ORIGINAL RESEARCH ARTICLE

Predictive value of early pregnancy uric acid levels for adverse pregnancy outcomes

DOI: 10.29063/ajrh2024/v28i12.6

*Qiaohong Lai and Xin Zhang**

Department of Obstetrics, Xiaolan People's Hospital of Zhongshan (The Fifth People's Hospital of Zhongshan), Zhongshan,528415, China

***For Correspondence:** Email: *rsubmission153@gmail.com*; *15674815514@163.com*

Abstract

Elevated serum uric acid (SUA) levels in pregnancy are linked to adverse outcomes, including preterm birth, preeclampsia, and low birth weight. To assess the predictive value of SUA levels in early pregnancy for adverse pregnancy outcomes (APOs). A cohort of 4,240 pregnant women admitted for delivery from January 2021 to December 2022 was analyzed. APOs were compared between women with hyperuricemia (HUA) (UA > 360 μmol/L) and those without HUA. Logistic regression (LR) analysis was used to identify risk factors for APOs. Among the cohort, 295 women (6.9%) had HUA. Compared to the non-HUA group, the HUA group had a higher BMI (22.45 vs. 21.34), higher rates of hypertension (6.1% vs. 3.4%), preterm birth (10.2% vs. 6.3%), and low birth weight (10.2% vs. 5.9%). Multivariate LR analysis identified elevated UA levels, BMI, diabetes, and preeclampsia as significant risk factors for APOs. The optimal UA threshold for predicting preterm birth was 253.855 μmol/L (sensitivity: 71.4%, specificity: 55.2%). Early pregnancy SUA levels are predictive of adverse pregnancy outcomes, providing a foundation for potential clinical interventions. Given the moderate sensitivity and specificity of the identified SUA threshold for predicting preterm birth, further research is warranted to refine these values and establish their clinical implications in obstetric practice. *(Afr J Reprod Health 2024; 28 [12]: 52-60).*

Keywords: Early pregnancy; uric acid; adverse pregnancy outcomes

Résumé

Des taux élevés d'acide urique sérique (SUA) pendant la grossesse sont liés à des conséquences indésirables, notamment une naissance prématurée, une prééclampsie et un faible poids à la naissance. Évaluer la valeur prédictive des niveaux de SUA en début de grossesse pour les issues indésirables de la grossesse (APO). Une cohorte de 4 240 femmes enceintes admises pour un accouchement de janvier 2021 à décembre 2022 a été analysée. Les APO ont été comparées entre les femmes atteintes d'hyperuricémie (HUA) (UA > 360 μmol/L) et celles sans HUA. Une analyse de régression logistique (LR) a été utilisée pour identifier les facteurs de risque d'APO. Parmi la cohorte, 295 femmes (6,9 %) souffraient d'HUA. Comparé au groupe non-HUA, le groupe HUA présentait un IMC plus élevé (22,45 contre 21,34), des taux d'hypertension plus élevés (6,1 % contre 3,4 %), une naissance prématurée (10,2 % contre 6,3 %) et un faible poids à la naissance. (10,2% contre 5,9%). L'analyse LR multivariée a identifié des taux élevés d'UA, d'IMC, de diabète et de prééclampsie comme facteurs de risque importants d'APO. Le seuil optimal d'UA pour prédire l'accouchement prématuré était de 253,855 μmol/L (sensibilité : 71,4 %, spécificité : 55,2 %). Les niveaux de SUA en début de grossesse sont prédictifs d'issues indésirables de la grossesse, fournissant ainsi une base pour des interventions cliniques potentielles. Compte tenu de la sensibilité et de la spécificité modérées du seuil SUA identifié pour prédire l'accouchement prématuré, des recherches supplémentaires sont justifiées pour affiner ces valeurs et établir leurs implications cliniques dans la pratique obstétricale. *(Afr J Reprod Health 2024; 28 [12]: 52-60).*

Mots-clés: Grossesse précoce; acide urique; issues défavorables de la grossesse

Introduction

Uric acid (UA) is a metabolic byproduct of the human body's metabolism. The UA at normal levels helps protect against oxidative stress and DNA damage. Still, high concentrations can lead to increased oxidative stress, endothelial dysfunction, and vascular proliferation, resulting in a series of diseases.[1]

Adverse outcomes during pregnancy frequently include preeclampsia, Preterm birth (PTB), and low birth weight. Identifying the causes

of adverse pregnancy outcomes (APOs) and preventing their occurrence are important research topics in the field of medicine[2,3] Various studies have shown that having elevated levels of UA in the blood during the latter stages of pregnancy may increase the chances of experiencing negative pregnancy outcomes, including preeclampsia, gestational diabetes, and fetal growth restriction (FGR).[4,5] Therefore, the assessment of UA levels in serum has become an important indicator for evaluating the prognosis of pregnant women and neonates.

