Association Between Serum Uric Acid Levels and Premature Rupture of Membranes at Adam Malik Hospital and Affiliated Hospitals

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Abstract

Premature rupture of membranes (PROM) is an important obstetric complication associated with adverse maternal and neonatal outcomes. Oxidative stress and degradation of the fetal membrane extracellular matrix are recognized mechanisms involved in membrane weakening and rupture. Serum uric acid (SUA) is an endogenous antioxidant that may protect against oxidative damage; however, both excessively low and elevated SUA concentrations may be associated with adverse biological effects. Evidence regarding the relationship between maternal SUA and PROM remains limited and inconsistent, particularly in non-diabetic pregnant populations. This study aimed to compare maternal serum uric acid levels between pregnant women with and without PROM and to determine the association between SUA status and PROM. The study also evaluated the difference in body mass index (BMI) between the two groups and examined the distribution of overweight and obesity according to PROM status. An analytical cross-sectional study was conducted at Adam Malik Hospital, Prof. Dr. Chairuddin P. Lubis Hospital, and Pirngadi Regional General Hospital, Medan, from March to July 2025. Fifty pregnant women were included, comprising 25 women with PROM and 25 women without PROM, selected using consecutive sampling. Serum uric acid levels and BMI were assessed. Differences in continuous variables were analyzed using the Mann–Whitney U test, while categorical variables were analyzed using the Chi-square or Fisher's exact test, as appropriate. The median BMI was higher among women with PROM than among women without PROM (29.2 vs. 27.5 kg/m²; p = 0.001), representing an absolute difference of 1.7 kg/m². When the analysis was restricted to overweight and obese women, obesity was more frequent in the PROM group (11/25, 44%) than in the non-PROM group (4/22, 18.2%); however, this difference did not reach statistical significance using Fisher's exact test (p = 0.070). Median serum uric acid was substantially lower in the PROM group than in the non-PROM group (3.7 vs. 5.4 mg/dL; p = 0.001), corresponding to an absolute difference of 1.7 mg/dL or approximately 31.5% lower median SUA in the PROM group. Normal SUA levels were observed in 92.0% of women with PROM compared with 60.0% of women without PROM, whereas hyperuricemia was present in 8.0% and 40.0%, respectively (p = 0.008). Maternal serum uric acid levels were significantly lower among pregnant women with PROM than among those without PROM. The findings support a potential association between maternal SUA status and PROM, although causality cannot be established because of the cross-sectional design. Further prospective studies with larger sample sizes and adjustment for potential confounders are warranted.

Keywords: Serum Uric Acid, Premature Rupture of Membranes, Pregnancy, Oxidative Stress, Body Mass Index.

INTRODUCTION

Premature rupture of membranes (PROM), defined as rupture of the fetal membranes before the onset of labor, remains an important obstetric problem because it

is associated with maternal and neonatal morbidity. The clinical consequences depend on gestational age at membrane rupture and may include intra-amniotic infection, chorioamnionitis, preterm birth, neonatal infection, and prolonged hospitalization. PROM occurs in approximately 3–4% of pregnancies and contributes substantially to preterm birth and adverse perinatal outcomes (Garg & Jaiswal, 2023; Lin et al., 2024). The integrity of the fetal membranes depends largely on their collagen-rich extracellular matrix (ECM), which provides tensile strength and structural stability. Membrane rupture is influenced by inflammatory and biochemical processes that promote degradation of the ECM. In particular, inflammation can increase the activity of matrix metalloproteinases (MMPs), including MMP-2, MMP-8, and MMP-9, which degrade collagen and other ECM components. Increased MMP activity has been implicated in both physiological membrane rupture and pathological rupture associated with preterm PROM (Nguyen et al., 2023).

Oxidative stress is another mechanism that may contribute to fetal membrane weakening. An imbalance between reactive oxygen species and antioxidant defenses can promote cellular and extracellular matrix damage, thereby reducing membrane integrity. Previous studies have demonstrated increased oxidative stress and reduced antioxidant capacity in women with preterm PROM, supporting the role of oxidative-antioxidative imbalance in the pathophysiology of membrane rupture (Soydinc et al., 2013).

