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Original Research

The Inter-Trimester Variation and Prognostic Value of Creatinine, Cystatin C and Uric Acid in Preeclamptic Patients: A Retrospective Study

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Abstract

Background: This study aimed to evaluate the clinical significance of maternal serum creatinine, cystatin C, and uric acid levels in relation to fetal death in pregnant women with preeclampsia. **Methods**: This retrospective study evaluated 708 women with preeclampsia, and 738 healthy pregnant women were selected as control. Medical records were reviewed to collect obstetric, neonatal, and biochemical data, including creatinine, cystatin C, and uric acid concentrations. **Results**: Maternal serum creatinine, cystatin C, and uric acid concentrations were significantly higher in the preeclamptic group than in the control ($p < 0.05$). Preeclamptic women in the fetal death group had significantly higher creatinine levels during their second and third trimesters, and higher uric acid concentrations throughout the pregnancy compared to the fetal survival group. Preeclamptic patients were divided into four groups based on quartiles of uric acid levels. The overall fetal survival rate in patients with upper-quartile uric acid concentrations was significantly lower than those with low uric acid levels during pregnancy. Multivariate logistic regression analysis revealed that uric acid concentration was a significant risk factor for fetal death in the first and second trimesters in the preeclamptic group ($p < 0.05$). **Conclusions**: In pregnant women with preeclampsia, fetal death was associated with upper-quartile uric acid concentrations in the first and second trimesters. Uric acid levels can be an indicator of fetal death in the early and middle stage of pregnancy.

Keywords: preeclampsia; creatinine; cystatin C; uric acid; fetal death

1. Introduction

Preeclampsia (PE) is the most common hypertensive disorder of pregnant women, with a morbidity of 3%–10% globally, causing significant maternal complications and fetal mortality [1]. In spite of this, the etiology of PE remains unclear; endothelial dysfunction and inflammation are thought to play a central role in its occurrence [2,3].

Kidney damage is one of the key components of the pathophysiological process involved in PE [4]. Being of critical importance in blood pressure regulation via salt and water homeostasis [5], kidney function frequently deteriorates in patients with PE even before proteinuria is evident [6]. Renal blood flow volume and glomerular filtration rate (GFR) decreases by 30%–40% in preeclamptic patients, mostly due to tubular cell and podocyte dysfunction [7,8]. Creatinine, cystatin C, and uric acid are common biomarkers of kidney function. The first two are significantly related to GFR [9] and uric acid is a useful indicator of pregnancy outcomes in preeclamptic patients [10,11]. Although serum creatinine is a diagnostic indicator of renal injury, this biomarker only shows a significant increase when the GFR falls to at least 50% [12]. Cystatin C is produced by nucleated cells at a constant rate. It could be a promising biomarker for the detection of PE in the late stages of the pregnancy [13]. Additionally, it has the potential to predict preterm delivery in patients with severe PE [14]. Similarly, elevated uric acid levels are an early biomarker of kidney injury in women with PE and is a predictive factor of adverse fetal outcomes [15,16].

Few studies have addressed their predictive value in relation to different trimesters and their variations during pregnancy remain unclear. Therefore, this study was designed to detect the inter-trimester variabilities and tendencies of serum creatinine, cystatin C, and uric acid concentrations in preeclamptic patients, to further evaluate the clinical implication of these biomarkers and their relationship to fetal death in preeclamptic women.

2. Material and Methods

2.1 Subjects

In this multi-center study, we reviewed the electronic medical records of pregnant women who underwent general

physical examinations between December 2018 and December 2021 at the People's Hospital of Guangxi Zhuang Autonomous Region, China. We selected 3340 total potentially eligible participants, including 784 pregnant women that diagnosed of PE as potentially eligible PE participants and 2556 healthy singleton pregnant women as potentially eligible controls. Data on 708 women with PE were collected after screening, and 738 randomized healthy pregnant women were selected from 2556 women as a control group. PE was defined as the new onset of hypertension and proteinuria after the 20th gestational week, or hypertension without proteinuria but with hematological complications, renal dysfunction, impaired hepatic function, and neurologic symptoms. The study protocol was approved by the ethics committee at the People's Hospital of Guangxi Zhuang Autonomous Region, and the study was conducted in accordance with the Declaration of Helsinki.

