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Elevated serum uric acid before 20 weeks of gestation increases the risk of preeclampsia

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This study aimed to investigate the association between serum uric acid level before gestational age of 20 weeks and preeclampsia. This study included pregnant women of three hospitals from January 2018 to June 2024. Clinical data were extracted using electronic medical record systems. The exposure factor was serum uric acid measured before gestational age of 20 weeks, with the primary outcome being preeclampsia, and secondary outcomes being preterm birth. Smooth curve fitting, ROC analysis, threshold effects, multivariate logistic regression, and subgroup analysis were employed to examine the relationship between uric acid and preeclampsia. The Kaplan-Meier method and log-rank test were used to evaluate the impact of serum uric acid on the gestational age at delivery. A total of 44,609 singleton pregnancies were included. There was a nonlinear relationship between serum uric acid level and the risk of preeclampsia, with a turning point at a uric acid level of 240 μmol/L. After adjusting for confounders, compared to non-preeclampsia cases, the risk of preeclampsia increased 1.38 times (95% CI: 1.28-1.48) for uric acid level between 240~360 μmol/L and 2.14 times (95% CI: 1.61-2.85) for UA levels ≥ 360 μmol/L. Similar positive associations were observed between uric acid level and preterm birth. Subgroup analysis maintained this positive correlation. Interaction tests indicated that BMI might influence the strength of the association between uric acid and preeclampsia ($P < 0.05$). Elevated serum uric acid level before gestational age of 20 weeks increase the risk of preeclampsia. Elevated uric acid levels in early pregnancy are associated with an increased risk of preeclampsia, suggesting that monitoring uric acid may help identify women at higher risk.

Keywords Serum uric acid, Preeclampsia, Early pregnancy, Multicenter, Cohort study

Preeclampsia (PE) is a severe complication of pregnancy, accounting for 10% to 15% of maternal deaths globally, posing a significant threat to maternal and neonatal health[1]. The hallmark symptoms of PE include new-onset hypertension, proteinuria, or multi-organ dysfunction occurring after the 20th week of gestation[2]. While the exact etiology of PE remains unclear, inadequate trophoblast invasion, impaired remodeling of placental spiral arteries, and placental dysfunction are considered primary causes[3]. Currently, there is no effective cure for PE; once diagnosed, the only definitive treatment is termination of the pregnancy. Therefore, identifying serum markers that enhance the predictive power for PE risk is clinically significant for its prediction and management.

Uric acid (UA) is not only the end product of exogenous purine metabolism but also its serum concentration can be increased by diets high in purines or other factors that induce purine nucleotide degradation, such as alcohol and fructose intake[4]. Our previous single-center cohort study indicated that elevated serum UA at 20 weeks of gestation may be a causative factor for PE, with particularly strong evidence for measurements taken between 8 and 12 weeks of pregnancy[5]. Several other studies have reported similar findings. One study demonstrated that increased UA levels before 10 weeks of gestation were linked to a higher risk of PE[6]. Another two studies found that elevated UA levels before 18 weeks[7] and before 20 weeks[8] of gestation were independent risk factors for PE. However, inconsistent results have also been reported. One prospective cohort study showed

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no significant difference in UA levels between women who developed PE and those who did not during early and mid-pregnancy. Serum UA levels rose significantly only after clinical symptoms of PE appeared[9]. The inconsistency across studies may stem from limited sample sizes or insufficient adjustment for confounding variables. Another important possible explanation is that most prior studies focused on the timing of UA elevation during pregnancy, without adequately considering that the degree of elevation itself might be a key driver of the observed associations with PE. To date, few studies have systematically examined the relationship between stratified UA levels and the risk of PE. Therefore, further investigation into how varying concentrations of UA before gestational age of 20 weeks influence PE risk may help clarify its potential predictive value and provide new insights for early identification and intervention.

To address these gaps, this study categorized pregnant women based on UA levels to explore the association between different concentrations of UA before gestational age of 20 weeks and the risk of PE. Using multicenter clinical data with a large sample size, we applied smoothed curve fitting and threshold effect analysis to assess the dose-response relationship between UA and PE. Multivariable logistic regression was conducted to evaluate the independent association between UA levels and PE risk. Subgroup analyses were also performed to examine whether age, body mass index (BMI), or parity modified the observed association. Our findings may support risk stratification for PE based on UA levels before gestational age of 20 weeks. Interventions targeting UA reduction could potentially serve as preventive strategies against PE and related adverse pregnancy outcomes, offering valuable reference for clinical practice.