Uric acid is an important endogenous antioxidant in human plasma and contributes to the neutralization of reactive oxygen species. However, its biological effects are complex and may vary according to its concentration and cellular environment. While adequate uric acid concentrations may contribute to antioxidant defense, alterations in uric acid homeostasis may reflect or influence oxidative stress and inflammatory pathways (Sautin & Johnson, 2008).

The potential relationship between uric acid and PROM is biologically plausible. Reduced serum uric acid may indicate diminished antioxidant capacity, potentially increasing susceptibility of the fetal membranes to oxidative damage. Conversely, elevated uric acid may also be associated with oxidative and inflammatory processes under certain conditions. Therefore, the relationship between maternal serum uric acid and PROM may not simply reflect hyperuricemia but may involve the balance between antioxidant protection, oxidative stress, and membrane degradation. A previous cross-sectional study in pregnant women with gestational diabetes mellitus demonstrated an association between serum uric acid levels and PROM, supporting the possibility that uric acid may have a

protective role against membrane rupture (Guo et al., 2021).

Maternal nutritional and metabolic characteristics may further influence the risk of PROM. A recent systematic review and meta-analysis involving more than 18,000 participants identified several factors associated with PROM, including previous PROM, previous preterm birth, gestational diabetes, gestational hypertension, reproductive tract infection, and abnormal vaginal discharge. BMI was also associated with PROM, although the direction and magnitude of this association may vary across populations and BMI categories (Lin et al., 2024).

Despite the biological plausibility of the relationship between uric acid, oxidative stress, and fetal membrane integrity, evidence regarding the association between maternal serum uric acid and PROM remains limited, particularly among pregnant women in Indonesian clinical settings. Previous research has primarily evaluated uric acid in specific metabolic populations, such as women with gestational diabetes mellitus, leaving uncertainty regarding whether the observed association is applicable to pregnant women with PROM in broader clinical populations (Guo et al., 2021).

The present study therefore aimed to evaluate the association between maternal serum uric acid levels and the occurrence of PROM among pregnant women at Adam Malik Hospital and affiliated hospitals. In addition, the study evaluated the distribution of BMI categories and their association with PROM to provide a broader assessment of maternal factors potentially related to membrane rupture. We hypothesized that maternal serum uric acid levels would differ between women with and without PROM and that serum uric acid category would be significantly associated with PROM.

METHODS

Study design and setting

This analytical cross-sectional study was conducted at Adam Malik Hospital, Prof. Dr. Chairuddin P. Lubis Hospital, and Pirngadi Regional General Hospital, Medan, Indonesia, between March and July 2025. Participants were consecutively recruited and classified into two groups according to the presence or absence of PROM.

PROM was defined as spontaneous rupture of the fetal membranes before the onset of labor, based on clinical assessment documented by the attending obstetrician. Women with preterm PROM should be analyzed separately from term PROM when gestational age information is available.

Participants and eligibility criteria

Pregnant women diagnosed with PROM constituted the case group, while pregnant women without evidence of membrane rupture constituted the comparison group. Inclusion criteria were: (1) pregnant women who received obstetric care at the participating hospitals during the study period; (2) pregnancy with documented PROM for the PROM group or no evidence of PROM for the comparison group; (3) availability of serum uric acid measurement; and (4) complete clinical information regarding age, parity, and BMI. Exclusion criteria: Women with incomplete laboratory or clinical data were also excluded.

Sample size

A total of 50 participants were included, consisting of 25 women with PROM and 25 women without PROM. The sample size was determined to provide a minimum of 25 participants in each group based on the study design and the expected difference in serum uric acid between groups.

Statistical analysis

Continuous variables were assessed for distribution and presented as mean ± standard deviation or median with minimum–maximum values, as appropriate. Differences in BMI and serum uric acid concentrations between the PROM and non-PROM groups were assessed using the Mann–Whitney U test.

For categorical analyses, the association between SUA category and PROM was assessed using the Chi-square test. Fisher's exact test was used when expected cell frequencies were small. In accordance with the reviewer's suggestion, BMI categorical analysis was restricted to comparison between overweight and obese participants. Effect estimates were reported using absolute differences and odds ratios (ORs) with 95% confidence intervals (CIs), where appropriate. Potential confounding by age, BMI, and parity should be evaluated using multivariable logistic regression if individual-level data are available. Given the small number of PROM events, the number of covariates should be limited to avoid model overfitting.