Hyperuricemia-induced hypertension results from the combined effects of multiple factors. High levels of UA not only hinder the growth of endothelial cells stimulated by vascular endothelial growth factor but also result in damage to the endothelium and impaired blood vessel function by decreasing nitric oxide and increasing the secretion of inflammatory cytokines through the nuclear factor-κB pathway. This ultimately leads to an increase in blood pressure.[6] Hypertension-induced systemic arteriolar spasm leads to constriction of renal arterioles and placental vessels. The former reduces effective filtration and UA excretion[7]. while the latter causes fetal hypoperfusion, hypoxia, and increased lactate due to enhanced glycolysis, competitively inhibiting renal clearance of UA and resulting in increased UA levels. Hyperuricemia increases inflammation, endothelial dysfunction, and oxidative stress contribute to the progression of cardiovascular disorders.[8] Recent studies have found that monosodium urate (MsU) crystals induce interleukin-1-dependent pro-inflammatory responses in human trophoblast cells and placental explants, accompanied by apoptosis of trophoblast cells and reduced syncytialization[9]. This suggests that UA may directly affect the fetus, and excessive UA deposition in the placenta can lead to the impairment of fetal growth. Nuclear factor-κB (NF-κB) plays a critical role in endothelial dysfunction by mediating inflammatory responses and oxidative stress.

Upon activation by stressors such as elevated uric acid, NF-κB translocates to the nucleus, where it binds to DNA and promotes the transcription of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and adhesion molecules (e.g., VCAM-1, ICAM-1). This leads to endothelial cell activation, increased vascular permeability, and leukocyte recruitment, contributing to vascular inflammation. Additionally, NF-κB activation stimulates reactive oxygen species (ROS) production, further damaging endothelial cells and impairing endothelial nitric oxide synthase (eNOS) activity, resulting in reduced nitric oxide availability. The imbalance between vasodilators and vasoconstrictors, coupled with vascular smooth muscle proliferation, ultimately increases vascular tone and promotes hypertension. Understanding these mechanisms highlights the significance of NF-κB in the pathophysiology of hyperuricemia-related endothelial dysfunction and its adverse cardiovascular implications.

Currently, the mechanisms underlying the relation between hyperuricemia and adverse pregnancy consequences remain unclear in clinical practice, necessitating further research to establish their link. Some studies suggest that during early pregnancy, elevated UA levels can induce placental inflammation and dysfunction, leading to APOs.[10] However, research on the correlation between UA in the early stages of pregnancy and unfavorable outcomes is limited, and there is a lack of authoritative conclusions for reference, which hinders the provision of guiding principles for clinical management. Therefore, the current study aimed to analyze the link between early pregnancy SUA levels and APOs and explore the predictive value of early pregnancy SUA levels for APOs.

Methods

Ethical consideration

The Medical Ethics Committee of Xiaolan People's Hospital of Zhongshan has granted approval for this research (Approval No: ZSXL-LL2020-009).

Study population

A retrospective study was conducted on the cohort data of pregnant women who were hospitalized for delivery at Xiaolan People's Hospital in Zhongshan between January 2021 and December 2022. Data were collected from women who gave birth to singleton infants between 28 and 42 weeks of gestation and underwent serum biochemical testing in early pregnancy. Relevant data includes age,

body mass index (BMI), parity (number of previous pregnancies), and gestational age at delivery, newborn weight, and maternal outcomes were obtained from medical records and used solely for research purposes. Exclusion criteria were as follows: (1) multiple pregnancies; (2) comorbidities including cardiovascular diseases, endocrine disorders (including a history of chronic hypertension or diabetes before pregnancy), (3) history of liver or kidney diseases, infectious diseases, autoimmune diseases, or gout; (4) use of medications affecting UA metabolism during pregnancy.

Diagnostic criteria

The diagnostic criteria for gestational hypertension and preeclampsia during pregnancy were based on the 9th edition of "Obstetrics and Gynecology" published by the People's Health Publishing House. A PTB was characterized as the delivery of a baby before reaching 37 weeks of gestation. The definition of gestational diabetes was established according to the "Guidelines for the Diagnosis and Treatment of Gestational Diabetes (2022)" by the Chinese Society of Perinatal Medicine. Fetal growth restriction was characterized according to the "Expert Consensus on the Diagnosis and Treatment of Fetal Growth Restriction (2019)" by the Chinese Society of Perinatal Medicine. Low birth weight refers to a newborn weighing < 2500 g. Small for gestational age (SGA) is defined as a newborn whose birth weight falls below the 10th percentile for their gestational age.