2.2 Methods

Blood pressure was gauged using a mercury sphygmomanometer. A sustained systolic blood pressure of $\geq$140 mmHg and/or diastolic blood pressure of $\geq$90 mmHg, detected during two consecutive checks within a 6-hour interval was defined as hypertension. The first, second and third trimesters were defined as $<12+0$, $(12+0)$–$(27+6)$, and $\geq 28+0$ gestational weeks respectively. Gestational weight gain time was calculated from the date of pregnancy until childbirth or stillbirth for these patients. Patients with history of stillbirth, spontaneous abortion and birth defect were defined as adverse pregnancy history. Creatinine concentrations were detected by enzymatic methods (Diasys, Shanghai, China), cystatin C concentrations by the particle-enhanced nephelometric immunoassay method (Diasys), and uric acid concentrations by the color comparison method (Diasys). All samples were assessed using an Beckman Coulter AU5800 chemistry analyzer (Beckman Coulter, Bria, CA, USA).

2.3 Anthropometric Characteristics

The body mass index (BMI) of women was calculated as kg/m^2. Routine clinical data including the number of abortions, parities, rates of adverse pregnancy history and fetal death, gestational weight gain, neonatal weight, Apgar score and gestational age at delivery were collected. Patients with history of stillbirth, spontaneous abortion and birth defect were defined as adverse pregnancy history. Serum creatinine, cystatin C, and uric acid concentrations were determined regularly during the first, second and third trimesters. Fasting blood samples were collected by plain tubes without anticoagulant (Becton, Dickinson and Company, Franklin Lake, NJ, USA) and then centrifuged at 1500 g for 5 min. The serum was analyzed within 60 min. The normal range for creatinine is 45–84 μmol/L, cystatin C is 0.59–1.03 mg/L and uric acid is 155–357 μmol/L in females of China.

The cut off values for quartiles of uric acid levels in the study were calculated by SPSS (software version 11.0, IBM Corp., Armonk, NY, USA) and divided into four groups of data. For the first trimester: quartile I $<$213 μmol/L; quartile II 213–252.99 μmol/L; quartile III 253–296.85 μmol/L; and quartile IV $>$296.85 μmol/L. For the second trimester: quartile I $<$271 μmol/L; quartile II 271–331.99 μmol/L, quartile III 332–394 μmol/L; and quartile IV $>$394 μmol/L. For the third trimester: quartile I $<$360 μmol/L; quartile II 360–426.99 μmol/L; quartile III 427–496.25 μmol/L; and quartile IV $>$496.25 μmol/L.

2.4 Statistical Analysis

Results are shown as numbers (%), mean standard deviation ($\pm$SD), or median (25th to 75th percentiles, data not normally distributed). A chi-squared test, *t*-test, or Mann-Whitney U test were used to facilitate comparisons. Variation tendencies of creatinine, cystatin C, and uric acid concentrations were evaluated by paired *t*-test. Receiver operating characteristic (ROC) curves were used to assess the predictive value of creatinine, cystatin C, and uric acid concentrations. Kaplan-Meier analysis was constructed to evaluate the prognostic value of uric acid concentration during pregnancy. Furthermore, the risk factors of fetal death were evaluated by logistic regression analysis. All statistics were performed using SPSS (software version 11.0, IBM Corp.). Two-sided p-values < 0.05 were considered statistically significant.

3. Results

3.1 Patients

This study collected data from pregnant women who underwent examinations from 2018 and 2021 at the People's Hospital of Guangxi Zhuang Autonomous Region. In 784 potentially eligible PE participants, 43 patients with pre-existing hypertension, nephropathy, tumors, or cardiovascular disease were excluded from the analysis. From the 741 included PE patients, 33 PE patients were lost due to invalid phone number, out of touch, or transferred to another hospital. Ultimately, 708 PE patients satisfied the research requirements of this study as a PE group. Of these, 38 preeclamptic women miscarried due to stillbirths in the second trimester.

We selected 2556 health singleton pregnancy women from electronic medical records and ordered them by alphabetical using the last names, and we randomly selected 738 healthy controls from them as a control group, randomized-selection was implemented with SPSS. The study's recruitment process is shown in Fig. 1.