A two-sided p-value <0.05 was considered statistically significant.

Ethical approval

Ethical approval was obtained from the Ethics Committee of Universitas Sumatera Utara with number No: 1398/ KEPK/USU/2024 before commencement of the study.

RESULTS

Of the 50 study subjects, 25 were pregnant women with PROM, and 25 were normal pregnant women. The distribution of subject characteristics is presented in Table 1.

Table 1. Characteristics of Respondents (n=50)

Variable	PROM (n) (%)	Normal (n) (%)	Total (n) (%)
Age			
< 20 years	0	1 (2%)	1 (2%)
20-30 years	19 (38%)	14 (28%)	33 (66%)
> 30 years	6 (12%)	10 (20%)	16 (32%)
BMI category			
Normal weight	0	3 (6%)	3 (6%)
Overweight	14 (28%)	18 (36%)	32 (64%)
Obese	11 (22%)	4 (8%)	15 (30%)
BMI, mean ± SD/median (min-max)	29.8 ± 1.7 / 29.2 (26.5-34.2)	27.8 ± 3.5 / 27.5 (18.5-38.7)	28.8 ± 2.9 / 28.7 (18.5-38.7)

Table 1 (continued)

Variable	PROM	Normal	Total
Parity, n (%)			
Primi / Secundi / Multi / Grandemulti	15 / 2 / 7 / 1	13 / 8 / 2 / 2	28 / 10 / 9 / 3
Serum uric acid, mean ± SD	4.1 ± 1.4	5.6 ± 1.4	4.9 ± 1.5
Serum uric acid, median (min-max)	3.7 (2.5-7.4)	5.4 (3.9-9.0)	4.6 (2.5-9.0)

Most respondents were aged 20-30 years (66%), had an overweight BMI category (64%), and were predominantly primigravida (56%). Mean serum uric acid was 4.1 ± 1.4 mg/dL in the PROM group and 5.6 ± 1.4 mg/dL in the normal pregnancy group.

Table 2. Difference in BMI by PROM Status

Variable	PROM	Normal	p-value
BMI, median (min-max)	29.2 (26.5-34.2)	27.5 (18.5-38.7)	0.001

**Mann-Whitney test*

Median BMI was significantly higher among women with PROM than among women without PROM (29.2 vs. 27.5 kg/m²; p = 0.001), with an absolute median difference of 1.7 kg/m². This difference represents approximately a 6.2% higher median BMI in the PROM group relative to the non-PROM group.

Table 3. Association Between BMI Category and PROM

BMI category	PROM (n) (%)	Normal (n) (%)	Total	p-value
Overweight	14 (56%)	18 (81.8%)	32	0.070
Obese	11 (44%)	4 (18.2%)	15	

**Fisher's Exact test*

Among participants with overweight or obesity, obesity was more frequent in the PROM group than in the non-PROM group (44.0% vs. 18.2%). However, the difference was not statistically significant when the analysis was restricted to overweight and obese participants (Fisher's exact test, p = 0.070). This finding suggests a possible trend toward a higher proportion of obesity among women with PROM, although the small sample size

limits statistical precision.

Table 4. Difference in Serum Uric Acid Levels Between Groups

Variable	PROM	Normal	p-value
Serum uric acid, median (min-max)	3.7 (2.5-7.4)	5.4 (3.9-9.0)	0.001

**Mann-Whitney test*

Median serum uric acid was significantly lower among women with PROM than among women without PROM (3.7 vs. 5.4 mg/dL; p = 0.001). The absolute median difference was 1.7 mg/dL, corresponding to approximately a 31.5% lower median SUA in the PROM group. This difference is potentially clinically relevant because serum uric acid contributes to systemic antioxidant capacity; however, the cross-sectional design prevents determination of whether lower SUA preceded or resulted from membrane rupture.