Sample collection

Serum samples were collected from fasting participants in early pregnancy (8–12 weeks) via venipuncture, centrifuged, and stored at -80°C before analysis. To control for confounders in logistic regression, adjustments were made for maternal age, pre-pregnancy BMI, history of hypertension, diabetes, smoking status, and socioeconomic factors, allowing for an independent assessment of SUA's predictive value for APOs."
"SUA levels were measured using an enzymatic colorimetric assay on the Roche Cobas c702 analyzer, which utilizes the uricase-peroxidase method for quantifying uric acid concentrations in serum samples. In this assay, uric acid is first oxidized by uricase to produce allantoin and hydrogen peroxide. The hydrogen peroxide then reacts with a chromogenic substrate in the presence of peroxidase, producing a color change proportional to the uric acid concentration. Absorbance was measured at 520 nm, with results expressed in μmol/L. This method offers high sensitivity and specificity, with a detection range of 50-800 μmol/L and intra-assay and inter-assay coefficients of variation below 3%."

Statistical analysis

The data were analyzed using IBM's Statistic Package for Social Science (SPSS) version 22.0 software, located in Armonk, NY, USA. The data that adhered to a normal distribution were presented as the mean the standard deviation (± s) and were examined using t-tests. On the other hand, the data that did not follow a normal distribution were characterized as the median along with the 25th and 75th percentiles (P25, P75) and were analyzed using the Kruskal-Wallis test. Categorical data were reported as frequencies and percentages, with group comparisons performed using the chi-square test. Univariate and multivariate binary logistic regression (LR) analysis were performed to determine the variables that influence unfavorable pregnancy outcomes. Variables that displayed statistically significant differences ($p < 0.1$) in the univariate LR analysis were included in the Multivariate LR (MLR) analysis. Differences with a p-value < 0.05 were considered to be statistically significant. Multiple regression analysis was used to investigate the influence of SUA levels during early pregnancy on SGA, infant birth weight, FGR, gestational hypertension, and gestational diabetes. Risk factors for adverse outcomes and the interaction between these factors and UA were investigated.

Results

Comparison of clinical data

The study included 4,240 pregnant women, of whom 295 (6.9%) were diagnosed with hyperuricemia (HUA), defined as UA levels greater than 360 μmol/L (HUA, UA > 360 μmol/L). The HUA group had an increased BMI as compared to the non-HUA group, with measurements of 22.45 (20.11, 25.01) versus 21.34 (19.53, 23.81), a higher proportion of hypertension at 6.1% vs. 3.4%, PTB at 10.2% vs. 6.3%, and low birth weight infants at 10.2% vs. 5.9%, with $p < 0.05$.

Table 1: Comparison of basic characteristics between hyperuricemia and non-hyperuricemia groups

Parameter	Control Group (n = 3945)	Hyperuricemia Group (n = 295)	*p*-value
Age (years, M (P25, P75))	30 (26, 33)	30 (27, 33)	0.911
BMI (kg/m2, M (P25, P75))	21.34 (19.53, 23.81)	22.45 (20.11, 25.01)	<0.001
Gravidity (times, M (P25, P75))	2 (1, 3)	2 (1, 3)	0.838
Parity (times, M (P25, P75))	2 (1, 2)	2 (1, 2)	0.374
Birth weight (g, M (P25, P75))	3170 (2900, 3440)	3180 (2877.5, 3450)	0.880
Neonatal asphyxia (n/%)	9 (0.2%)	2 (0.7%)	0.175
Gestational hypertension (n/%)	136 (3.4%)	18 (6.1%)	0.034
Primary hypertension (n/%)	35 (0.9%)	3 (1.0%)	0.746
Low birth weight (n/%)	234 (5.9%)	30 (10.2%)	0.006
Diabetes mellitus (n/%)	1292 (32.8%)	104 (35.3%)	0.404
Oligohydramnios (n/%)	265 (6.7%)	17 (5.8%)	0.754
Polyhydramnios (n/%)	29 (0.7%)	1 (0.3%)	0.640
Placental abruption (n/%)	32 (0.8%)	3 (8.6%)	0.871
PTB (n/%)	249 (6.3%)	30 (10.2%)	0.035
IVF (n/%)	87 (2.7%)	10 (3.4%)	0.435
Nephritis (n/%)	1 (0%)	0 (0%)	0.866
Hepatitis (n/%)	19 (0.5%)	2 (0.7%)	0.844
Thalassemia (n/%)	346 (8.8%)	31 (10.5%)	0.578
Hyperthyroidism (n/%)	28 (0.7%)	1 (0.3%)	0.664
Hypothyroidism (n/%)	170 (4.3%)	13 (4.4%)	0.928
Hypertension (n/%)	321 (8.2%)	35 (11.9%)	0.025

