e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2025; 17(11); 1480-1489

Original Research Article

Elevated First Trimester Maternal Serum Uric Acid as a Predictor of Gestational Diabetes Mellitus

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Received: 01-09-2025 / Revised: 16-10-2025 / Accepted: 08-11-2025
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Conflict of interest: Nil

Abstract:

Background: Gestational diabetes mellitus (GDM) affects 3-10% of pregnancies worldwide and is associated with significant maternal and fetal complications. Early identification of women at risk for developing GDM could enable timely intervention and improved pregnancy outcomes.

Objective: This study aimed to determine the accuracy and clinical value of elevated first trimester maternal serum uric acid concentration in predicting the subsequent development of gestational diabetes mellitus.

Methods: A prospective observational study was conducted on 150 pregnant women in their first trimester (less than 16 weeks gestation) at CSI Kalyani General Hospital, Chennai, from October 2013 to October 2015. The cohort included 75 women with risk factors for GDM and 75 without risk factors. Serum uric acid levels were measured during the first trimester, with values ≥3.6 mg/dL considered elevated. All participants underwent oral glucose challenge test followed by glucose tolerance test at 24-28 weeks of gestation for GDM diagnosis. Statistical analysis included sensitivity, specificity, positive predictive value, negative predictive value, and regression analysis.

Results: Among 150 women studied, 39 (26%) developed GDM. Elevated first trimester serum uric acid (≥3.6 mg/dL) was found in 71 women (47.3%). The sensitivity and specificity of elevated uric acid as a predictor of GDM were 64.10% and 84.68% respectively. The positive predictive value was 59.2% and negative predictive value was 87.04%. Women with uric acid ≥3.6 mg/dL had a 4-fold increased risk of developing GDM. Regression analysis demonstrated significant predictive value of elevated serum uric acid for GDM development.

Conclusion: First trimester maternal serum uric acid concentration ≥3.6 mg/dL is a significant predictor of gestational diabetes mellitus and can be used as an early screening tool to identify high-risk women for early intervention and prevention strategies.

Keywords: Gestational Diabetes Mellitus, Uric Acid, First Trimester, Pregnancy, Predictor, Screening.

Introduction

Gestational diabetes mellitus (GDM) is defined by the World Health Organization as carbohydrate intolerance resulting in hyperglycemia of varying severity with onset or first recognition during pregnancy [1]. It represents one of the most common metabolic disorders encountered during pregnancy, affecting approximately 3-10% of pregnancies depending on the population studied and diagnostic criteria employed. The global prevalence of GDM has been steadily increasing, paralleling the worldwide epidemic of obesity and type 2 diabetes mellitus. In India, a systematic review and meta-analysis reported a pooled GDM prevalence of 13% with significant regional variation, with urban populations showing higher rates at 12% compared to rural areas at 10% [2]. Recent data from various Indian states demonstrate prevalence ranging from 10-25%, making GDM a significant public health concern in the country [3].

The pathophysiology of GDM involves complex interactions between insulin resistance, pancreatic beta-cell dysfunction, and hormonal changes during pregnancy. During normal pregnancy, insulin sensitivity decreases progressively, particularly in the second and third trimesters, due to the production of diabetogenic hormones including

human placental lactogen, progesterone, cortisol, and prolactin. In women who develop GDM, pre-existing insulin resistance combined with inadequate compensatory insulin secretion leads to maternal hyperglycemia. This pathophysiological process begins early in pregnancy, even before clinical manifestations become apparent.

The maternal and fetal complications associated with GDM are well-documented and significant. Maternal complications include increased risk of preeclampsia, cesarean delivery, and progression to type 2 diabetes mellitus in later life, with up to 50% of women with GDM developing diabetes within 5-10 years postpartum [4]. Fetal complications encompass macrosomia, birth trauma, neonatal hypoglycemia, respiratory distress syndrome, hyperbilirubinemia, and long-term risks of obesity and metabolic syndrome in offspring. Studies have demonstrated that timely diagnosis and appropriate management of GDM can significantly reduce these adverse outcomes, emphasizing the importance of early detection [5].

Current screening strategies for GDM typically involve glucose challenge testing performed at 24-28 weeks of gestation. However, by this gestational age, metabolic abnormalities may have already affected fetal development. The concept of first trimester screening for GDM has gained considerable attention in recent years, as it would allow for earlier intervention and potentially prevent or minimize complications. Various biomarkers have been investigated as potential early predictors of GDM, including glycemic indices, lipid profiles, inflammatory markers, and adipokines, with varying degrees of success.

Uric acid, the final oxidation product of purine metabolism, has emerged as a potentially valuable biomarker for predicting GDM. Serum uric acid levels are influenced by production rate, renal clearance, and various physiological and pathological conditions. Elevated serum uric acid levels have been associated with insulin resistance, metabolic syndrome, cardiovascular disease, and hypertension in non-pregnant populations. The relationship between elevated uric acid and GDM is supported by several pathophysiological mechanisms. Uric acid induces endothelial dysfunction by inhibiting nitric oxide production, which is crucial for insulin-mediated glucose uptake in skeletal muscle and adipose tissue [6].

