2) | 0.084 |
| | Others | 219 (4.3) | 122 (4.8) | 97 (3.8) | |
| Maternal education | Middle school or below | 1547 (30.5) | 932 (36.8) | 615 (24.3) | <0.001 |
| | High school | 1032 (20.4) | 553 (21.8) | 479 (18.9) | |
| | University or above | 2487 (49.1) | 1048 (41.4) | 1439 (56.8) | |
| Residence during pregnancy | City | 2324 (45.9) | 991 (39.2) | 1333 (52.6) | <0.001 |
| | Small town | 1965 (38.8) | 1047 (41.3) | 918 (36.2) | |
| | Countryside | 777 (15.3) | 495 (19.5) | 282 (11.1) | |
| Family income monthly per person (dollars) | <300 | 395 (7.8) | 254 (10.0) | 141 (5.6) | <0.001 |
| | 300–1500 | 3802 (75.0) | 1889 (74.6) | 1913 (75.5) | |
| | >1500 | 869 (17.2) | 390 (15.4) | 479 (18.9) | |

Note: *Median (P25, P75).

**Table 3. Results arising from univariate analysis of the risk factors for PTB (n, %).**

| Characteristics | Categories | Total n = 5066 | Preterm n = 2533 | Term n = 2533 | *p* value |
|---|---|---|---|---|---|
| Preeclampsia | No | 4655 (91.9) | 2165 (85.5) | 2490 (98.3) | <0.001 |
| | Yes | 411 (8.1) | 368 (14.5) | 43 (1.7) | |
| Previous preterm birth | No | 4877 (96.3) | 2379 (93.9) | 2498 (98.6) | <0.001 |
| | Yes | 189 (3.7) | 154 (6.1) | 35 (1.4) | |
| Smoking in pregnancy | No | 4757 (93.9) | 2337 (92.3) | 2420 (95.5) | <0.001 |
| | Yes | 309 (6.1) | 196 (7.7) | 113 (4.5) | |
| Gestational diabetes | No | 4195 (82.8) | 2042 (80.6) | 2153 (85.0) | <0.001 |
| | Yes | 871 (17.2) | 491 (19.4) | 380 (15.0) | |
| Chronic renal disease | No | 5062 (99.9) | 2529 (99.8) | 2533 (100.0) | 0.125 |
| | Yes | 4 (0.1) | 4 (0.2) | 0 (0.0) | |
| Hypothyroidism | No | 4830 (95.3) | 2417 (95.4) | 2413 (95.3) | 0.790 |
| | Yes | 236 (4.7) | 116 (4.6) | 120 (4.7) | |
| Placenta problems | No | 4443 (87.7) | 2038 (80.5) | 2405 (94.9) | <0.001 |
| | Yes | 623 (12.3) | 495 (19.5) | 128 (5.1) | |
| Pre-pregnancy BMI ($kg/m^2$) | <24 | 3930 (77.6) | 1923 (75.9) | 2007 (79.2) | 0.005 |
| | ≥24 | 1136 (22.4) | 610 (24.1) | 526 (20.8) | |
| Assisted reproduction | No | 4835 (95.4) | 2408 (95.1) | 2427 (95.8) | 0.201 |
| | Yes | 231 (4.6) | 125 (4.9) | 106 (4.2) | |
| Prenatal examination | No | 253 (5.0) | 106 (4.2) | 147 (5.8) | 0.010 |
| | Yes | 4813 (95.0) | 2427 (95.8) | 2386 (94.2) | |
| Supplementation of FA before pregnancy | No | 2884 (56.9) | 1522 (60.1) | 1362 (53.8) | <0.001 |
| | Yes | 2182 (43.1) | 1011 (39.9) | 1171 (46.2) | |
| Supplementation of folic acid in early pregnancy | No | 1032 (20.4) | 587 (23.2) | 445 (17.6) | <0.001 |
| | Yes | 4034 (79.6) | 1946 (76.8) | 2088 (82.4) | |
| Family history of hypertension | No | 4875 (96.2) | 2432 (96.0) | 2443 (96.4) | 0.416 |
| | Yes | 191 (3.8) | 101 (4.0) | 90 (3.6) | |

PTB, preterm birth; FA, folic acid; BMI, body mass index.

prior PTB (aOR = 4.306; 95% CI: 2.917–6.357) in relation to the occurrence of all PTBs.

