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Interaction between maternal CRP levels and diabetes on preterm delivery risk: a retrospective observation study

Na Wang[1*†], Shuruo Zhang[2†], Sumiao Hong[1], Yongyi Liu[3], Xiang Li[4], Guankai Lin[5], Xiaoyang Xu[1], You Zhou[1], Xiaoting Wen[1], Baochang Sun[5], Hexing Wang[2], Min Huang[1], Jiwei Wang[2*], Yue Chen[6] and Qingwu Jiang[2]

Abstract

Background Preterm delivery (PTD) is a major cause of neonatal morbidity and mortality, and maternal C-reactive protein (CRP) may serve as an inflammatory marker linked to its risk, with diabetes potentially influencing this association.

Objectives To evaluate the association between maternal CRP levels and PTD risk and assess whether diabetes modifies this relationship.

Methods This retrospective observational study included 3,089 singleton pregnancies with available CRP and covariate data from 2015 to 2022. Maternal serum CRP was measured using immuno-turbidimetry and categorized into tertiles (cut-points at 2.3 mg/L and 4.7 mg/L). Logistic regression models estimated odds ratios (ORs) for PTD, and stratified analyses evaluated interaction by diabetes status.

Results Among 3,089 pregnancies, 208 (6.7%) were preterm. CRP concentrations were slightly higher in PTD cases than in term births (3.5 vs. 3.3 mg/L; $P = 0.042$). Logistic regression showed a positive association between the highest CRP tertile and PTD in both unadjusted ($\beta = 0.28$) and adjusted models ($\beta = 0.42$). Diabetes significantly modified this association. In stratified analyses, CRP tertiles were not associated with PTD among women without diabetes (T3 vs. T1: OR = 1.16, 95% CI: 0.75–1.78), whereas among women with diabetes, being in the highest CRP tertile was associated with a substantially higher risk of PTD (OR = 2.73, 95% CI: 1.44–5.15).

Conclusion Elevated maternal CRP levels were associated with higher PTD risk only among women with diabetes, suggesting that inflammation may play a more prominent etiologic role in this subgroup.

Keywords Preterm delivery, C-reactive protein, Inflammation, Diabetes mellitus, Retrospective cohort study

†Shuruo Zhang and Na Wang contributed equally to this work.

*Correspondence:
Na Wang
Wangna760320@163.com
Jiwei Wang
jiweiwang@fudan.edu.cn

Full list of author information is available at the end of the article

Introduction

Preterm delivery (PTD), defined as birth before 37 weeks of gestation, remains a major global public health challenge. According to the World Health Organization (2015), approximately 10.6% of live births worldwide in 2014 were preterm, with 91% occurring in low- and middle-income countries [1]. Population-based data indicate that the national PTD rate in China is approximately 6%–7% [2, 3], with an estimated 1.17 million preterm births annually [4]. PTD complications are the leading cause of death among children under 5 years of age, accounting for approximately 900,000 deaths in 2019 [5].

With the implementation of the three-child policy in China, the proportion of older pregnant women has increased [6], and the national PTD burden is expected to rise further. These demographic shifts underscore the importance of understanding the biological mechanisms underlying PTD.

PTD is considered a syndrome triggered by multiple factors, including intrauterine infection or inflammation, placental ischemia or bleeding, uterine overdistension, hormonal imbalances, and other immune-mediated processes [7]. Despite substantial research efforts, the exact mechanisms driving PTD are yet to be fully elucidated.

Inflammation is a central pathway implicated in PTD. C-reactive protein (CRP), a widely used acute-phase inflammatory marker, increases rapidly in response to infection or tissue injury. Although elevated CRP levels measured in early or mid-pregnancy have been associated with PTD in previous studies [8, 9], fewer studies have evaluated CRP levels measured close to delivery, which may more directly reflect peripartum inflammatory activation immediately preceding birth. In high-risk populations such as women with preterm labor or preterm prelabor rupture of membranes (PPROM), elevated maternal CRP concentrations within a few days before delivery have been associated with intra-amniotic infection, histologic chorioamnionitis, funisitis, and early-onset neonatal sepsis [10–13], although the overall diagnostic performance of CRP as a stand-alone marker is modest.

Diabetes is a well-established risk factor for PTD [14], with studies showing that women with gestational diabetes or pre-existing diabetes are at higher risk for spontaneous PTD [15, 16]. Hyperglycemia induces the release of pro-inflammatory cytokines, activating inflammation-related signaling pathways that disrupt placental and uterine function, further elevating the risk of PTD [17].