Methods

Design and participants

This multicenter retrospective cohort study included 44,609 singleton pregnancies from three hospitals—Obstetrics and Gynecology Hospital of Fudan University, the First People's Hospital of Chenzhou, and Wuxi Maternal and Child Health Care Hospital—between January 2018 and June 2024. Of these, 2,444 women were diagnosed with PE, and 42,165 were non-cases. All pregnant women established their prenatal records and delivered at one of the above three hospitals. Clinical data were obtained from the hospital information system (HIS). The study included women meeting the following criteria: (1) age of 18 years or older, (2) singleton pregnancy, and (3) receipt of prenatal care and delivery at one of the participating hospitals. Exclusion criteria were: (1) initial UA measurement obtained after 20 weeks of gestation, (2) multiple pregnancies, (3) pre-existing hypertension, (4) pre-pregnancy diagnosis of conditions such as type 1 or type 2 diabetes, hyperlipidemia, or metabolic syndrome, as well as known kidney disease, heart disease, or other chronic medical or surgical conditions, and (5) incomplete clinical or laboratory records. Complete maternal and infant records should include basic demographic characteristics of the mother (such as height, weight, blood pressure, education level, and past medical history), laboratory test results, as well as delivery data covering gestational age at birth and newborn weight. This study was approved by the ethics committees of three above Hospital. All participants provided broad informed consent at the time of registration. This study adheres to the principles outlined in the Declaration of Helsinki.

Variables and measurements

In this study, the first serum UA measured before gestational age of 20 weeks was used as the exposure factor. Venous blood samples were collected during the early pregnancy visits and UA levels were analyzed using an automated biochemical analyzer. In the nonpregnant population, hyperuricemia is usually defined as a serum UA level higher than 7.0 mg/dl in men and 6.0 mg/dl in women. In pregnant women, UA levels are 25%~35% lower than in nonpregnant women, and serum UA levels usually fall below 4 mg/dl (1 mg/dl = 60 μmol/l)[10,11].

Smooth curve fitting indicated that 240 μmol/L was the inflection point in the association between uric acid levels and the risk of PE. Although Receiver Operating Characteristic (ROC) curve analysis suggested an optimal cutoff of 216 μmol/L(Supplementary Table S1), threshold effect analysis further supported the appropriateness of 240 μmol/L as the inflection point. In conjunction with previous studies showing that hyperuricemia in non-pregnant women is typically defined as serum uric acid > 360 μmol/L and that uric acid levels during pregnancy are generally below 240 μmol/L[10,12], we categorized uric acid levels into three groups: < 240 μmol/L, 240~360 μmol/L, and ≥ 360 μmol/L. Additional stratified analyses were conducted per 50 μmol/L and per 100 μmol/L increase in uric acid levels to comprehensively evaluate its association with PE.

Based on previous research and clinical experience[13,14], we summarized the following covariates that may influence the relationship between UA and PE. The covariates included in this study are: age (years), BMI (kg/m^2), systolic pressure, diastolic pressure, use of aspirin, use of antihypertensives, family history of hypertension, tobacco, alcohol consumption, in vitro fertilization (IVF), parity, alanine transaminase (U/L), total cholesterol (mmol/L), triglycerides (mmol/L), fasting blood glucose (mmol/L), test week, and adverse pregnancy history. All covariates were collected during the first prenatal visit, with the exact gestational week of blood collection recorded as 11.42 ± 3.84 weeks. Age was categorized into normal (< 35 years) and advanced maternal age (≥35 years). BMI was classified as underweight/normal (< 24 kg/m^2) and overweight (≥ 24 kg/m^2). Supplementary Table S2 showed the definition of variables.

Outcomes and measurements

The primary outcome measure was PE. According to the 2020 edition of the American College of Obstetricians and Gynecologists (ACOG) guidelines[15], the diagnostic criteria for PE include a normal pre-pregnancy blood pressure, followed by the onset of systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg after 20 weeks of gestation, accompanied by a urine dipstick protein level of 2+ or greater, or a 24-hour urinary protein excretion exceeding 300 mg. Alternatively, the diagnosis can be made in the absence of proteinuria if any of the following conditions are present: platelet count < 100 × 10^9/L, liver function impairment (serum

transaminases more than twice the upper limit of normal), renal impairment (serum creatinine > 1.1 mg/dL or more than twice the upper limit of normal), pulmonary edema, new-onset headache not attributable to another condition, or visual disturbances.

The secondary outcome was preterm birth (delivery before 37 weeks of gestation), with gestational age determined by ultrasound before gestational age of 20 weeks.