The clinical parameters of patients with PE and control patients are shown in Table 1. Comparing the two groups, patients with PE had higher serum levels of creatinine ($p < 0.05$), cystatin C ($p < 0.05$), and uric acid ($p < 0.05$) compared to the control group. They also were older in age ($p < 0.05$), higher BMI ($p < 0.05$), more abortion ($p <$

Table 1. Comparing the clinical characteristics of the control group and the group with PE.

	Preeclampsia	Control	*p*
	N = 708	N = 738	
Age (years)	32.68 ± 5.28	30.78 ± 4.69	<0.0001
Creatinine			
First trimester (μmol/L)	46.65 ± 9.48	47.47 ± 7.03	0.062
Second trimester (μmol/L)	52.71 ± 14.73	48.91 ± 7.95	<0.0001
Third trimester (μmol/L)	62.77 ± 21.06	48.68 ± 9.46	<0.0001
Cystatin C			
First trimester (mg/L)	0.59 ± 0.15	0.49 ± 0.09	<0.0001
Second trimester (mgl/L)	1.00 ± 0.31	0.73 ± 0.18	<0.0001
Third trimester (mg/L)	1.37 ± 0.40	0.95 ± 0.23	<0.0001
Uric acid			
First trimester (μmol/L)	263.00 ± 68.92	225.00 ± 53.06	<0.0001
Second trimester (μmol/L)	339.96 ± 94.75	264.58 ± 62.20	<0.0001
Third trimester (μmol/L)	436.29 ± 110.63	337.15 ± 82.74	<0.0001
Gestational weight gain (kg)	12.44 ± 5.17	13.02 ± 3.79	0.016
Body mass index (kg/m^2)	28.32 ± 3.61	25.96 ± 2.99	<0.0001
Neonatal weight (kg)	2.06 ± 0.89	3.16 ± 0.37	<0.0001
Previous abortions	1 (0, 2)	0 (0, 1)	<0.0001*
Parity	0 (0, 1)	1 (0, 1)	<0.0001*
Gestational age at delivery (weeks)	35.44 ± 4.30	39.21 ± 1.11	0.002
Adverse pregnancy history (n)	63 (8.90%)	17 (2.30%)	<0.0001
Fetal death (n)	73 (10.31%)	1 (0.14%)	<0.0001

Data are shown as mean ± standard deviation, number (percentage), or median (25th to 75th percentiles). *: Mann-Whitney U test.

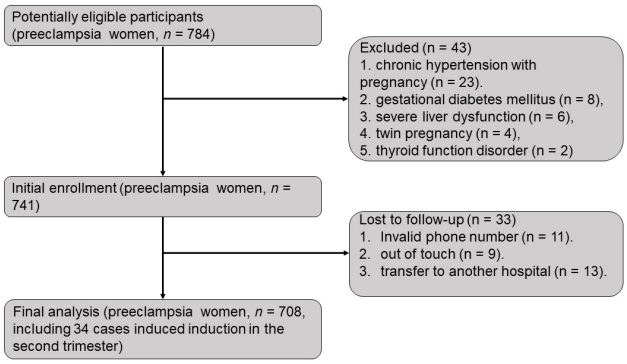

Fig. 1. Flow chart of participants enrollment.

0.05) and parity times ($p < 0.05$), higher rates of adverse pregnancy history ($p < 0.05$) and fetal death ($p < 0.05$), lower gestational weight gain ($p < 0.05$), lower neonatal weight ($p < 0.05$) and gestational age at delivery ($p < 0.05$).

The clinical characteristics of patients with PE are shown in Table 2. The fetal death group had significantly higher serum creatinine levels during the second ($p < 0.001$) and third trimesters ($p = 0.001$), higher cystatin C concentrations during the second trimester ($p = 0.045$), and higher uric acid levels throughout their pregnancy ($p < 0.05$). Women who experienced fetal death had significantly lower gestational weight gain ($p < 0.001$), BMI ($p = 0.009$), neonatal weight ($p < 0.001$), Apgar score (5 min) ($p < 0.001$), and gestational age at delivery ($p < 0.001$) (Table 1).