Table 2: Logistic regression analysis of risk factors for gestational hypertensive disorders

Variable	Univariate		Multivariate	
	OR (95%CI)	P	OR (95%CI)	P
Uric acid	0.99 (0.99 ~ 0.99)	0.002	0.99 (0.99 ~ 0.99)	0.048
Age	0.96 (0.94 ~ 0.98)	<.001	0.99 (0.96 ~ 1.01)	0.387
BMI	0.86 (0.84 ~ 0.89)	<.001	0.88 (0.85 ~ 0.90)	<.001
Parity	0.99 (0.92 ~ 1.06)	0.791		
Gravidity	0.98 (0.85 ~ 1.12)	0.780		
Diabetes mellitus	1.86 (1.49 ~ 2.32)	<.001	1.39 (1.10 ~ 1.76)	0.006
Oligohydramnios	1.38 (0.93 ~ 2.03)	0.109		
Polyhydramnios	5.84 (2.69 ~ 12.65)	<.001	4.02 (1.80 ~ 8.95)	<.001
IVF	1.93 (1.08 ~ 3.45)	0.026	2.02 (1.12 ~ 3.67)	0.020
Thalassemia	1.61 (1.16 ~ 2.24)	0.005	1.75 (1.25 ~ 2.45)	0.001
Hypothyroidism	1.28 (0.78 ~ 2.08)	0.325		
Hyperthyroidism	1.30 (0.39 ~ 4.34)	0.667		

In the HUA group, the mean BMI was 22.45 (20.11, 25.01), the proportion of hypertension was 6.1%, the rate of PTB was 10.2%, and the rate of low-birth-weight infants was 10.2%, which were greater than those in the non-HUA group (BMI: 21.34 (19.53, 23.81), hypertension: 3.4%, PTB: 6.3%, low birth weight: 5.9%). The *p*-value was < 0.05. See Table 1.

Risk factors analysis for APOs

Gestational hypertensive disorders

Through multiple LR analysis, risk factors for gestational hypertensive disorders include UA (OR = 0.99, 95% CI 0.99 - 0.99), BMI (OR = 0.88, 95% CI 0.85 - 0.90), diabetes mellitus (OR = 1.39, 95% CI 1.10 - 1.76),

Table 3: Logistic Regression Analysis of Factors Influencing PTB

Variable	Univariate		Multivariate	
	OR (95%CI)	P	OR (95%CI)	P
Uric acid	0.99 (0.99 ~ 0.99)	<.001	0.99 (0.99 ~ 0.99)	<.001
Age	0.94 (0.92 ~ 0.97)	<.001	0.97 (0.94 ~ 1.00)	0.077
BMI	0.97 (0.94 ~ 1.00)	0.058	1.03 (0.99 ~ 1.07)	0.109
Parity	0.89 (0.83 ~ 0.96)	0.003	0.94 (0.86 ~ 1.02)	0.138
Gravidity	0.89 (0.77 ~ 1.04)	0.137		
Diabetes mellitus	2.69 (2.10 ~ 3.43)	<.001	2.56 (1.97 ~ 3.33)	<.001
Oligohydramnios	0.84 (0.50 ~ 1.42)	0.520		
Polyhydramnios	1.64 (0.49 ~ 5.44)	0.422		
IVF	1.91 (1.01 ~ 3.62)	0.049	1.67 (0.85 ~ 3.25)	0.136
Thalassemia	0.97 (0.63 ~ 1.50)	0.893		
Hypothyroidism	0.47 (0.21 ~ 1.07)	0.072	0.35 (0.15 ~ 0.82)	0.016
Hyperthyroidism	2.37 (0.82 ~ 6.88)	0.112		
Hypertension	0.28 (0.18 ~ 0.43)	<.001	0.27 (0.17 ~ 0.42)	<.001