Table 5. Association Between Serum Uric Acid Category and PROM

Uric acid category	PROM (n) (%)	Normal (n) (%)	p-value
Normal	23 (92%)	15 (60%)	0.008
Hyperuricemia	2 (8%)	10 (40%)	

**Chi-square test*

Normal serum uric acid concentrations were more frequent among women with PROM than among women without PROM (92.0% vs. 60.0%), whereas hyperuricemia was more frequent in the non-PROM group (40.0% vs. 8.0%; p = 0.008). The unadjusted odds ratio for having normal SUA compared with hyperuricemia was 7.67 (95% CI 1.47–39.99), indicating a substantial association between SUA category and PROM. However, this estimate should be interpreted cautiously because of the small sample size and wide confidence interval.

DISCUSSION

This study demonstrated that maternal serum uric acid levels were significantly lower among pregnant women with PROM than among those without PROM (3.7 vs. 5.4 mg/dL; $p = 0.001$). This finding suggests that differences in maternal serum uric acid concentrations may be associated with fetal membrane integrity. Uric acid is an important endogenous antioxidant that contributes to the neutralization of reactive oxygen species, while oxidative stress has been implicated in the degradation of the extracellular matrix and weakening of the fetal membranes (Le et al., 2019; Menon, 2014).

The present finding is consistent with previous research by Guo et al., who reported that pregnant women with gestational diabetes mellitus and PROM had lower serum uric acid concentrations than those without PROM. Their study also demonstrated that higher serum uric acid levels were associated with a lower likelihood of PROM, suggesting a potential protective role of uric acid against membrane rupture (Guo et al., 2021). The

similarity between their findings and those of the present study supports the possibility that serum uric acid may contribute to the biological mechanisms involved in maintaining fetal membrane integrity

One possible explanation for this association is the antioxidant function of uric acid. At physiological concentrations, uric acid can scavenge reactive oxygen species and contribute to systemic antioxidant defense (Sautin & Johnson, 2008). Excessive oxidative stress may result in cellular injury, apoptosis, lipid peroxidation, and degradation of extracellular matrix components within the amnion and chorion. These processes may subsequently reduce the tensile strength of the fetal membranes and increase their susceptibility to rupture (Menon, 2014; Moore et al., 2018).

However, the relationship between serum uric acid and PROM is not necessarily linear. In contrast to the present findings, a retrospective cohort study reported that higher third-trimester serum uric acid concentrations were associated with an increased risk of PROM (Wu et al., 2022). This discrepancy may be related to differences in gestational age at measurement, maternal metabolic status, study population, and the concentration range of serum uric acid. At physiological concentrations, uric acid may function predominantly as an antioxidant, whereas elevated concentrations may be associated with oxidative stress, inflammation, and endothelial dysfunction (Lin et al., 2024; Sautin & Johnson, 2008).

The categorical analysis in the present study also demonstrated a significant association between serum uric acid status and PROM. Normal serum uric acid was more frequently observed in the PROM group, whereas hyperuricemia was more frequent in the non-PROM group ($p = 0.008$). This finding is consistent with the lower median serum uric acid observed in the PROM group. Nevertheless, the result should be interpreted cautiously because the number of participants with hyperuricemia was relatively small, which may result in an imprecise estimate of the association.

The observed difference in serum uric acid may also be influenced by physiological changes during pregnancy. Serum uric acid concentrations are affected by glomerular filtration, renal tubular handling, dietary intake, gestational age, and maternal metabolic status (Kang & Ha, 2014). Consequently, serum uric acid levels may vary considerably between pregnant women even in the absence of PROM. The cross-sectional design of the present study also prevents determination of whether lower serum uric acid preceded membrane rupture or occurred concurrently with the pathological process associated with PROM.

The present study also demonstrated a significant difference in BMI between the

two groups, with a higher median BMI among women with PROM than among women without PROM (29.2 vs. 27.5 kg/m²; p = 0.001). Maternal adiposity may influence inflammatory and oxidative pathways and may therefore contribute to fetal membrane vulnerability. Obesity has been associated with chronic low-grade inflammation, altered adipokine signaling, and increased oxidative stress, which may influence extracellular matrix remodeling and membrane integrity (Lin et al., 2024; Sun et al., 2023).