3.2 Changes in Creatinine, Cystatin C, and Uric Acid Concentrations and Their Relation to Fetal Death

The results of the paired *t*-test indicated that creatinine, cystatin C, and uric acid concentrations increased progressively in women with PE throughout pregnancy in both the survival and fetal death groups ($p < 0.05$, Fig. 2A–F).

ROC curves results revealed the significant ability of creatinine and uric acid concentrations to predict the risk of fetal death (Fig. 2G,I). Besides, maternal serum uric acid threshold that predicted fetal death at delivery in the second and third trimesters were 390.5 μmol/L (sensitivity, 0.738; specificity, 0.772) and 423.57 μmol/L (sensitivity, 0.833; specificity, 0.507) respectively.

3.3 Predictive Factors of Fetal Death

The fetal death rate increased significantly with quartiles of uric acid concentrations, from 6.67% to 18.08% in the first trimester, from 3.35% to 26.14% in the second trimester, and from 1.78% to 10.71% in the third trimester (Fig. 3A,B). Fetal mortality in patients with PE that had a high serum uric acid level was higher than in patients with low serum uric acid levels during pregnancy ($p < 0.05$). Overall survival time was calculated from the date of pregnancy until childbirth or stillbirth for these patients (Fig. 3C–E). Moreover, risk factors of fetal death were investigated, and multivariable analysis revealed that uric acid was an independent risk factors of fetal death in patients with PE in the first and second trimesters (Table 3).

Table 2. Comparison of clinical characteristics between the survival and fetal death groups.

	Survival	Fetal death	*p*-value
	N = 635	N = 73	
Age (years)	32.63 ± 5.32	32.23 ± 4.86	0.319
Creatinine (μmol/L)			
First trimester	46.44 ± 9.09	48.43 ± 12.30	0.091
Second trimester	51.57 ± 13.11	62.70 ± 22.43	<0.001
Third trimester	61.18 ± 19.22†	71.18 ± 23.53†	0.001
Cystatin C (mg/L)			
First trimester	0.59 ± 0.15	0.58 ± 0.15	0.776
Second trimester	0.99 ± 0.31	1.06 ± 0.29	0.045
Third trimester	1.35 ± 0.37†	1.43 ± 0.52†	0.327
Uric acid (μmol/L)			
First trimester	260.04 ± 67.77	288.74 ± 73.81	0.002
Second trimester	329.05 ± 87.23	434.89 ± 104.68	<0.001
Third trimester	425.65 ± 103.06†	512.15 ± 123.32†	<0.001
Gestational weight gain (kg)	12.88 ± 4.95	8.59 ± 5.48	<0.001
Body mass index (kg/m^2)	28.44 ± 3.59	27.25 ± 3.61	0.009
Neonatal weight (kg)	2.21 ± 0.80	0.80 ± 0.56	<0.001
Previous abortions	1.00 (0, 2)	1.00 (0, 2)	0.145*
Parity	0.00 (0, 1)	1.00 (0, 1)	0.930*
Gestational age at delivery (weeks)	36.24 ± 3.49	28.53 ± 4.50	<0.001
Adverse pregnancy history (n)	53 (9.06%)	10 (0.14%)	0.130

Data are shown as mean ± standard deviation, number (percentage), or median (25th to 75th percentiles). †Survival group, N = 631, fetal death group, N = 43, *: Mann-Whitney U test.