Numerous studies have shown that interactions between various factors significantly affect the risk of PTD. For instance, advanced maternal age combined with parity [18], hypertension with polycystic ovary syndrome [19], and hypertension with a history of PTD [20], all substantially increase this risk. Diabetes is also linked to elevated risk through its interaction with maternal characteristics like age and smoking [21, 22], with gestational diabetes and advanced maternal age together posing an especially high risk. Additionally, research indicates that diabetes interacting with inflammatory factors significantly raises the incidence of cardiovascular and endpoint events [23, 24]. However, studies directly examining the interaction between diabetes and inflammatory factors in PTD risk are limited.

This study aims to explore the effects of diabetes and inflammation on PTD, and further examine the interaction between CRP levels and diabetes.

Materials and methods

Study design and population

This study was a retrospective observational study based on obstetric medical records from the People's Hospital of Pingyang, Wenzhou, Zhejiang Province, China. The hospital is the primary healthcare provider in Pingyang County and serves as the only tertiary hospital in the region and most expectant mothers in the area choose this hospital for their deliveries consequently. The hospital utilizes an efficient information system to record the demographic and clinical data of all patients.

All singleton pregnancies resulting in live births between January 2016 and December 2022 were eligible for inclusion. We excluded women who (1) lacked data on the last menstrual period (LMP), CRP or any of the covariates included in the final models, (2) were younger than 18 years, or (3) experienced intrauterine fetal death. A flow diagram of the study population selection is provided in Fig. 1.

This study was approved by the Medical Research Ethics Committee of the School of Public Health, Fudan University (IRB00002408; FWA00002399). As this retrospective study used existing de-identified clinical data with no contact with participants, the requirement for informed consent was waived by the Ethics Committee.

Assessment of the main variables

The primary outcome of this study was PTD, defined as birth before 37 weeks of gestation [25]. Gestational age was initially calculated based on the last menstrual period (LMP) and subsequently confirmed and corrected using ultrasound measurements. CRP levels were obtained from the most recent antenatal examination records prior to delivery and serum CRP was measured using an immuno-turbidimetry assay (Pumo PA-990 Pro, Pumo, China). In clinical obstetric practice, CRP is commonly measured during antenatal care or at hospital admission when clinicians need to evaluate maternal inflammatory status or rule out potential infection. If multiple CRP measurements were available for the same

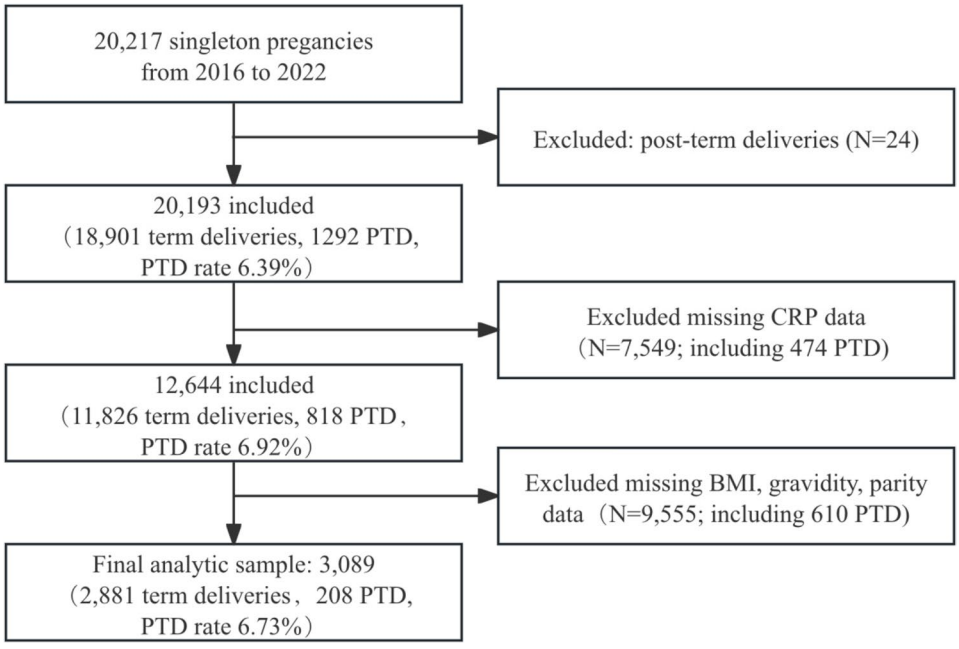

Fig. 1 Flowchart of the study population. CRP, C-reactive protein; PTD, preterm delivery

pregnancy, only the value closest to delivery and prior to labor onset was used.