Statistical analysis

Continuous variables are expressed as means and standard deviations (SD), while categorical variables are presented as percentages (%). The statistical analysis includes four main steps to comprehensively analyze the relationship between UA levels and the primary outcome of PE, as well as the secondary outcome of preterm birth. Firstly, participants were divided into PE and non-PE groups according to clinical guidelines. Baseline covariate differences between the two groups were tested using chi-square tests for categorical variables and Student' s t-tests for continuous variables. Secondly, smooth curve fitting plots were utilized to explore the shape of the relationship between UA and PE. ROC analysis was performed to determine the optimal cutoff value for the association between uric acid levels and PE. Threshold effect analysis was conducted to confirm the nonlinear relationship between UA and PE. Log-likelihood ratio tests were performed on single-segment linear regression models and double-segment linear models, comparing segmented regression model I and model II. A P-value < 0.05 indicates a significant non-linear relationship. Thirdly, multivariate logistic regression models were used to test the association between UA and PE in both models. Model I did not adjust for any covariates. Model II adjusted for age, BMI, systolic pressure, diastolic pressure, aspirin use, depressor use, hypertension history, tobacco, alcohol, IVF, parity, alanine transaminase, total cholesterol, triglycerides, fasting blood glucose, gestational week of the test, and adverse pregnancy history. UA was categorized into three levels: < 240 μmol/L, 240~360 μmol/L, and ≥ 360 μmol/L. Stratified analyses were conducted for each 50 μmol/L and 100 μmol/L increase in UA levels. Fourthly, the impact of serum UA on gestational age at delivery was assessed using the Kaplan-Meier method and log-rank test. To evaluate the robustness of the relationship between UA and PE, subgroup analyses were performed based on age, BMI, and parity to test the effect of different subgroups on the outcomes, as these are well-established risk factors for PE according to previous studies[16]. Interaction tests were used to detect potential heterogeneity among these subgroups, with a p-value > 0.05 indicating no significant heterogeneity.

All reported p-values are two-tailed. Software IBM SPSS (version 21.0. IBM; Armonk, NY) and the R statistical packages (R Foundation; https://www.r.project.org; version 4.4.1) were used for statistical analysis.

Results

Baseline characteristics

As shown in Table 1, the study included a total of 44,609 singleton pregnant women, consisting of 2,444 PE and 42,165 non-PE. Significant differences (P < 0.05) were observed between the PE group and the non-PE group regarding age, BMI, UA levels, systolic pressure, diastolic pressure, alanine transaminase, total cholesterol, triglycerides, fasting blood glucose, use of aspirin, use of antihypertensives, family history of hypertension, alcohol consumption, IVF, and parity. No significant differences (P > 0.05) were found in terms of the gestational week of the test, smoking, and adverse pregnancy history.

Identification of non-linear relationship

As shown in Figure 1 by the results of the generalized additive model (GAM) and smooth curve fitting, there exists a non-linear association between UA and PE. The segmented regression model results in Table 2 indicate that the turning point in the relationship between UA levels and PE is 240 μmol/L. When UA is < 240 μmol/L, every increase of 100 μmol/L in UA is associated with an 81% increase in the risk of PE (OR = 1.81, 95% CI: 1.55–2.11.55.11). When UA is ≥ 240 μmol/L, every increase of 100 μmol/L in UA is associated with a 154% increase in the risk of PE (OR = 2.54, 95% CI: 2.24–2.88.24.88). The log-likelihood ratio test showed P = 0.006, indicating a non-linear relationship between UA and the risk of developing PE.

Association between UA and PE

As illustrated in Figure 2, among pregnant women with serum UA levels greater than 240 μmol/L before gestational age of 20 weeks, the incidence of PE reached 8.05%, which is 1.8 times the incidence observed in those with serum UA levels less than 240 μmol/L before gestational age of 20 weeks. Among all cases of PE, 41.04% of the pregnant women had serum UA levels greater than 240 μmol/L before gestational age of 20 weeks.

As shown in Table 3, UA levels exhibit a significant positive correlation with the primary outcome of PE and the secondary outcome of preterm birth. In Model I, compared to UA levels < 240 μmol/L, the OR for the development of PE was 1.75 (95% CI: 1.61–1.91.61.91) for UA levels in the range of 240~360 μmol/L, and the OR was 6.03 (95% CI: 4.73–7.69.73.69) for UA levels ≥ 360 μmol/L. Similar positive correlations were observed between UA levels and preterm birth. Model II adjusted for age, BMI, systolic pressure, diastolic pressure, aspirin use, depressor use, family history of hypertension, tobacco, alcohol, IVF, parity, alanine transaminase, total cholesterol, triglycerides, fasting blood glucose, gestational week of the test, and adverse pregnancy history. Even after these adjustments, the ORs for PE and preterm birth remained positively correlated with UA levels. Specifically, when UA levels were ≥360 μmol/L, the ORs for PE and preterm birth were 1.74 (95% CI: 1.23–2.48.23.48) and 2.15 (95% CI: 1.46–3.17.46.17), respectively.