However, when BMI analysis was restricted to the overweight and obese categories, the difference in the proportion of obesity between the PROM and non-PROM groups was not statistically significant (p = 0.070). Therefore, the present findings do not provide sufficient evidence that obesity independently increases the risk of PROM. The discrepancy between the significant difference in continuous BMI and the non-significant categorical analysis may be related to the relatively small sample size and limited statistical power.

Previous studies have also reported inconsistent associations between BMI and PROM. A systematic review and meta-analysis identified several maternal risk factors for PROM but demonstrated variability in the direction and magnitude of associations according to BMI category and population characteristics (Huang et al., 2024; Sfregola et al., 2023). Other observational studies have suggested that maternal overweight or obesity may be associated with pregnancy complications through inflammatory and metabolic mechanisms (Lin et al., 2024). These differences highlight the importance of considering BMI together with other maternal and pregnancy-related factors rather than interpreting BMI as an isolated determinant of PROM.

The findings of this study may have potential clinical implications. Serum uric acid is relatively inexpensive and can be measured using routinely available laboratory methods. The observed difference between the PROM and non-PROM groups suggests that serum uric acid may have potential as an adjunctive biomarker for assessing maternal risk. However, based on the present cross-sectional study, serum uric acid should not be considered a standalone diagnostic or predictive test for PROM. Prospective studies are required to determine whether serum uric acid measured before membrane rupture can predict subsequent development of PROM.

The main strength of this study is that it directly compared serum uric acid concentrations between pregnant women with PROM and those without PROM and evaluated serum uric acid both as a continuous measurement and as a categorical variable. In addition, BMI was evaluated as an important maternal characteristic that may be related to PROM.

Several limitations should be acknowledged. First, the cross-sectional design prevents the determination of temporal and causal relationships between serum uric acid and PROM. Second, the sample size was relatively small, with only 25 participants in each group, limiting statistical power and generalizability. Third, potential confounding factors such as gestational age, maternal age, parity, infection, gestational diabetes, hypertensive disorders, renal function, nutritional status, and medication use were not comprehensively evaluated using multivariable analysis. Fourth, direct oxidative stress biomarkers and antioxidant enzymes were not measured; therefore, the proposed antioxidant mechanism cannot be directly confirmed by the present study.

Future research should involve larger prospective cohorts with serial measurements of serum uric acid throughout pregnancy. Studies should also distinguish term PROM from preterm PROM and evaluate potential confounders such as gestational age, BMI, infection, gestational diabetes, hypertensive disorders, and renal function. The inclusion of oxidative stress biomarkers, inflammatory markers, and matrix metalloproteinases would further clarify the biological pathway linking serum uric acid with fetal membrane integrity.

Overall, this study supports an association between maternal serum uric acid levels and PROM, with significantly lower serum uric acid concentrations observed among women with PROM. Nevertheless, the association should not be interpreted as causal. Further prospective and adequately powered studies are needed to determine whether serum uric acid has independent predictive value and whether it could eventually be incorporated into clinical risk assessment for PROM.

CONCLUSIONS

Maternal serum uric acid concentrations were significantly lower in pregnant women with PROM than in pregnant women without PROM, with a median difference of 1.7 mg/dL. Normal SUA concentrations were more frequently observed among women with PROM, whereas hyperuricemia was more frequent among women without PROM. These findings indicate a significant association between maternal SUA status and PROM in the study population.

Maternal BMI was also significantly higher among women with PROM. However, when BMI analysis was restricted to overweight and obese participants, the difference in obesity frequency did not reach statistical significance. Therefore, the association between BMI and PROM should be interpreted as a potential contributory factor rather than an independent determinant. Serum uric acid may have potential as an adjunctive biomarker for

identifying pregnant women who warrant closer assessment for PROM risk, but it should not yet be considered a standalone predictive marker. Because this study was cross-sectional and involved a small sample, the observed association should not be interpreted as evidence that low serum uric acid causes PROM. Prospective multicenter studies with larger sample sizes, standardized gestational-age specific SUA measurements, distinction between term PROM and PPROM, and adjustment for relevant confounding factors are required to establish the clinical and predictive significance of maternal SUA.

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