Covariates

The covariates included maternal age, parity (number of previous live births), gravidity, diabetes mellitus during pregnancy, hypertensive disorders of pregnancy, pre-pregnancy BMI category, and the time interval between CRP measurement and delivery (days). Information on age, parity, and gravidity was recorded by the physician at the first pregnancy registration visit. Pre-pregnancy BMI was categorized as < 18.5, 18.5–23.9, 24.0–27.9, and ≥ 28.0 kg/m² according to the Chinese adult BMI classification criteria [26].

Diabetes mellitus during pregnancy was defined according to the 2022 Chinese guideline on hyperglycemia in pregnancy [27]. In this study, diabetes status during pregnancy encompassed both pre-gestational diabetes mellitus (PGDM) and gestational diabetes mellitus (GDM), representing the two major categories under the broader concept of "hyperglycemia in pregnancy." GDM was diagnosed using a one-step 75-g oral glucose tolerance test (OGTT) at 24–28 weeks of gestation, with diagnostic thresholds of fasting plasma glucose ≥ 5.1 mmol/L, 1-hour glucose ≥ 10.0 mmol/L, or 2-hour glucose ≥ 8.5 mmol/L. For analysis, diabetes status during pregnancy was treated as a binary variable (yes/no), indicating the presence of either PGDM or GDM.

Hypertensive disorders of pregnancy included chronic hypertension, gestational hypertension, preeclampsia, and eclampsia. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on at least two occasions after 20 weeks of gestation. Preeclampsia was diagnosed as new-onset hypertension accompanied by proteinuria (≥ 0.3 g/24 h or protein–creatinine ratio ≥ 0.3) or other maternal organ dysfunction or uteroplacental complications, in accordance with the 2020 Chinese guideline [28]. Hypertensive disorders of pregnancy were treated as a binary variable (yes/no), defined as the presence of any of these conditions.

Statistical analysis

Statistical analyses were performed using R software (version 4.4.1; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were summarized as means and standard deviations (SDs) or medians and interquartile ranges (IQRs), depending on distribution. Categorical variables were summarized as counts and percentages. Group differences were assessed using the chi-square test or Fisher's exact test for categorical variables, and the Wilcoxon rank-sum test for non-normally distributed continuous variables.

CRP levels were categorized into tertiles based on the distribution of serum CRP concentrations within the study population, consistent with previous epidemiological studies that employed tertile-based grouping to represent increasing inflammatory levels [29–31]. Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between CRP tertiles and the risk of PTD, using

the lowest tertile as the reference category. Three logistic regression models were fitted:

Model 1:
$$\log\left(\frac{P(\mathrm{PTD}=1)}{1-P(\mathrm{PTD}=1)}\right) = \beta_0 + \beta_1 \mathrm{CRP}_{T2} + \beta_2 \mathrm{CRP}_{T3}.$$

Model 2:

$$\log\left(\frac{P(\mathrm{PTD}=1)}{1-P(\mathrm{PTD}=1)}\right) = \beta_0 + \beta_1 \mathrm{CRP}_{T2} + \beta_2 \mathrm{CRP}_{T3} + \sum_i \gamma_i X_i.$$

Model 3:

$$\log\left(\frac{P(\mathrm{PTD}=1)}{1-P(\mathrm{PTD}=1)}\right) = \beta_0 + \beta_1 \mathrm{CRP}_{T2} + \beta_2 \mathrm{CRP}_{T3} + \beta_3 \mathrm{DM} + \beta_4 (\mathrm{CRP}_{T2} \times \mathrm{DM}) + \beta_5 (\mathrm{CRP}_{T3} \times \mathrm{DM}) + \sum_i \gamma_i X_i.$$

denotes the probability of PTD, and are indicator variables for the middle and highest CRP tertiles, includes maternal age, BMI category, gravidity, parity, hypertension status, diabetes status, and time from CRP measurement to delivery. Interaction effects were evaluated using likelihood ratio tests comparing Model 3 with Model 2.