Table 4: Logistic regression analysis of factors influencing low birth weight

Variable	Univariate		Multivariate	
	OR (95%CI)	P	OR (95%CI)	P
Uric acid	0.99 (0.99 ~ 0.99)	<.001	0.99 (0.99 ~ 0.99)	<.001
Age	0.99 (0.96 ~ 1.02)	0.467		
BMI	0.99 (0.96 ~ 1.03)	0.772		
Parity	1.09 (1.00 ~ 1.19)	0.051	1.23 (1.11 ~ 1.37)	<.001
Gravidity	1.10 (0.93 ~ 1.29)	0.262		
Diabetes mellitus	1.84 (1.43 ~ 2.36)	<.001	1.12 (0.81 ~ 1.54)	0.505
Oligohydramnios	1.66 (1.09 ~ 2.52)	0.018	2.10 (1.27 ~ 3.46)	0.004
Polyhydramnios	0.53 (0.07 ~ 3.93)	0.537		
IVF	2.25 (1.21 ~ 4.18)	0.010	1.82 (0.83 ~ 4.02)	0.137
Thalassemia	1.30 (0.87 ~ 1.94)	0.202		
Hypothyroidism	1.47 (0.87 ~ 2.50)	0.152		
Hyperthyroidism	1.81 (0.54 ~ 6.02)	0.336		
PTB	43.46 (32.08 ~ 58.87)	<.001	44.71 (32.10 ~ 62.27)	<.001
Hypertension	0.18 (0.12 ~ 0.26)	<.001	0.21 (0.13 ~ 0.36)	<.001

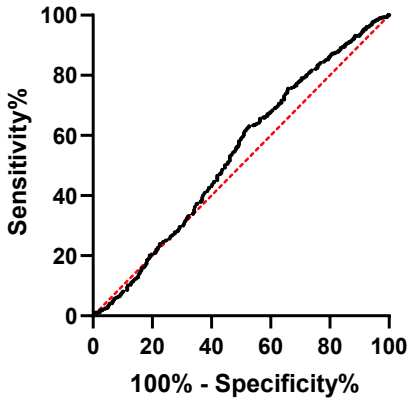

Figure 1: ROC Curve of risk factors for gestational hypertensive disorders

polyhydramnios (OR = 4.02, 95% CI 1.80 - 8.95), in vitro fertilization (OR = 2.02, 95% CI 1.12 - 3.67), and thalassemia (OR = 1.75, 95% CI 1.25 - 2.45). Refer to Table 2.

Through ROC curve analysis, the optimal threshold for predicting high UA was 288.915, with a sensitivity of 39.5%, specificity of 74%, and Youden index (*J*) of 0.135. Refer to Figure 1.

PTB

Through multiple LR analysis, risk factors for PTB include elevated UA (OR= 0.99, 95% CI 0.99 - 0.99), diabetes mellitus (OR = 2.56, 95% CI 1.97 - 3.33), hypothyroidism (OR = 0.35, 95% CI 0.15 - 0.82), hypertension (OR = 0.27, 95% CI 0.17 - 0.42). Refer to Table 3.

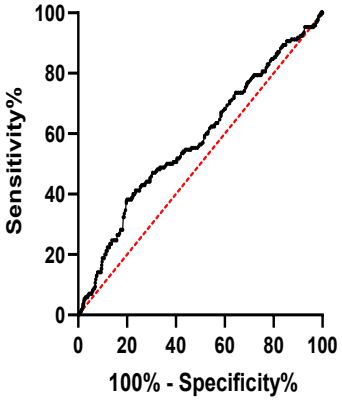

Figure 2: ROC Curve of risk factors for PTB

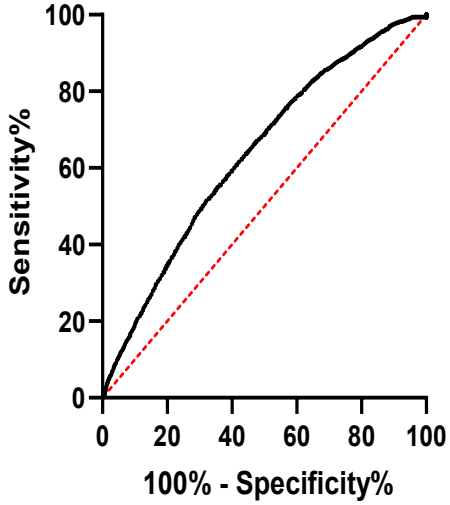

Figure 3: ROC Curve risk factors for low birth weight

Through ROC curve analysis, the optimal threshold for predicting high UA was 253.855, with a sensitivity and specificity of 71.4% and 55.2% respectively, and a J = 0.266. Refer to Figure 2.

Low birth weight

Through MLR analysis, risk factors for low birth weight include UA (OR = 0.99, 95% CI 0.99 - 0.99), oligohydramnios (OR = 2.10, 95% CI 1.27 - 3.46), PTB (OR = 44.71, 95% CI 32.10 - 62.27), and hypertension (OR = 0.21, 95% CI 0.13 - 0.36). See Table 4. Using ROC curve analysis, the optimal threshold for predicting high UA was 289.85, with a sensitivity of 41.6% and specificity of 74.4%, yielding an area under the curve of 0.16. See Figure 3.