Subgroup analysis

As shown in Table 4, a consistent positive correlation between UA and PE was observed across different subgroups, confirming the robustness of the association. No interaction was observed between age, parity, and

Characteristic	<240 (μmol/L) n=32155	240~360 (μmol/L) n=12055	≥360 (μmol/L) n=399	*P* value
Age (years)	31.38 ± 4.08	31.30 ± 4.24	31.26 ± 4.56	0.155
BMI (kg/m^2)	21.03 ± 2.69	22.63 ± 3.62	25.14 ± 4.77	<0.001
UA (μmol/L)	194.01 ± 28.62	272.38 ± 27.10	396.19 ± 41.22	<0.001
Test week	11.16 ± 3.19	12.15 ± 4.89	15.04 ± 8.97	<0.001
SBP (mmHg)	114.36 ± 11.97	116.96 ± 13.47	123.04 ± 16.38	<0.001
DBP (mmHg)	69.23 ± 9.35	71.01 ± 10.19	75.49 ± 12.19	<0.001
ALT (U/L)	17.33 ± 14.65	20.11 ± 18.25	26.58 ± 35.13	<0.001
TC (mmol/L)	4.52 ± 0.80	4.75 ± 0.90	5.01 ± 1.02	<0.001
TG (mmol/L)	1.29 ± 0.61	1.59 ± 0.85	2.37 ± 1.63	<0.001
FPG (mmol/L)	4.51 ± 0.46	4.54 ± 0.59	4.73 ± 1.00	<0.001
Aspirin (%)				<0.001
No	31667 (98.48%)	11733 (97.33%)	370 (92.73%)	
Yes	488 (1.52%)	322 (2.67%)	29 (7.27%)	
Depressor (%)				<0.001
No	32113 (99.87%)	11981 (99.39%)	384 (96.24%)	
Yes	42 (0.13%)	74 (0.61%)	15 (3.76%)	
Family history of hypertension (%)				0.003
No	27828 (86.56%)	10299 (85.45%)	332 (83.42%)	
Yes	4322 (13.44%)	1753 (14.55%)	66 (16.58%)	
Tobacco (%)				0.032
No	28392 (97.93%)	9668 (97.43%)	299 (97.41%)	
Yes	602 (2.07%)	255 (2.57%)	8 (2.59%)	
Alcohol (%)				0.301
No	27719 (95.47%)	9510 (95.84%)	295 (95.78%)	
Yes	1315 (4.53%)	413(4.16%)	13 (4.22%)	
IVF (%)				<0.001
No	30384 (94.49%)	11228 (93.14%)	365 (91.48%)	
Yes	1771 (5.51%)	827 (6.86%)	34 (8.52%)	
Parity (%)				0.635
Primipara	22786 (72.32%)	8484 (72.13%)	272 (70.28%)	
Multipara	8721 (27.68%)	3278 (27.87%)	115 (29.72%)	
Adverse pregnancy history (%)				<0.001
No	30486 (94.81%)	11230 (93.16%)	370 (92.73%)	
Yes	1669 (5.19%)	825 (6.84%)	29 (7.27%)	
Preeclampsia				<0.001
No	30714 (95.52%)	11140 (92.41%)	311 (77.94%)	
Yes	1441 (4.48%)	915 (7.59%)	88 (22.06%)	
Preterm birth (%)				<0.001
No	30354 (95.00%)	11027 (92.35%)	335 (84.81%)	
Yes	1598 (5.00%)	914 (7.65%)	60 (15.19%)	

Table 1. Baseline Characteristics of the study participants. Mean ± SD for continuous variables: *P* value was calculated by linear regression model. % for categorical variables: *P* value was calculated by chi-square test. BMI, body mass index; PE, preeclampsia; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; TC, total cholesterol; TG, triglycerides; FPG, fasting plasma glucose; IVF, in vitro fertilization.

UA (interaction $P > 0.05$), suggesting that the correlation between UA and PE is not influenced by age or parity. However, BMI did impact the association between UA and PE (interaction $P < 0.05$), with pregnant women having a BMI < 24 kg/m^2 showing a higher risk of PE at equivalent UA levels compared to those with a BMI ≥ 24 kg/m^2. This indicates that BMI may modify the correlation between UA and PE, with underweight or normal-weight pregnant women exhibiting a stronger association.

Kaplan-Meier curves

UA was closely associated with delivery time, and the gestational age at delivery in the higher UA group, especially in the group of UA ≥ 360 μmol/L, was generally earlier (P<0.0001) (Figure 3). The result suggest that

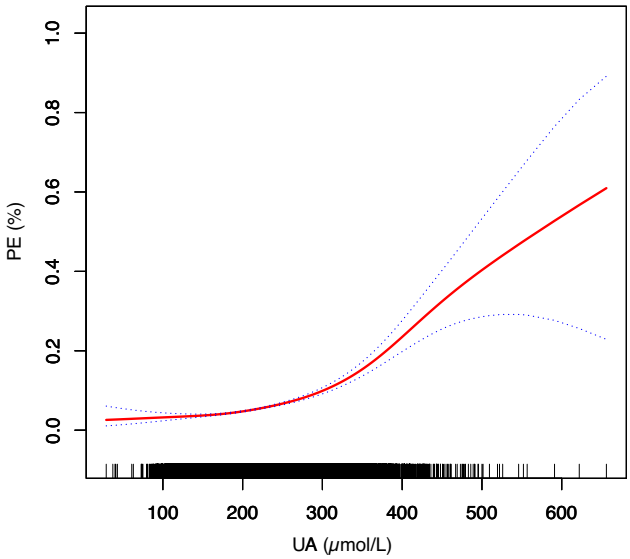

Fig. 1. Smoothed curve fitting reflected the dose-response relationship between UA and PE. The red line represents the fitted curve of UA and PE, and the blue line represents the 95% confidence interval of the curve. UA, uric acid; PE, preeclampsia; BMI, body mass index.