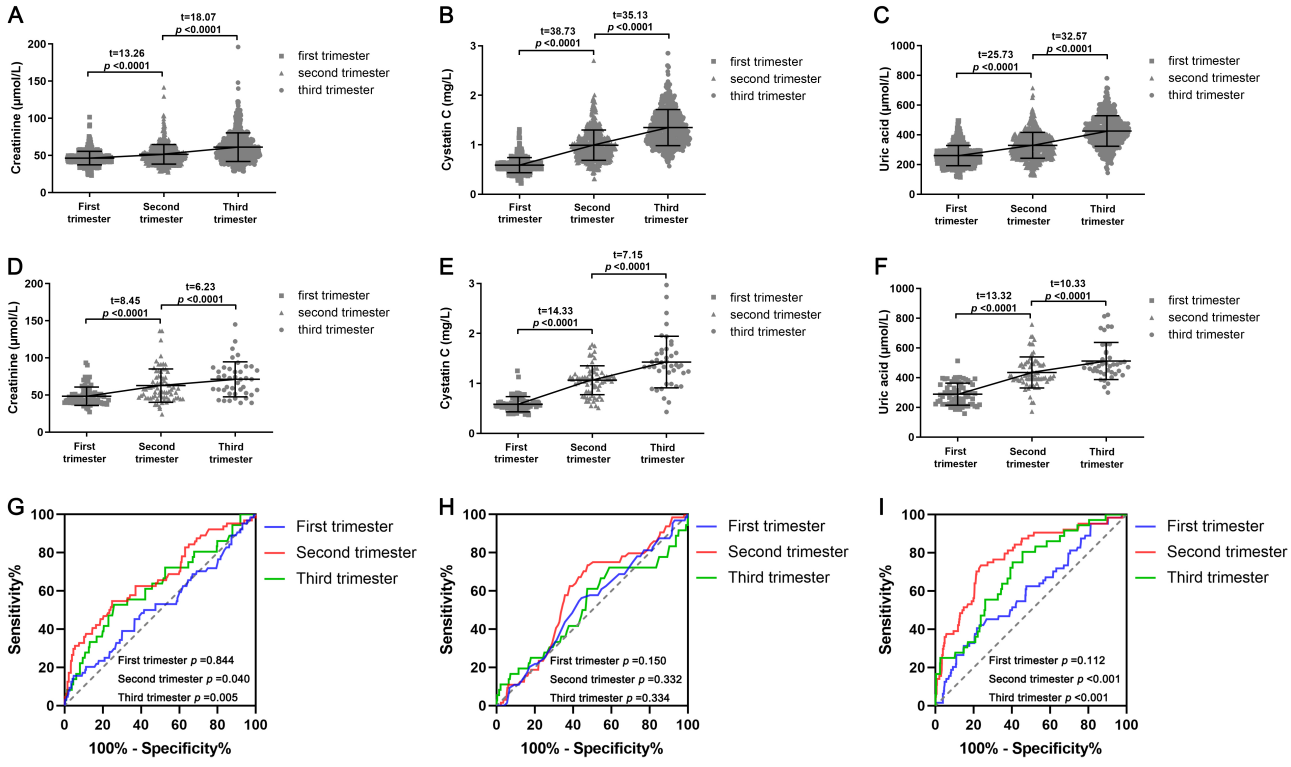

Fig. 2. The mean ± standard deviation values according to fetal survival status among patients with PE. Creatinine (A), cystatin C (B), and uric acid (C) concentrations in the survival group and creatinine (D), cystatin C (E), and uric acid (F) concentrations in the fetal death group. ROC curve was adopted to evaluate predictive values of creatinine (G), cystatin C (H), and uric acid (I) during pregnancy according to fetal survival status.