### *3.3 Individual and Joint Effects of Preeclampsia and Previous Preterm Birth on PTB and Measures of Interaction*

In the cohort of PTBs, a total of 1131 cases were attributed to iatrogenic PTB (iPTB), while 1402 cases were due to spontaneous PTB (sPTB). Table 5 presents the findings concerning the individual and combined influences of preeclampsia and prior PTB on the overall incidence of PTB as well as on the subcategories (iPTB, sPTB), alongside the measures of interaction (Table 5).

After controlling for confounding variables, the conditional multivariate analysis indicated a significant increase in the risk for all PTBs when both risk factors (preeclampsia and prior PTB) were present, yielding an $aOR_{11}$ of 25.577 (95% CI 3.445–189.919). The interaction effect between preeclampsia and prior PTB was found to be positive (S = 2.072 > 1), leading to a 12.707-fold increase in the risk of all PTBs (RERI = 12.707). 50.1% (AP = 0.501) of the risk in the joint exposure group is due to the interaction of preeclampsia and previous preterm birth (Table 5).

For the group iPTBs (1131 cases), a comparison was made with their matched control group. After adjusting for potential confounders, the conditional multivariate analysis revealed a substantial increase in the risk of iPTB ($aOR_{11}$ = 80.273; 95% CI 10.712–601.512) when both preeclampsia and previous preterm birth were present. The interaction effect between these two factors was positive (S = 2.402 > 1), resulting in a 46.205-fold increase in the risk of iatrogenic PTB (RERI = 46.205). 58.3% (AP = 0.583) of the risk in the joint exposure group is due to the interaction of preeclampsia and previous preterm birth (Table 5).

In the analysis of the 1402 cases of sPTB against their corresponding control group, after adjustment for confounding variables, a significant association was identified between previous preterm birth and sPTB ($aOR_{01}$ = 4.768; 95% CI: 3.170–7.172). In contrast, preeclampsia was not significantly associated with sPTB ($aOR_{11}$=1.045; 95% CI: 0.635–1.721, $p$ = 0.861). Furthermore, the combined effect of preeclampsia and prior preterm birth was not significantly linked to sPTB ($aOR_{11}$ = 4.129; 95% CI: 0.418–40.781, $p$ = 0.225) (Table 5).

**Table 4. Multivariate conditional logistic regression analysis of risk factors for all PTB.**

| Variable | Categories | aOR value | 95% CI | *p* value |
|---|---|---|---|---|
| Maternal age (years old) | <20 | **2.245** | 1.294–3.894 | **0.004** |
| | 20–34 | 1.000 | | |
| | ≥35 | 1.024 | 0.870–1.204 | 0.779 |
| Parity | Multipara | 1.012 | 0.886–1.156 | 0.862 |
| Race | Han | 1.000 | | |
| | Others | 1.015 | 0.749–1.377 | 0.923 |
| Maternal education | Middle school or below | **1.488** | 1.255–1.764 | **<0.001** |
| | High school | **1.350** | 1.144–1.593 | **<0.001** |
| | University or above | 1.000 | | |
| Residence during pregnancy | City | 1.000 | | |
| | Small town | **1.420** | 1.240–1.626 | **<0.001** |
| | countryside | **1.512** | 1.223–1.869 | **<0.001** |
| Family income monthly per person (dollars) | <300 | 0.907 | 0.769–1.071 | 0.252 |
| | 300–1500 | 0.996 | 0.739–1.343 | 0.979 |
| | >1500 | 1.000 | | |
| Preeclampsia | Yes | **9.509** | 6.838–13.224 | **<0.001** |
| Previous preterm birth | Yes | **4.306** | 2.917–6.357 | **<0.001** |
| Smoking in pregnancy | Yes | **1.671** | 1.292–2.162 | **0.001** |
| Gestational diabetes | Yes | **1.310** | 1.112–1.542 | **0.001** |
| Placenta problems | Yes | **4.800** | 3.888–5.925 | **<0.001** |
| Pre-pregnancy BMI (kg/m$^2$) | ≥24 | 0.946 | 0.814–1.099 | 0.469 |
| Assisted reproduction | Yes | 1.096 | 0.811–1.482 | 0.551 |
| Prenatal examination | No | **1.923** | 1.428–2.590 | **<0.001** |
| Supplementation of FA before pregnancy | No | 1.074 | 0.942–1.225 | 0.284 |
| Supplementation of folic acid in early pregnancy | No | **1.269** | 1.066–1.510 | **0.007** |

Note: Conditional logistic regression analysis was performed. The control group was the reference group.