Discussion

The high morbidity rates of APOs such as gestational hypertension, PTB, and low birth weight pose significant public health challenges and have long-term effects for maternal health. Identifying the etiology of these conditions, early detection, and timely intervention during early pregnancy is of paramount importance in preventing the occurrence of these diseases and improving overall population health. Elevated SUA levels during pregnancy can influence the occurrence and progression of various pregnancy complications and may lead to APOs.

Some studies suggest that UA serves as an important endogenous antioxidant, exerting protective effects against oxidative stress-induced damage to the cardiovascular system.[11] The UA functions by inhibiting protein nitrosylation mediated by peroxynitrite, as well as lipid and protein peroxidation, and tetrahydrobiopterin inactivation, thereby acting as a chelator of metal ions and a scavenger of free radicals.[12] Administration of soluble UA to healthy subjects has been reported to reduce the generation of reactive oxygen species (ROS) in the body.[13] However, clinical practice and laboratory research indicate that UA predominantly displays pro-oxidant and pathogenic effects. The UA is known to play a crucial role in the development of gout and kidney stones. Elevated SUA level is also strongly linked to the onset of chronic cardiovascular diseases, hypertension, diabetes, coronary heart disease, and chronic kidney disease. For these conditions, if accompanied by hyperuricemia, the administration of UA-lowering agents leads to improvement or alleviation of symptoms.[14] Moreover, numerous laboratory studies have mechanistically demonstrated the pro-oxidative damage caused by UA. Oxidative stress response is the initial reaction of cells exposed to a UA environment. The UA mediates the generation of ROS, leading to imbalanced nitric oxide production, insulin resistance, renin-angiotensin system activation, and fat accumulation. Animal models of hyperuricemia gradually develop symptoms of hypertension, accompanied by increased oxidative stress response, which can be alleviated by antioxidant therapy. The majority of cell experiments, including those involving endothelial cells, renal tubular cells, hepatocytes, adipocytes,

etc., have demonstrated the oxidative stress damage caused by UA.[15-19]

Various studies have proposed different conclusions regarding the adverse effects of UA on pregnancy outcomes. One study indicated that UA could inhibit amino acid transport within the placenta, leading to intrauterine growth restriction in fetuses.[20] In early pregnancy, UA concentrations are dependent on reduced trophoblast invasion function and decreased invasion into the uterine vascular endothelial cell layer, resulting in incomplete placental development.[21, 22] In late pregnancy, UA salt crystals activate the NOD-like receptor protein 3 (NLRP3) inflammasome pathway dependent on interleukin (IL)-1β released by leukocytes. This activation leads to inflammation at the placental interface, which in turn affects the development of the fetus.[23,24] Some studies have also shown that UA can stimulate the expression of nuclear factor kappa B, mitogen-activated protein kinase, and cyclooxygenase-2 (COX-2), contributing to fetal growth restriction and the occurrence of conditions such as preeclampsia.[25] In conclusion, both mechanistic insights and clinical evidence suggest that UA -induced placental inflammation and dysfunction are significant pathogenic mechanisms leading to APOs.

There is currently no unified standard for the average level of UA in healthy women during early pregnancy. In early pregnancy, the increased estrogen levels, increased glomerular filtration rate, and reduced tubular reabsorption led to increased UA excretion, resulting in a decrease in blood UA compared to pre-pregnancy levels. In mid to late pregnancy, fetal excretion of UA through the amniotic fluid increases, and the kidney's ability to clear UA decreases, which may result in elevated UA levels.[26]

The present study identified the correlation between UA levels in early pregnancy and APOs. Research has indicated that elevated uric acid levels in early pregnancy are linked with an increased risk of PTB, pregnancy-induced hypertension, and low birth weight. The metabolic status during fetal development can have a lasting impact on the body's metabolism and serve as the origin of many adult-onset diseases. Multivariate regression analyses in this study consistently demonstrated that increased UA levels in early pregnancy were independent risk factors for pregnancy-induced hypertension, PTB, and low birth weight. Elevated UA levels during pregnancy are associated with long-term outcomes for both the mother as well as newborn.[27] Screening for hyperuricemia during pregnancy is necessary as it has the potential to be a successful approach in lowering the incidence of APOs and enhancing prognosis.

Due to the lack of large-scale epidemiological research data, there is currently no unified standard for the treatment initiation and target goals for hyperuricemia during pregnancy.[28,29] The available treatment options for hyperuricemia during pregnancy are extremely limited. Interventions such as alkalinization of urine, increased fluid intake (recommended daily intake > 2000 mL), and promoting urination are feasible and safe measures for managing hyperuricemia during pregnancy.[30] Based on the correlation between hyperuricemia during pregnancy and pregnancy-induced hypertension, PTB, and low birth weight, early prevention, timely non-pharmacological interventions, and elimination of precipitating factors play a more practical role in preventing the occurrence and development of APOs caused by hyperuricemia during pregnancy.