Models	Risk of PE Adjusted OR (95%CI)	*P* value
Model I		
One line slope	2.20 (2.04, 2.37)	<0.0001
Model II		
Turning point (K)	240 μmol/L	
UA < 240 slope 1	1.81 (1.55, 2.11)	<0.0001
UA ≥ 240 slope 2	2.54 (2.24, 2.88)	<0.0001
Slope 2–Slope 1	1.41 (1.11, 1.78)	0.0053
Predicted at 240	−2.81 (−2.88, −2.74)	
P for Log-likelihood ratio		0.006

Table 2. Threshold effect analysis of the relationship between each 100 μmol/L increase in UA and PE. Model I, linear analysis; Model II, non-linear analysis. Adjust for age, BMI, systolic pressure, diastolic pressure, aspirin, depressor, family history of hypertension, tobacco, alcohol, IVF, parity, alanine transaminase, total cholesterol, triglycerides, fasting blood glucose, test week, adverse pregnancy history. UA, uric acid; PE, preeclampsia; CI, confidence interval.

elevated serum UA before gestational age of 20 weeks in PE patients significantly increases the cumulative risk of preterm birth.

Discussion

This study aimed to investigate the dose-response relationship between serum UA level before gestational age of 20 weeks and PE. The results show a significant positive correlation between UA and PE, with a nonlinear association where a UA level of 240 μmol/L acts as a turning point. Subgroup analysis indicates that this association is consistent across different subgroups. Interaction tests reveal that this association is independent of age and parity. Interestingly, compared to pregnant women with a BMI ≥ 24 kg/m^2, those with a BMI < 24 kg/m^2 had a higher risk of PE at equivalent UA levels.

The relationship between UA and PE has been extensively studied in previous research. Nair et al. reported that the mean serum UA levels were significantly higher in women with PE compared to normotensive pregnant women[17]. A recent systematic review has concluded that UA levels are elevated in PE patients during early, mid, and late pregnancy, and that UA can serve as a predictor of the severity of PE and related complications[18]. However, some studies have yielded inconsistent results. One prospective study found no significant difference in serum UA levels between those who did and did not develop PE during early and mid-pregnancy, although elevated serum UA levels in late pregnancy were associated with the onset and severity of PE[19]. Building upon previous research, our study categorized early pregnancy UA levels and used dose-response analysis to identify a nonlinear relationship between UA and PE, emphasizing the varying degrees of impact different UA levels have

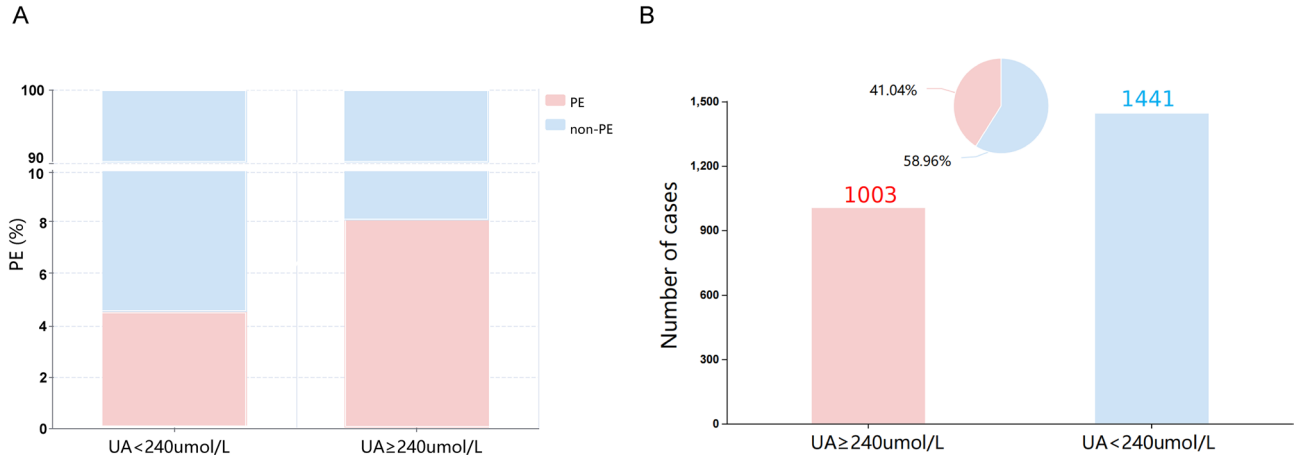

Fig. 2. (**A**) The incidence of PE in groups defined by serum UA levels ≥240 and < 240 μmol/L, respectively. The y-axis represents the percentage of participants who developed PE in each group. (**B**) The distribution of serum UA levels (≥240 vs. <240 μmol/L) among all women who developed PE, showing the number and proportion in each category. UA, uric acid; PE, preeclampsia.