CI, confidence interval; aOR, Adjusted odds ratio.

Bold values are significant. $p < 0.05$ was considered significant.

**Table 5. Individual and joint effects of preeclampsia and previous preterm birth on PTB and measures of interaction.**

| Variable | Case/control number | aOR value | 95% CI | *p* value | RERI | AP | S |
|---|---|---|---|---|---|---|---|
| **All preterm birth (n = 2533)/Control group (n = 2533)** | | | | | | | |
| None $OR_{00}$ | 2036/2455 | 1.000 | | | | | |
| Previous preterm birth $OR_{01}$ | 129/35 | **4.400** | 2.972–6.513 | <0.001 | | | |
| Preeclampsia $OR_{10}$ | 343/41 | **9.470** | 6.797–13.203 | <0.001 | | | |
| Preeclampsia + Previous preterm birth $OR_{11}$ | 25/2 | **25.577** | 3.445–189.919 | 0.002 | **12.707** | 0.501 | 2.072 |
| **Iatrogenic preterm birth (n = 1131)/paired control group (n = 1131)** | | | | | | | |
| None $OR_{00}$ | 752/1096 | 1.000 | | | | | |
| Previous preterm birth $OR_{01}$ | 41/16 | **3.446** | 2.040–5.822 | <0.001 | | | |
| Preeclampsia $OR_{10}$ | 316/18 | **31.622** | 22.382–44.674 | <0.001 | | | |
| Preeclampsia + Previous preterm birth $OR_{11}$ | 22/1 | **80.273** | 10.712–601.512 | <0.001 | **46.205** | 0.583 | 2.402 |
| **Spontaneous preterm birth (n = 1402)/paired control group (n = 1402)** | | | | | | | |
| None $OR_{00}$ | 1284/1359 | 1.000 | | | | | |
| Previous preterm birth $OR_{01}$ | 88/19 | **4.768** | 3.170–7.172 | <0.001 | | | |
| Preeclampsia $OR_{10}$ | 27/23 | 1.045 | 0.635–1.721 | 0.861 | | | |
| Preeclampsia + Previous preterm birth $OR_{11}$ | 3/1 | 4.129 | 0.418–40.781 | 0.225 | - | - | - |

Note: Conditional logistic regression analysis was performed. $p < 0.05$ was considered significant.

aOR, adjusted odds ratio; RERI, relative excess risk due to interaction; AP, proportion attributable to interaction; S, synergy index.

Bold values are significant.

## 4. Discussion

Our research revealed a significant positive additive interaction between preeclampsia and a history of prior PTB, which notably elevated the risk of all types of PTB, encompassing both iatrogenic and spontaneous PTB. Specifically, this interaction increased the risk of all PTBs by twelve-fold (RERI = 12.707) and the risk of iPTB (RERI = 46.205). To our knowledge, this investigation is an inaugural study that elucidated the positive interactive effects of preeclampsia and prior preterm birth on the risk of PTB.

A similar study showed that there was a significant interaction between gestational hypertension and the history of preterm birth on preterm birth risk [16]. Gestational hypertension and the history of preterm birth have a common cause in placental insufficiency or heredity, or both [16]. Preeclampsia is a pregnancy-specific, multisystemic inflammatory disorder that not only has hypertension, but also end-organ dysfunction [11]. The two-stage model of preeclampsia proposes that preeclampsia results from placental dysfunction causing syncytiotrophoblast stress (stage 1), which leads to the maternal clinical manifestation of preeclampsia (stage 2) [8]. The severity of preeclampsia is greater than gestational hypertension. Heightened systemic inflammation may account for the observed rise in preterm births linked to multiple risk factors. After preterm birth without preeclampsia in the first pregnancy, the risk of preterm preeclampsia in the second pregnancy was 4–7 fold higher than after term birth, which suggests that preterm birth and preeclampsia share pathophysiologic mechanisms (remodelling of the uterine spiral arteries and generalized systemic inflammation) [28]. The mechanisms are unclear, but when preeclampsia and a history of preterm birth coexist, the superposition of systemic inflammation increases the risk of preterm birth. This can explain why the interaction between preeclampsia and a history of preterm birth (RERI = 12.707) in our study is greater than the interaction between gestational hypertension and a history of preterm birth (RERI = 1.222). However, additional research is necessary to clarify the fundamental mechanisms that contribute to the fascinating interplay between preeclampsia and a history of preterm birth in relation to premature delivery in women.