Conclusion

The findings indicating a serum uric acid (SUA) threshold of 253.855 μmol/L as a predictor for preterm birth offer a preliminary reference point for clinicians assessing early pregnancy risk profiles. Although this threshold demonstrates moderate sensitivity (71.4%) and specificity (55.2%), clinicians should interpret it as an indicator of increased risk rather than a definitive predictive tool, given the moderate predictive power. The SUA level could be integrated into a broader set of early screening markers to help identify patients at higher risk for adverse pregnancy outcomes (APOs) and enable closer monitoring, early intervention, or preventive measures, especially for those with additional risk factors like elevated BMI or preexisting hypertension. However, the moderate sensitivity and specificity values highlight that SUA alone is insufficient as a stand-alone predictor for clinical decision-making.

While SUA measurement is accessible and cost-effective, more research is needed to validate this threshold across diverse populations and in combination with other

biomarkers. Studies exploring larger cohorts, varied demographics, and multi-biomarker panels could strengthen the clinical utility of SUA and potentially inform future guidelines. For now, clinicians may consider SUA levels as part of an individualized risk assessment approach, pending further research to confirm and refine these findings for clinical guideline recommendations.

Funding

This work was supported by The Predictive effect of serum and urine uric acid determination at different gestational weeks on the occurrence and development of hypertensive diseases during pregnancy (Zhongshan Science and Technology Bureau (No.2020B1055)).

Conflict of interests

The authors declared no conflict of interest.

References

1. de Oliveira EP and Burini RC. High plasma uric acid concentration: causes and consequences. Diabetol Metab Syndr 2012; 4: 12.
2. Tangeras LH, Austdal M, Skrastad RB, Tangerås LH, Austdal M, Skråstad RB, Salvesen KÅ, Austgulen R, Bathen TF and Iversen AC. Distinct First Trimester Cytokine Profiles for Gestational Hypertension and Preeclampsia. Arterioscl Throm Vas 2015; 35(11): 2478-2485.
3. Pleskacova A, Bartakova V, Chalasova K, Pacal L, Kankova K and Tomandl J. Uric Acid and Xanthine Levels in Pregnancy Complicated by Gestational Diabetes Mellitus-The Effect on Adverse Pregnancy Outcomes. Int J Mol Sci 2018; 19(11): 3696.
4. Wu Y, Xiong X, Fraser WD and Luo ZC. Association of uric acid with progression to preeclampsia and development of adverse conditions in gestational hypertensive pregnancies. Am J Hypertens 2012; 25(6): 711-717.
5. Leng J, Wang L, Wang J, Li W, Liu H, Zhang S, Li L, Tian H, Xun P, Yang X and Yu Z. Uric acid and diabetes risk among Chinese women with a history of gestational diabetes mellitus. Diabetes Res Clin Pr 2017; 134: 72-79.
6. Zhen H and Gui F. The role of hyperuricemia on vascular endothelium dysfunction. Biomed Rep 2017; 7(4): 325-330.
7. Wang SF, Shu L, Wang S, Wang XQ, Mu M, Hu CQ, Liu KY, Zhao QH, Hu AL, Bo QL and Tao FB. Gender difference in the association of hyperuricemia with hypertension in a middle-aged Chinese population. Blood Pressure 2014; 23(6): 339-344.
8. Wang J, Tan GJ, Han LN, Bai YY, He M and Liu HB. Novel biomarkers for cardiovascular risk prediction. J Geriatr Cardiol 2017; 14(2): 135-150.
9. Brien ME, Duval C, Palacios J, Boufaied I, Hudon-Thibeault AA, Nadeau-Vallée M, Vaillancourt C, Sibley CP, Abrahams VM, Jones RL and Girard S. Uric Acid Crystals Induce Placental Inflammation and Alter Trophoblast Function via an IL-1-Dependent Pathway: Implications for Fetal Growth Restriction. J Immunol 2017; 198(1): 443-451.
10. Murata M, Fukushima K, Takao T, Seki H, Takeda S and Wake N. Oxidative stress produced by xanthine oxidase induces apoptosis in human extravillous trophoblast cells. J Reprod Develop 2013; 59(1): 7-13.
11. Pasalic D, Marinkovic N and Feher-Turkovic L. Uric acid as one of the important factors in multifactorial disorders--facts and controversies. Biochem Medica 2012; 22(1): 63-75.
12. Kang DH and Ha SK. Uric Acid Puzzle: Dual Role as Anti-oxidantand Pro-oxidant. Electrolyte Blood Press 2014; 12(1): 1-6.
13. Waring WS, Webb DJ and Maxwell SR. Systemic uric acid administration increases serum antioxidant capacity in healthy volunteers. J Cardiovasc Pharm 2001; 38(3): 365-371.
14. Sharaf EDU, Salem MM and Abdulazim DO. Uric acid in the pathogenesis of metabolic, renal, and cardiovascular diseases: A review. J Adv Res 2017; 8(5): 537-548.
15. Corry DB, Eslami P, Yamamoto K, Nyby MD, Makino H and Tuck ML. Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin-angiotensin system. J Hypertens 2008; 26(2): 269-275.
16. Petrasek J, Iracheta-Vellve A and Saha B. Metabolic danger signals, uric acid and ATP, mediate inflammatory cross-talk between hepatocytes and immune cells in alcoholic liver disease. J Leukocyte Biol 2015; 98(2): 249-256.
17. Yu MA, Sanchez-Lozada LG, Johnson RJ and Kang DH. Oxidative stress with an activation of the renin-angiotensin system in human vascular endothelial cells as a novel mechanism of uric acid-induced endothelial dysfunction. J Hypertens 2010; 28(6): 1234-1242.
18. Sodhi K, Hilgefort J, Banks G, Gilliam C, Stevens S, Ansinelli HA, Getty M, Abraham NG, Shapiro JI and Khitan Z. Uric Acid-Induced Adipocyte Dysfunction Is Attenuated by HO-1 Upregulation: Potential Role of Antioxidant Therapy to Target Obesity. Stem Cells Int 2016; 2016: 8197325.
19. Ryu ES, Kim MJ, Shin HS, Jang YH, Choi HS, Jo I, Johnson RJ and Kang DH. Uric acid-induced phenotypic transition of renal tubular cells as a novel mechanism of chronic kidney disease. Am J Physiol-Renal 2013; 304(5): F471-F480.
20. Bainbridge SA, von Versen-Hoynck F and Roberts JM. Uric acid inhibits placental system A amino acid uptake. Placenta 2009; 30(2): 195-200.
21. Bainbridge SA, Roberts JM, von Versen-Hoynck F, Koch J, Edmunds L and Hubel CA. Uric acid attenuates trophoblast invasion and integration into endothelial