Exposure	Model I		Model II	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Primary outcome				
PE				
<240 (μmol/L)	Reference		Reference	
240~360 (μmol/L)	1.75 (1.61–1.91)	<0.0001	1.15 (1.04–1.28)	0.0084
≥360 (μmol/L)	6.03 (4.73–7.69)	<0.0001	1.74 (1.23–2.48)	0.0018
Continuous UA per 50 μmol/L	1.48 (1.43–1.54)	<0.0001	1.14 (1.09–1.20)	<0.0001
Continuous UA per 100 μmol/L	2.20 (2.04–2.37)	<0.0001	1.31 (1.19–1.45)	<0.0001
Secondary outcome				
Preterm birth				
<240 (μmol/L)	Reference		Reference	
240~360 (μmol/L)	1.56 (1.43–1.70)	<0.0001	1.45 (1.30–1.61)	<0.0001
≥360 (μmol/L)	3.22 (2.42–4.30)	<0.0001	2.15 (1.46–3.17)	<0.0001
Continuous UA per 50 μmol/L	1.32 (1.27–1.37)	<0.0001	1.24 (1.18–1.30)	<0.0001
Continuous UA per 100 μmol/L	1.73 (1.60–1.87)	<0.0001	1.53 (1.39–1.69)	<0.0001

Table 3. The independent effect of uric acid measures in first trimester of gestation on the risk of primary and secondary outcome. Model I: None covariates were adjusted;. Model II: age, BMI, systolic pressure, diastolic pressure, aspirin, depressor, family history of hypertension, tobacco, alcohol, IVF, parity, alanine transaminase, total cholesterol, triglycerides, fasting blood glucose, test week, adverse pregnancy history were adjusted. UA, uric acid; PE, preeclampsia; OR, odds ratio; CI, confidence interval.

on PE. Notably, when early pregnancy UA levels are ≥ 360 μmol/L, the risk of PE significantly increases. This association is unaffected by factors such as age and parity.

Additionally, we found that among pregnant women with serum UA levels greater than 240 μmol/L before gestational age of 20 weeks, the incidence of PE reached 8.05%, which is 1.8 times higher than the incidence observed in those with serum UA levels less than 240 μmol/L. Among all cases of PE, 41.04% of the pregnant women had serum UA levels greater than 240 μmol/L before gestational age of 20 weeks. These cases can be defined as a UA-related PE, which has important implications for the classification and treatment of PE and may become a focus for future research.

Further subgroup analysis yielded interesting results: compared to pregnant women with a BMI ≥ 24 kg/m^2, those with a BMI < 24 kg/m^2 had a higher risk of PE at equivalent UA levels. This suggests that UA, as a serum biomarker predicting PE, may be even more relevant for underweight or normal-weight pregnant women. However, the underlying mechanisms by which UA influences the age-related aspects of PE remain unclear and require further exploration in future scientific research.

Moreover, we observed that elevated serum UA levels before gestational age of 20 weeks increased the risk of preterm birth, with the risk of preterm birth increasing as UA levels rose. Previous research supports our conclusions. Prior studies have found that high UA levels are associated with preterm birth[20], and that elevated

PE	Odds Ratio (95% CI)	*P* value	*P* for interaction	Adjust Odds Ratio (95% CI)	P value	*P* for interaction
Age (years)			0.6251			0.2129
Age < 35						
<240 (μmol/L)	Reference			Reference		
240~360 (μmol/L)	1.75 (1.59–1.93)	<0.0001		1.19 (1.05–1.34)	0.0047	
≥360 (μmol/L)	5.61 (4.22–7.45)	<0.0001		1.61 (1.07–2.40)	0.0212	
Age ≥ 35						
<240 (μmol/L)	Reference			Reference		
240~360 (μmol/L)	1.74 (1.46–2.08)	<0.0001		1.02 (0.81–1.29)	0.8468	
≥360 (μmol/L)	7.35 (4.57–11.84)	<0.0001		2.26 (1.09–4.68)	0.0283	
BMI (kg/m^2)			0.9704			0.0234
BMI < 24						
<240 (μmol/L)	Reference			Reference		
240~360 (μmol/L)	1.45 (1.29–1.62)	<0.0001		1.21 (1.06–1.38)	0.0050	
≥360 (μmol/L)	3.99 (2.54–6.28)	<0.0001		2.33 (1.33–4.09)	0.0032	
BMI ≥ 24						
<240 (μmol/L)	Reference			Reference		
240~360 (μmol/L)	1.46 (1.26–1.68)	<0.0001		1.07 (0.90–1.27)	0.4681	
≥360 (μmol/L)	3.74 (2.71–5.16)	<0.0001		1.55 (1.00–2.42)	0.0497	
Parity			0.1685			0.5051
Primipara						
<240 (μmol/L)	Reference			Reference		
240~360 (μmol/L)	1.77 (1.61–1.95)	<0.0001		1.15 (1.02–1.29)	0.0218	
≥360 (μmol/L)	5.42 (4.04–7.26)	<0.0001		1.58 (1.07–2.34)	0.0226	
Multipara						
<240 (μmol/L)	Reference			Reference		
240~360 (μmol/L)	1.70 (1.40–2.07)	<0.0001		1.15 (0.89–1.49)	0.2843	
≥360 (μmol/L)	8.94 (5.68–14.06)	<0.0001		2.66 (1.20–5.91)	0.0161	