Because Model 3 included interaction terms between CRP tertiles and diabetes status, the odds ratios for CRP tertiles varied by diabetes status. Therefore, stratified effects were derived from the coefficients of the interaction model as follows:

Among women without diabetes (DM = 0):

$$\mathrm{OR}(T_2 \text{ vs } T_1 \mid DM=0) = e^{\beta_1}, \ \mathrm{OR}(T_3 \text{ vs } T_1 \mid DM=0) = e^{\beta_2}$$

Among women with diabetes (DM = 1):

$$\mathrm{OR}(T_2 \text{ vs } T_1 \mid DM=1) = e^{\beta_1+\beta_4}, \ \mathrm{OR}(T_3 \text{ vs } T_1 \mid DM=1) = e^{\beta_2+\beta_5}$$

The variance of each combined coefficient (e.g.,) was computed using the model's variance–covariance matrix, and 95% confidence intervals were obtained as:

$$CI_{95\%} = \exp\left[\beta_{\mathrm{comb}} \pm 1.96 \cdot SE(\beta_{\mathrm{comb}})\right],$$

$$SE(\beta_{\mathrm{comb}}) = \sqrt{\mathrm{Var}(\beta_i) + \mathrm{Var}(\beta_j) + 2 \cdot \mathrm{Cov}(\beta_i, \beta_j)}$$

.

To assess model adequacy, we additionally conducted diagnostic evaluations for all multivariable logistic regression models. Model fit was examined using the Hosmer–Lemeshow goodness-of-fit test, multicollinearity was assessed using variance inflation factors (VIF), and calibration was evaluated using bootstrap-based calibration curves derived from the rms package. As a sensitivity analysis, CRP was additionally modeled as a log-transformed continuous variable, and regression models analogous to Models 2 and 3 were fitted using log-transformed CRP. We additionally performed an exploratory analysis of CRP tertile distribution across detailed gestational-age subgroups (very preterm, moderate preterm, late preterm, and term births). All analyses were performed on complete cases, as pregnancies with missing data on exposure or covariates were excluded. A two-sided p-value < 0.05 was considered statistically significant.

Results

Descriptive statistics and univariate analysis

A total of 3,089 singleton pregnancies were included in the final analysis, of which 208 (6.7%) resulted in preterm delivery (PTD). The comparison of maternal and clinical characteristics between women who delivered preterm and those who delivered at term is presented in Table 1. The PTD group displayed distinct clinical characteristics compared with women who delivered at term. Those with preterm delivery were more frequently aged ≥ 35 years (31.7% vs. 21.2%, $P < 0.001$) and had a markedly higher prevalence of diabetes (37.0% vs. 22.5%, $P < 0.001$). Although pre-pregnancy BMI categories differed significantly between groups ($P = 0.032$), no clear directional pattern emerged, and BMI did not show a consistent association with PTD. In addition, gravidity and parity distributions varied significantly between groups ($P = 0.012$ and $P = 0.020$, respectively). Additionally, women in the PTD group had a substantially shorter gestational age at delivery (median 35.0 weeks [IQR: 34.0–36.0] vs. 39.0 weeks [IQR: 38.0–40.0], $P < 0.001$) and gave birth to infants with significantly lower birth weight (2.58 ± 0.46 kg vs. 3.34 ± 0.38 kg, $P < 0.001$), as expected. Median CRP levels were also elevated among preterm cases (3.5 mg/L) compared with term deliveries (3.3 mg/L, $P = 0.042$).

Association between CRP and preterm delivery

Results of the logistic regression analyses are summarized in Table 2. In the unadjusted model (Model 1), women in the highest CRP tertile (> 4.7 mg/L) had a higher likelihood of experiencing PTD (β = 0.28, $P < 0.05$). After adjustment for all covariates—including maternal age, BMI, hypertension, diabetes, gravidity, parity, and the interval from CRP testing to delivery—the association observed for the highest CRP tertile was significant (β = 0.42, $P < 0.05$) in Model 2. Notably, adding an interaction term between CRP tertiles and diabetes status significantly improved model performance (Model 3 vs. Model 2: $\chi^2 = 6.32$, $P = 0.042$). The interaction effect for the highest CRP tertile and diabetes was statistically significant (β = 0.911, $P < 0.05$).