cell monolayers. Am J Physiol-Cell Ph 2009; 297(2): C440-C450.
22. Mulla MJ, Salmon JE, Chamley LW, Brosens JJ and Boeras CM, Kavathas PB and Abrahams VM. A role for uric acid and the Nalp3 inflammasome in antiphospholipid antibody-induced IL-1beta production by human first trimester trophoblast. Plos One 2013; 8(6): e65237.
23. Owen JC, Garrick SP, Peterson BM, Berger PJ, Nold MF, Sehgal A and Nold-Petry CA. The role of interleukin-1 in perinatal inflammation and its impact on transitional circulation. Front Pediatr 2023; 11: 1130013.
24. Shirasuna K, Karasawa T and Takahashi M. Role of the NLRP3 Inflammasome in Preeclampsia. Front Endocrinol 2020; 11: 80.
25. Kanellis J, Watanabe S, Li JH, Kang DH, Li P, Nakagawa T, Wamsley A, Sheikh-Hamad D, Lan HY, Feng L and Johnson RJ. Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. Hypertension 2003; 41(6): 1287-1293.
26. Cheung KL and Lafayette RA. Renal physiology of pregnancy. Adv Chronic Kidney D 2013; 20(3): 209-214.
27. Hromadnikova I, Kotlabova K, Dvorakova L and Krofta L. Maternal Cardiovascular Risk Assessment 3-to-11 Years Postpartum in Relation to Previous Occurrence of Pregnancy-Related Complications. J Clin Med 2019; 8(4): 544.
28. Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castañeda-Sanabria J, Coyfish M, Guillo S, Jansen TL, Janssens H and Lioté F. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 2017; 76(1): 29-42.
29. Cnossen JS, de Ruyter-Hanhijarvi H, van der Post JA, Mol BW, Khan KS and ter Riet G. Accuracy of serum uric acid determination in predicting pre-eclampsia: a systematic review. Acta Obstet Gyn Scan 2006; 85(5): 519-525.
30. Flint J, Panchal S, Hurrell A, van de Venne M, Gayed M, Schreiber K, Arthanari S, Cunningham J, Flanders L, Moore L and Crossley A. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology 2016; 55(9): 1693-1697.