Table 4. Subgroup analysis for the association between UA and PE. Adjusted for age, BMI, systolic, diastolic,aspirin, depressor, family history of hypertension, tobacco, alcohol, IVF, parity, alanine transaminase, total cholesterol, triglycerides, fasingt blood glucose, test week, adverse pregnancy history. UA, uric acid; PE, preeclampsia; CI, confidence interval; BMI, body mass index.

UA levels increase the risk of PE[19,21]. However, our study focuses on UA levels before gestational age of 20 weeks, whereas the timing of UA measurements in these previous studies was mainly during late pregnancy or after the diagnosis of PE.

In normal early pregnancy, due to increased blood volume, the concentration of serum UA tends to decrease relatively. In PE patients, impaired renal function leading to a decreased glomerular filtration rate is considered the cause of elevated UA levels[22]. Indeed, during the progression of PE, UA plays multiple pathological roles. Previous studies have shown that elevated UA can induce endothelial dysfunction, oxidative stress, and mitochondrial dysfunction[23,24], which may represent a potential mechanism by which UA contributes to the development of PE. Additionally, UA reduces nitric oxide production in endothelial cells, leading to impaired trophoblast invasion and resulting in defective remodeling of spiral arteries[25]. UA can also induce trophoblast shedding, contributing to the occurrence of placental abnormalities[26]. Combining these mechanistic studies with our findings, elevated UA may be a critical factor in the early pathological processes of the placenta.

Previous studies have consistently demonstrated that both PE and fetal growth restriction (FGR) are major adverse pregnancy outcomes associated with underlying placental insufficiency, often arising from impaired trophoblast invasion and defective remodeling of the uterine spiral arteries during early placentation[27–29]. As such, PE and FGR are widely regarded as clinical manifestations of abnormal placentation and can serve as external indicators of placental dysfunction. However, due to the retrospective nature of this study and limitations in data availability, we were unable to systematically collect FGR diagnoses based on standardized criteria, such as customized fetal growth charts, serial ultrasound assessments of fetal biometry, Doppler velocimetry of the umbilical or middle cerebral arteries, or composite clinical algorithms. This represents a key limitation of our analysis. In the absence of rigorously defined FGR, we cannot disentangle whether the observed associations between maternal uric acid levels and adverse birth outcomes are primarily driven by preterm delivery, true fetal growth pathology, or a combination of both. The use of less specific outcomes such as low birth weight or gestational age at delivery may lead to outcome misclassification and reduce the precision of our estimates. This lack of granularity limits the interpretability of the relationship between early uric acid elevation and distinct placental phenotypes. Future prospective studies incorporating serial fetal growth monitoring and standardized