Table 1 Descriptive statistics and univariate analysis of maternal characteristics

Characteristic		Preterm (*n* = 208)	Term (*n* = 2881)	*P*-value
		N (%)	*N* (%)	
Maternal age(year)	< 35	142 (68.3%)	2269 (78.8%)	< 0.001[a]
	≥ 35	66 (31.7%)	612 (21.2%)	
Pre-pregnancy body mass index (kg/m^2)	Underweight	1 (0.5%)	22 (0.8%)	0.027[b]
	Normal	61 (29.3%)	635 (22.0%)	
	Overweight	96 (46.2%)	1293 (44.9%)	
	Obese	50 (24.0%)	931 (32.3%)	
Diabetes Status	no	131 (63.0%)	2232 (77.5%)	< 0.001[a]
	yes	77 (37.0%)	649 (22.5%)	
Hypertension status	no	198 (95.2%)	2775 (96.3%)	0.524[a]
	yes	10 (4.8%)	106 (3.7%)	
Gravidity(times)	None	55 (26.4%)	875 (30.4%)	0.012[a]
	1–2	89 (42.8%)	1376 (47.8%)	
	3 or more	64 (30.8%)	630 (21.9%)	
Parity(times)	None	87 (41.8%)	1306 (45.3%)	0.020[b]
	1–2	116 (55.8%)	1558 (54.1%)	
	3 or more	5 (2.4%)	17 (0.6%)	
Neonatal birth weight (kg)	Mean ± SD	2.58 ± 0.46	3.34 ± 0.38	< 0.001 [c]
GA at delivery (weeks)	Median (IQR)	35 (34–36)	39 (38–40)	< 0.001[d]
GA at CRP measurement (weeks)	Median (IQR)	35.0 (34.0–36.0)	38.9 (37.9–39.3)	< 0.001[d]
Time from CRP measurement to delivery (days)	Median (IQR)	0.0 (0.0–1.0)	1.0 (0.0–2.0)	< 0.001[d]
CRP (mg/L)	Median (IQR)	3.5 (2.0–7.0)	3.3 (1.9–5.5)	0.042[d]

Abbreviations:N Number, *CRP* C-reactive protein, *IQR* Interquartile range, *GA* Gestational age

[a]P value was derived from the chi-square test. [b]P value was derived from the Fisher's exact test. [c]P value was derived from the Welch t-test. [d] P value was derived from the rank-sum test

The stratified analysis (Table 3) further demonstrated that diabetes status modified the association between CRP and PTD. Among women without diabetes (n = 2,363), CRP tertiles were not significantly related to PTD risk, including the comparison between the highest and lowest tertiles (T3 vs. T1: OR = 1.16, 95% CI: 0.75–1.78). In contrast, among women with diabetes (n = 726), those in the highest CRP tertile had a markedly increased risk of PTD (OR = 2.73, 95% CI: 1.44–5.15), with a significant trend of increasing risk across tertiles (P for trend = 0.002).

Table 2 ‖ Multivariable Logistic Regression Models

Predictor	β (Model 1)	β (Model 2)	β (Model 3)
Tertile 2 (2.3 < CRP ≤ 4.7 mg/L)	0.012	0.083	-0.157
Tertile 3 (CRP > 4.7 mg/L).	0.284	0.419*	0.124
Diabetes status		0.681***	0.071
Age ≥ 35 years		0.432*	0.417*
Gravidity (1–2 times)		0.128	0.126
Gravidity (> 3 times)		0.478	0.499
Parity (1–2 times)		-0.236	-0.229
Parity (> 3 times)		0.966	0.925
underweight		-0.827	-0.765
overweight		-0.337	-0.358*
obese		-0.773***	-0.791***
Hypertension		0.263	0.284
Time from CRP measurement to delivery (days)		–0.013	–0.013
Tertile 2 × Diabetes status		-	0.773
Tertile 3 × Diabetes status		-	0.911*

Abbreviations:PTD Preterm delivery, *CRP* C-reactive protein, *BMI* Body mass index

β coefficients were obtained from logistic regression models; a likelihood ratio test comparing Model 2 with Model 3 indicated that inclusion of the interaction terms significantly improved model fit (χ^2 = 6.32, df = 2, p = 0.042). * P < 0.05, ** P < 0.01, *** P < 0.001

Table 3 Odds Ratios for Preterm Delivery by CRP Tertiles Stratified by Maternal Diabetes Status