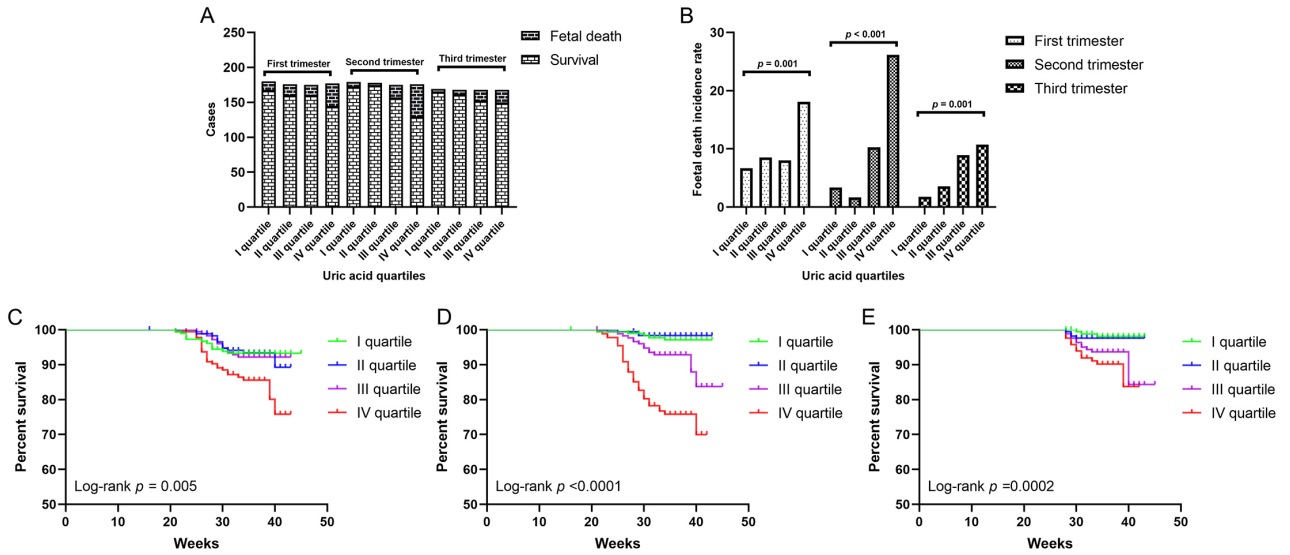

Fig. 3. The correlation between uric acid level and fetal death. Cases of survival and fetal death in patients with PE by quartiles of uric acid in pregnancy (A). Fetal mortality during pregnancy by quartiles of uric acid (B). Fetal survivorship curves in patients with PE by quartiles of uric acid during the first (C), second (D) and third (E) trimesters.

Table 3. Logistic regression analysis of fetal death during the different trimesters in patients with PE.

	Crude OR	Univariable Analysis	*p* value	Adjusted OR	Multivariable Analysis	*p* value
		HR (95% CI)			HR (95% CI)	
Age (years)	0.95	0.92–0.99	0.024	0.91	0.83–0.99	0.024
Creatinine (μmol/L)						
First trimester	1.02	0.997–1.04	0.092	-	-	-
Second trimester	1.04	1.03–1.05	<0.001	0.99	0.95–1.03	0.739
Third trimester	1.02	1.01–1.03	0.002	0.99	0.97–1.03	0.738
Cystatin C (mg/L)						
First trimester	0.79	0.16–3.97	0.776	-	-	-
Second trimester	2.07	0.99–4.33	0.054	-	-	-
Third trimester	1.69	0.78–3.67	0.182	-	-	-
Uric acid (μmol/L)						
First trimester	1.01	1.00–1.01	0.001	0.99	0.99–1.00	0.049
Second trimester	1.01	1.01–1.01	<0.001	1.01	1.00–1.02	0.007
Third trimester	1.01	1.00–1.01	<0.001	1.00	0.99–1.01	0.661
Gestational weight gain (kg)	0.81	0.76–0.86	<0.001	0.95	0.86–1.04	0.240
Body mass index (kg/m^2)	0.91	0.84–0.97	0.008	1.01	0.90–1.14	0.828
Neonatal weight (kg)	0.02	0.01–0.05	<0.001	0.08	0.03–0.26	<0.001
Previous abortions	1.13	0.92–1.39	0.233	-	-	-
Parity	1.42	1.00–2.01	0.048	2.72	1.37–5.40	0.004
Gestational age at delivery (weeks)	0.62	0.57–0.68	<0.001	0.97	0.82–1.15	0.706
Adverse pregnancy history	1.74	0.85–3.60	0.133	-	-	-

OR, odds ratio; HR: hazard ratio; CI, confidence interval.

4. Discussion

This study evaluated the predictive value of creatinine, cystatin C, and uric acid in pregnant women with PE, because they are the most widely used serum markers of renal function. Among our patients with PE, we found significantly higher levels of creatinine, cystatin C, and uric acid during their pregnancies compared to those observed in healthy controls. Calculations indicate a relationship between renal injury and PE. Moreover, preeclamptic pregnant women with fetal deaths had higher levels of creatinine during their second and third trimesters, higher serum cystatin C levels during the second trimester, and higher uric acid concentrations throughout pregnancy.