Preeclampsia is recognized as a significant risk factor contributing to preterm birth. In our research, we identified a significant positive association between preeclampsia and preterm birth. Prior investigations have demonstrated that preeclampsia considerably elevated the risk of preterm delivery, with odds ratios ranging from 6 to 11 as reported in two case-control studies conducted in Iran [29,30]. Furthermore, research from China has also indicated that preeclampsia was a significant risk factor for preterm birth in cases of twin pregnancies [31]. According to the Fetal Medicine Foundation (FMF) algorithm, as the risk of early pregnancy preeclampsia (PE) increases, the gestational age at which spontaneous delivery occurs in pregnant women significantly advances. Subclinical dysfunction of placental function may be a potential trigger for spontaneous delivery. The 'high-risk' signals captured by this model may essentially identify pregnant women with potential placental dysfunction [32]. These observations align with our findings, suggesting that the association between preeclampsia and preterm birth is likely to be prevalent across various pregnant women.

Furthermore, we observed that a history of prior preterm birth significantly increased the risk of both iatrogenic and spontaneous PTB, even after we adjusted for potential confounding variables. In alignment with our results, Hassen JA et al. [13] reported that a previous preterm birth history (aOR = 3.51; 95% CI = 1.40–8.81) was an independent predictor of subsequent preterm birth.

Our findings may be representative of the broader population in China because of the extensive sample size and the inclusion of various regions with differing economic development statuses (east, central, and west). Given the prospective cohort study design, we accounted for potential confounding factors associated with preterm birth, including the infant's sex, seasonal variations, environmental conditions, residence, maternal educational level, maternal age, parity, gestational diabetes, smoking status during pregnancy, placental complications, prepregnancy BMI, assisted reproductive techniques, and folic acid supplementation. Consequently, our results demonstrate a high degree of robustness.

*Limitations*

It is essential to acknowledge certain limitations of our study. Despite controlling for various confounding factors, the possibility of residual confounding cannot be entirely ruled out. Despite recalculating the sample sizes to assess the interaction between two factors on all PTBs (1896 cases for all PTBs by an aOR of 25 and an incidence of 0.08% in the control group) and on iPTBs (910 cases for iPTBs by an aOR of 80 and an incidence of 0.0009% in the control group), it was determined that the sample sizes in both groups were adequate. However, the CIs for the joint effect aORs are very wide ($aOR_{11}$ = 25.577, 95% CI 3.445–189.919; $aOR_{11}$ = 80.273, 95% CI 10.712–601.512). Such wide CIs indicate imprecise estimation of the effect size and considerable uncertainty, which is likely due to the small sample size. So, in order to avoid overinterpreting the point estimates, validation with larger sample sizes is required. Subgroup analysis for spontaneous PTB suffers from an insufficient sample size (11,678 cases for sPTBs by an OR of 4 and an incidence of 0.07% in the control group) and very wide CIs, reducing reliability.

## 5. Conclusions

In summary, our research demonstrated a synergistic effect between preeclampsia and a prior occurrence of preterm birth, which markedly increased the likelihood

of all forms of PTB, especially iatrogenic PTB. Counseling prior to pregnancy and prenatal medical supervision should prioritize women who have preeclampsia and previous preterm deliveries. It is crucial to manage hypertension effectively in these individuals. Enhancing the standard of healthcare provided to pregnant women facing these two conditions may significantly mitigate the risks associated with preterm births.

## Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Author Contributions

CC designed the research study and performed the research, and reviewed the draft. YJZ investigated the research, curated the data, analyzed the data, and wrote the original draft. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

The study was carried out in accordance with the guidelines of the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Children's Hospital of Fudan University (approval number: [2018] No.84). All patients or their families/legal guardians gave their informed consent for inclusion before they participated in the study.


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## Conflicts of Interest

The authors declare no conflicts of interest.

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