CRP groups	Without Diabetes (*n* = 2363)		With Diabetes (*n* = 726)	
	aOR	95%CI	aOR	95%CI
T1	1.00	reference	1.00	reference
T2	0.87	(0.55, 1.36)	1.87	(0.97, 3.61)
T3	1.16	(0.75, 1.78)	2.7	(1.44, 5.15)
Trend test		*p*		*p*
		0.703		0.002

T1, T2, and T3 represent tertiles of maternal CRP levels: T1 (CRP ≤ 2.3 mg/L), T2 (2.3 < CRP ≤ 4.7 mg/L), T3 (CRP > 4.7 mg/L)

Model diagnostics indicated that the multivariable logistic regression models demonstrated acceptable goodness-of-fit (Hosmer–Lemeshow test: p = 0.348 for Model 2; p = 0.936 for Model 3), and no evidence of problematic multicollinearity was observed (all VIF < 4). Bootstrap calibration curves suggested good agreement between predicted and observed probabilities.

Supplementary and robustness analyses

We performed multiple supplementary analyses to verify the robustness of our main results and to address methodological considerations.

First, to evaluate potential selection bias introduced by the complete-case analysis, we compared baseline characteristics of the final analytical cohort (n = 3,089) with those of participants who were excluded due to missing data. As shown in Supplementary Table 1, the preterm

birth rate among women with missing CRP data (6.28%) was similar to that of the CRP-available group (6.92%), indicating that exclusion due to missing CRP was unlikely to introduce substantial selection bias.

Second, a sensitivity analysis treating CRP as a log-transformed continuous variable yielded findings consistent with the main results. The positive association between CRP and PTD remained statistically significant in the fully adjusted Model 2 ($\beta = 0.300$, $P < 0.001$), and the interaction between CRP and diabetes status continued to be significant in Model 3 ($\beta = 0.371$, $P = 0.027$), as shown in Supplementary Table 2.

Third, we explored CRP distribution across more detailed gestational-age categories. After subdividing PTD into very preterm (28–31 weeks), moderate preterm (32–33 weeks), and late preterm (34–36 weeks), the distribution of CRP tertiles showed no significant differences across these PTD subtypes or term births ($\chi^2 = 9.55$, df = 6, $P = 0.1449$), as presented in Supplementary Table 3.

Finally, diagnostic checks indicated that the multivariable models demonstrated sound statistical properties. All variance inflation factors (VIFs) were below 4, indicating an absence of problematic multicollinearity among covariates. The Hosmer–Lemeshow goodness-of-fit tests further supported adequate calibration of the adjusted models ($P > 0.50$).

Discussion

The present retrospective observational study explored the association between maternal CRP levels close to delivery and the risk of PTD, finding that this association was significantly modified by the woman's diabetes status. The preterm birth rate observed in our analytic sample (6.7%) is also consistent with previously reported national estimates for China: a large pooled analysis reported a rate of 6.09% (95% CI: 5.86–6.31%) between 1990 and 2016 [2], and global estimates for 2015–2016 also indicated a national rate of approximately 6.9% [3]. Univariate analyses revealed that women who delivered preterm were significantly older and had a higher prevalence of diabetes, gravidity, and parity compared to the term group. In the multivariable models, higher CRP levels were associated with an increased risk of PTD, and this effect was notably concentrated and amplified among women with diabetes, confirming a statistically significant interaction. This finding highlights a potential synergistic pathway where chronic metabolic stress (diabetes) combined with heightened peripartum inflammatory status (elevated CRP) significantly increases the risk of preterm delivery.

We observed that the proportion of women aged ≥ 35 years was significantly higher in the preterm group compared to the term group. This finding is consistent with previous studies [32], which have demonstrated that advanced maternal age increases the risk of PTD due to physiological changes associated with aging. Data also shows that both nulliparity (first pregnancy) and high parity elevate the risk of PTD. Nulliparous women may be more prone to cervical insufficiency due to a lack of prior cervical dilation, while those with high parity may experience cervical damage from multiple pregnancies, further increasing PTD risk [33]. Although pre-pregnancy BMI differed significantly between groups, the distribution showed no clear directional trend, and thus BMI did not demonstrate a meaningful association with PTD risk. Diabetes may contribute to PTD through mechanisms such as hyperglycemia-induced endothelial dysfunction, oxidative stress, and impaired vasodilation [34]. Although we observed a statistically significant difference in the timing of CRP measurement between the PTD and term groups, the magnitude of this difference was clinically negligible, with highly overlapping interquartile ranges (median difference of only 1 day). Crucially, the sampling–delivery interval was not associated with PTD in any of the adjusted logistic regression models, indicating that it did not confound the relationship between CRP levels and PTD. These findings indicate that minor variability in CRP measurement timing may not have a major influence on the overall findings.