Elevated uric acid levels are caused by impaired renal clearance due to a decreased GFR and poor trophoblast invasion in women with PE. This promotes the production of lactic acid, which impairs uric acid excretion in the renal tubules [17]. Studies confirm that increased uric acid levels promote systemic hypertension, which subse-

quently induces kidney injury, vascular disease and endothelial cell apoptosis [18]. Uric acid can behave as a prooxidant molecule, leading to cellular oxidative damage in an antioxidant-depleted environment, where it plays a role in inflammation, oxidative stress, and endothelial dysfunction [19]. Hyperuricemia inhibits nitric oxide production in endothelial cells, leading to an abnormal trophoblast invasion and migration, and thus interferes with the circulation of nutrients and oxygen supply from the mother to the fetus [17]. Therefore, high levels of uric acid may affect the fetal prognosis in preeclamptic patients.

Previous studies have examined whether elevated uric acid concentrations in pregnancy are related to adverse outcomes. High uric acid levels performed better than creatinine in predicting low birth weight in Indian women [20]. Additionally, a study conducted in Korean found that in women with PE, uric acid levels were a good predictor of preterm birth and low birth weight [11]. Although Armando *et al*. [21] reported that serum uric acid levels >6 mg/dL in severe PE should alert to the possibility of maternal and fetal complications, Maryam *et al*. [22] found that levels of uric acid were unrelated to complications, including fetal death. In this regard, a study conducted at Yale University demonstrated that high uric acid caused placental dysfunction and increased the risk of adverse pregnancy outcomes [23]. Previous studies had only focused on uric acid concentrations during specific time points in pregnancy, so it remained unclear how uric acid may contribute specifically to the risk of fetal death.

In this study, ROC analysis indicated that only elevated creatinine and uric acid levels were predictive of fetal death. In contrast, cystatin C were poorly sensitive in this regard and proved to be of little utility for predicting fetal death, this indicates that a sustained increase in uric acid levels may lead to a higher risk of fetal death in patients with PE, and uric acid concentrations play different roles in predicting fetal death in different time points of the pregnancy. More importantly, we identified that inter-trimester variation is significant in patients with PE, so it is not appropriate to evaluate the prognostic value of uric acid levels only at specific time point in pregnancy.

Afterwards, the preeclamptic patients were divided into four groups based on quartiles of uric acid levels. Fetal death rates increased significantly with increased levels of uric acid during pregnancy, indicating that uric acid was related to fetal death in patients with PE. After adjusting for age, creatinine, gestational weight gain, BMI, parity and gestational age at delivery, multivariable logistic regression indicated that uric acid concentration was an independent risk factor associated with fetal death in patients with PE during the first and second trimesters, this study demonstrated that uric acid can affect fetal development in the first and second trimesters.

Previous studies showed that pregnant women with advanced maternal age were associated with an increasing proportion of adverse neonatal outcomes [24,25], and the risk for stillbirth was substantially elevated among very high and extremely high parity women [26], these are consistent with the results of this study, indicating that maternal status may affect the development of fetus. The present study suffers from some drawbacks. It failed to account for maternal factors that might affect uric acid concentrations, such as dietary habits, alcohol consumption, smoking and medical interventions. These factors should be considered in future studies.

5. Conclusions

In conclusion, the present study confirmed that in Chinese patients with PE, increased levels of uric acid in the first and second trimesters were significantly related to fetal death, it is not appropriate to evaluate the prognostic value of uric acid levels only at specific time point in pregnancy. Future prospective studies should address the utility of serial uric acid monitoring in the management of patients with PE.

Availability of Data and Materials

The datasets generated and analyzed during the current study are not publicly available due to patient privacy, but are available from the corresponding author on reasonable request.

Author Contributions

Conception and design—JPJ and WYQ, provision of study materials or patients—JPJ, JLW, GFH, XFW and WYQ, collection and assembly of data—JPJ, JLW, JL, GFH and WYQ, data analysis and interpretation—JPJ, WYQ and GFH, manuscript writing—JPJ and WYQ.

Ethics Approval and Consent to Participate

The study protocol was approved by the ethics committee at the People's Hospital of Guangxi Zhuang Autonomous Region (KY-KJT-2023-22).

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Conflict of Interest

The authors declare no conflict of interest.

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