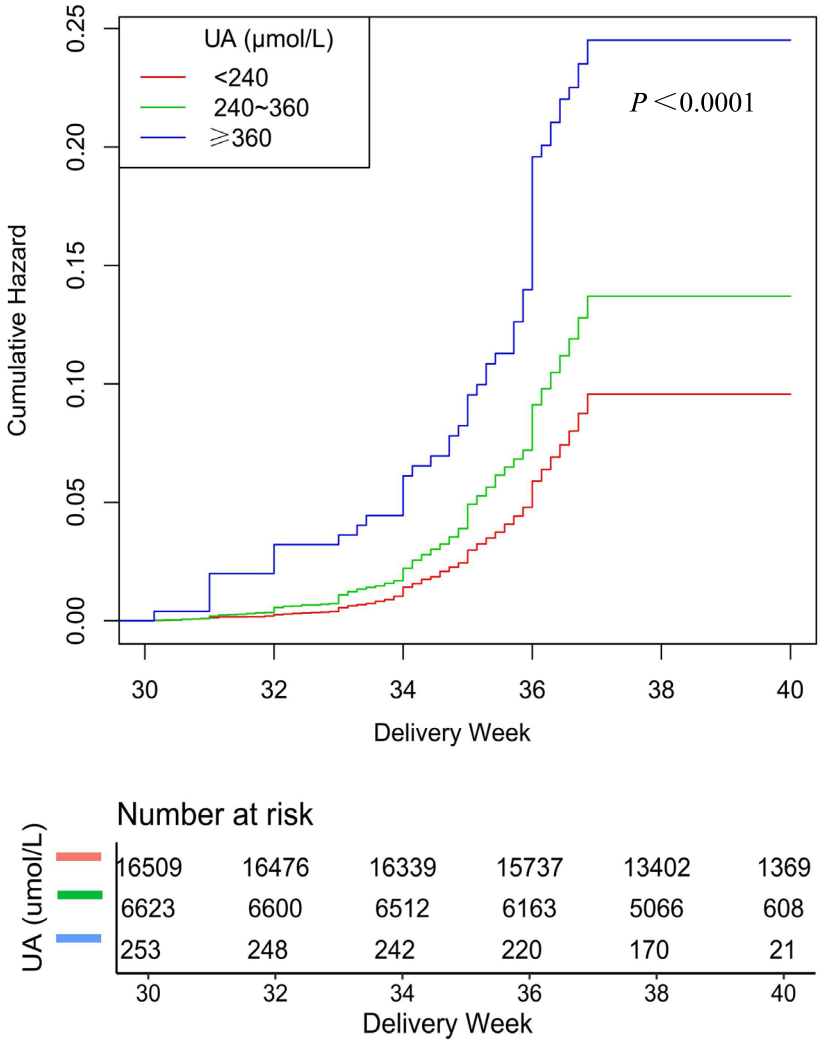

Fig. 3. Kaplan-Meier curve analysis of cumulative risk of preterm birth with different UA levels. The gestational age at delivery in the higher UA group was generally earlier compared to the lower UA group (P<0.0001). UA, uric acid.

FGR definitions are needed to clarify the specific role of maternal uric acid in different manifestations of placental insufficiency.

Our study has several advantages. Firstly, it included a large sample size of 44,609 singleton pregnant women from multiple centers, providing objective and robust results for accurately assessing the association between early pregnancy UA levels and PE. Secondly, the study employed various statistical methods, including GAM, smooth curve fitting, and threshold effect analysis, which confirmed the non-linear relationship between UA and PE and identified 240 μmol/L as the turning point in this association. Lastly, considering previous research and clinical experience, we accounted for various confounding covariates, thereby minimizing potential biases introduced by these factors. Our study has several limitations that should be considered. Firstly, due to its observational design, we cannot establish causality between UA levels and PE. The observed associations may be influenced by unmeasured confounding factors. Secondly, the study population was selected from retrospective datas, which may introduce selection bias and limit the generalizability of our findings. Moreover, the lack of multiple testing correction in the analyses of secondary outcomes may increase the possibility of type I error. But we believe that the exploratory nature of these analyses mitigates this concern to some extent. Thirdly, UA levels were measured once during early pregnancy, which may not reflect potential changes later in gestation, possibly affecting the accuracy of exposure classification. Lastly, while we found an association between UA and PE, the biological mechanisms underlying this relationship remain unclear, and the clinical utility of UA as a predictive marker for specific subtypes of PE requires further investigation. Lastly, the association between early-pregnancy uric acid levels and preterm birth may be confounded by preeclampsia-related clinical decisions, as many preterm deliveries in our cohort were iatrogenic. We cannot determine from this observational data whether uric acid has an independent effect on preterm birth or if the observed association is mediated through preeclampsia. Further prospective and mechanistic studies are needed to clarify this relationship.

Conclusion

In summary, our study demonstrates a significant positive correlation between elevated serum UA levels before gestational age of 20 weeks and PE, with this positive correlation presenting a non-linear relationship unaffected by confounding factors such as age and parity. This association is more pronounced in patients with a BMI < 24 kg/m^2, indicating that elevated UA levels before gestational age of 20 weeks may lead to an increased risk of PE. These findings underscore the importance of monitoring early pregnancy UA levels for predicting disease progression in PE, which holds significant clinical implications for the prediction and treatment of PE.

Data availability

Data will be provided by the corresponding author upon reasonable request.

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Author contributions

CYZ designed the study, collected and analyzed the data, interpreted the results, wrote and reviewed the manuscript. ML collected the data, reviewed the manuscript. QL designed the study, collected and analyzed the data, interpreted the results, wrote the manuscript.YJP and YL interpreted the results and reviewed the manuscript.

CYY designed the study, collected and analyzed the data, interpreted the results, and revised the manuscript. YC collected the data, reviewed the manuscript. DD interpreted the results, revised the manuscript. All authors approved the final version of the manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics
This study was approved by the ethics committees of Fudan University Obstetrics and Gynecology Hospital and Chenzhou First People's Hospital and Wuxi Maternity and Child Health Care Hospital. All participants provided broad informed consent.

Additional information
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