In our analysis, the increased risk of PTD was concentrated in the highest CRP tertile (> 4.7 mg/L), whereas the middle tertile showed little difference from the lowest tertile. Several studies have identified clinically meaningful CRP thresholds in relation to preterm birth. One study reported that CRP levels ≥ 8 mg/L in early pregnancy were associated with more than a two-fold increase in the risk of PTD [35], while another investigation found that a CRP cut-off of approximately 5.3 mg/L could predict preterm delivery with reasonable sensitivity and specificity [36]. Taken together, these findings suggest that higher CRP concentrations—particularly those in the upper tail of the distribution—may reflect a threshold above which inflammatory activation becomes more relevant to PTD risk.

As an inflammatory marker, the significant difference in CRP levels between the preterm and term groups further emphasizes the critical role of inflammation in the mechanism of PTD. Consistent with our findings, prior studies in obstetric populations have widely used CRP as a marker of maternal inflammatory status, reporting its associations with periodontal inflammation, metabolic dysregulation, and multiple adverse pregnancy outcomes [37, 38]. Inflammatory processes play an important role during labor, with inflammation activated in both maternal and fetal tissues during pregnancy and delivery. Premature imbalance or abnormal stimulation of various factors in inflammatory pathways may trigger PTD [39,

40]. We also noted a higher prevalence of diabetes in the preterm group. In the stratified analysis by diabetes status, the association between CRP and PTD was significantly stronger among women with diabetes. Women with diabetes in the highest CRP tertile had more than twice the risk of PTD compared to those in the lowest tertile. Other studies have also found a close relationship between diabetes and elevated CRP levels, suggesting that inflammation may play a key role in the increased risk of PTD associated with diabetes [41]. Diabetes may exacerbate pro-inflammatory pathways related to PTD, possibly through hyperglycemia-induced oxidative stress and insulin resistance, which further elevate inflammatory cytokine levels and sustain a chronic low-grade inflammatory state [17, 41, 42]. Moreover, the metabolic dysfunctions in women with diabetes, including β-cell dysfunction and insulin resistance, not only impair placental function but also exacerbate inflammation, which are key drivers of PTD [43]. This dual mechanism of metabolic dysfunction and heightened inflammation may explain the significant interaction between diabetes and CRP levels observed in this study. However, given the relatively smaller subsample of women with diabetes, this interaction finding should be interpreted with caution and considered exploratory in nature.

In this study, CRP measurements were obtained predominantly within a short interval before delivery; therefore, elevated values are more likely to reflect peripartum inflammatory status. Several previous studies have reported similar findings across different obstetric populations, showing that CRP measured closer to delivery tends to exhibit stronger correlations with markers of peripartum inflammation and adverse pregnancy outcomes [44, 45]. For example, in certain preterm birth cohorts, CRP levels obtained within 24–72 h before delivery outperform those measured at hospital admission in identifying the risk of chorioamnionitis, funisitis, or early-onset neonatal infection [13]. Although these studies vary in assay methods, cut-off values, and population characteristics, the overall body of evidence supports the notion that CRP measured shortly before delivery can, to some extent, capture the degree of inflammatory activation during the peripartum period.

The stronger CRP–PTD association observed among women with diabetes in our study is biologically plausible. Women with diabetes status typically exhibit heightened systemic inflammation, driven in part by chronic hyperglycemia–induced activation of immune pathways, leading to increased levels of inflammatory markers such as IL-6, TNF-α, and CRP [46]. Previous studies have shown that inflammation plays a central role in the pathophysiology of diabetes status, further impairing insulin sensitivity and contributing to placental dysfunction, thereby increasing the risk of complications such as preeclampsia and preterm birth [47]. Taken together with our findings, these data underscore the importance of adequately controlling inflammation among women with diabetes status in order to improve pregnancy outcomes and reduce adverse maternal and neonatal consequences.

From a clinical perspective, a single elevated CRP value should not be interpreted as a stand-alone predictor of preterm birth. Nevertheless, CRP is an accessible inflammatory marker obtained routinely in obstetric care and may provide additional insight into peripartum inflammatory status. This may be particularly relevant among women with impaired glucose metabolism, where elevated CRP levels shortly before delivery may signal the need for further evaluation of potential infectious or inflammatory sources. Although our study cannot determine whether such evaluations would reduce the risk of preterm birth, this epidemiologic observation highlights the importance of timely identification and management of inflammatory states during pregnancy.

Preterm birth is recognized as a heterogeneous condition arising from multiple pathways (Romero et al., 2014). In China, iatrogenic preterm birth accounts for approximately 40%–43% of cases [48, 49] and is often related to hypertensive disorders and placental complications, which themselves are associated with inflammatory activation [48, 50]. Therefore, although iatrogenic preterm birth reflects clinical intervention, inflammatory processes may still be involved. In our study, diabetes modified the association between CRP and preterm birth. Given the chronic inflammatory milieu in diabetic pregnancies, elevated CRP may reflect broader inflammatory stress that contributes to both spontaneous and medically indicated pathways. This may partly explain why the CRP–diabetes interaction remained observable in overall preterm birth. However, because delivery indications were unavailable, subtype-specific interpretations should be made cautiously.

Limitations

However, several limitations should be acknowledged. First, this study employed a retrospective observational design using routinely collected clinical records; therefore, it can only identify associations and cannot establish causal relationships. Second, although CRP was routinely measured as part of antenatal or admission laboratory testing, the database did not record whether individual tests were prompted by specific clinical indications—such as suspected infection or symptoms of threatened preterm labour—limiting our ability to distinguish routine screening from indication-based testing. In addition, only the most recent CRP value prior to delivery was extracted from the hospital system, which may be affected by short-term variability. Third, although several covariates were adjusted for, residual confounding

remains possible. Important factors such as a history of preterm birth, maternal infection status, smoking, medication use, socioeconomic conditions, and additional inflammatory markers were not available in the hospital information system. Although active smoking during pregnancy is reported to be relatively uncommon in Chinese populations [51, 52], the absence of individual-level data remains an important limitation. Fourth, spontaneous and medically indicated preterm births could not be distinguished in this study, which may introduce etiologic heterogeneity; therefore, the findings should be interpreted with caution. Fifth, CRP measured close to delivery should be interpreted as reflecting short-term peripartum inflammatory activation rather than long-range prediction. Thus, the clinical relevance of modest absolute differences in CRP must be interpreted cautiously, particularly in subgroup analyses such as those stratified by diabetes status. Because the stratified subgroups were smaller, the observed effect modification should be considered exploratory.

Conclusion

This study found that higher maternal CRP levels measured shortly before delivery were associated with an increased risk of preterm delivery, with a more pronounced association observed among women with diabetes. These findings raise the possibility that diabetic pregnant women may be more susceptible to inflammation-related pathways leading to preterm birth. However, the study's observational design and the smaller sample size of stratified subgroups indicate that these results should be considered hypothesis-generating rather than definitive. Further large, prospective studies are needed to confirm this potential interaction and to clarify the underlying biological mechanisms.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12884-026-08985-7.

Supplementary Material 1.

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Authors' contributions
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Data availability
The datasets analyzed during the current study are not publicly available due to privacy and ethical restrictions but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The studies involving human participants were reviewed and approved by the Medical Research Ethics Committee of the School of Public Health, Fudan University (The international registry nos. IRB00002408 and FWA00002399). All study procedures were carried out in compliance with local legislation, institutional requirements, and the Declaration of Helsinki. Because this was a retrospective study based on existing data and all personal identifiers had been removed, the ethics committee/institutional review board granted a waiver of written informed consent from the participants or their legal guardians/next of kin. Therefore, informed consent was not obtained, as approved by the Medical Research Ethics Committee of the School of Public Health, Fudan University.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of the obstetrics, The People's Hospital of Pingyang, Wenzhou, Zhejiang 325400, China
[2]Key Lab of Health Technology Assessment of Ministry of Health, School of Public Health, Fudan University, 130 Dong-An Road, Shanghai 200032, China
[3]The Joseph L. Mailman School of Public Health, Columbia University in the City of New York, New York NY 10032, USA
[4]Alberta Institute, Wenzhou Medical University, North 1st Floor, Biomedical Research Building, Wenzhou, Zhejiang 325035, China
[5]Wenzhou Center for Disease Control and Prevention, 490 Shifu Road, Wenzhou, Zhejiang 325000, China
[6]School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, 600 Peter Morand Crescent, Ottawa, Ontario, Canada

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