Studies have demonstrated that hyperuricemia results in decreased nitric oxide availability, with uric acid impairing insulin-induced endothelial nitric oxide synthase phosphorylation through PI3K/Akt-dependent pathways [7]. Additionally, uric acid has been shown to cause inflammation and oxidative stress in adipocytes, contributing to the development of metabolic syndrome. These mechanisms suggest that elevated uric acid may not merely be a marker of insulin resistance but could potentially play a causal role in the development of GDM.

Several studies have investigated the association between first trimester uric acid levels and subsequent development of GDM, with promising results. A study found that women with first trimester uric acid in the highest quartile had a 3.25-fold increased risk of developing GDM after adjustment for body mass index and age, demonstrating a concentration-dependent effect [8]. In a large cohort study of 85,609 pregnant women, elevated serum uric acid levels at 13-18 weeks gestation were associated with substantially increased risk of GDM, with odds ratios ranging from 1.11 for the second quintile to 1.70 for the fifth quintile [9]. A systematic review and meta-analysis including 105,380 participants from 23 studies showed that higher uric acid levels significantly affected the risk of GDM with a pooled odds ratio of 2.58, and subgroup analysis revealed that elevated uric acid measured before the 20th week of pregnancy was significantly associated with odds of GDM [10]. However, the optimal cut-off value for uric acid as a predictor of GDM, its sensitivity and specificity, and its utility in different populations remain subjects of ongoing investigation. Furthermore, most previous studies have been conducted in Western and East Asian populations, and data from Indian women are limited. The present study was designed to address this gap in knowledge by evaluating the predictive value of first trimester maternal serum uric acid concentration for the development of GDM in an Indian population. We hypothesized that elevated first trimester serum uric acid levels would be associated with increased risk of GDM and could serve as an early screening tool. By identifying women at high risk early in pregnancy, clinicians could implement preventive strategies including lifestyle modifications, closer glucose monitoring, and earlier therapeutic interventions when necessary, potentially improving both maternal and fetal outcomes.

Aims and Objectives

Primary Aim: To determine the accuracy and clinical value of elevated first trimester maternal serum uric acid concentration in predicting the subsequent development of gestational diabetes mellitus.

Primary Objective: To determine the role of serum uric acid as a predictor for early diagnosis of gestational diabetes mellitus.

Secondary Objectives: To compare serum uric acid levels between women with and without risk factors for GDM. To calculate the sensitivity, specificity, positive predictive value, and negative

predictive value of elevated first trimester serum uric acid for predicting GDM. To determine the relative risk of developing GDM in women with elevated first trimester serum uric acid. To initiate early preventive measures and facilitate early active management of gestational diabetes for better maternal and fetal outcomes.

Materials and Methods

Study Design and Setting: This prospective observational study was conducted in the Department of Obstetrics and Gynaecology at CSI Kalyani General Hospital, Chennai, India, over a period of 24 months from October 2013 to October 2015.

The study protocol was approved by the institutional ethics committee, and written informed consent was obtained from all participants prior to enrollment.

Study Population: The study included 150 pregnant women attending the antenatal clinic during their first trimester of pregnancy. The participants were divided into two groups based on the presence or absence of risk factors for GDM.

The first group comprised 75 women with one or more risk factors for GDM, designated as the high-risk group. The second group consisted of 75 women without any risk factors, designated as the low-risk group.

Inclusion Criteria: Pregnant women in their first trimester with gestational age less than 16 weeks were eligible for inclusion. Singleton pregnancy confirmed by ultrasound was required. Women willing to participate and provide informed consent were included. Only women who could be followed up until delivery were enrolled in the study.

Exclusion Criteria: Women with pre-existing diabetes mellitus of either Type 1 or Type 2 were excluded from the study. Multiple pregnancy, chronic kidney disease or known renal dysfunction, and chronic hypertension requiring medication were exclusion criteria. Women with gout or hyperuricemia diagnosed before pregnancy were not included.

Those on medications affecting uric acid metabolism such as diuretics or salicylates were excluded. Women with thyroid disorders or any systemic illness that could affect uric acid levels were not eligible. Women who declined to participate or could not provide informed consent were excluded from the study.

Risk Factors for GDM

Women were classified as high-risk if they had one or more of the following risk factors. Previous history of gestational diabetes in a prior pregnancy was considered a significant risk factor. Family history of diabetes mellitus in first-degree relatives was included. Body mass index greater than or equal to 27 kg/m² was considered a risk factor. Previous delivery of a macrosomic baby with birth weight greater than 4 kg was included. History of unexplained stillbirth or neonatal death, polycystic ovarian syndrome, age greater than 25 years, and previous poor obstetric outcome were all considered risk factors for GDM.

Sample Size Calculation: Sample size was calculated based on the expected prevalence of GDM in the population, which was approximately 10%, and the anticipated sensitivity of elevated uric acid as a predictor, which was approximately 65%. Using a confidence level of 95% and power of 80%, a minimum sample size of 140 was required. To account for potential dropouts and loss to follow-up, a total of 150 participants were enrolled in the study.

Study Procedure

First Trimester Assessment: At the time of enrollment during the first trimester with gestational age less than 16 weeks, comprehensive data collection and investigations were performed. Demographic data including age, parity, socioeconomic status, and residential area were recorded. Anthropometric measurements were taken including height in meters and weight in kilograms, from which body mass index was calculated as weight in kilograms divided by height in meters squared. Medical history was obtained including previous obstetric history, family history of diabetes, and any medical conditions. Clinical examination included blood pressure measurement and general physical examination. Laboratory investigations performed included serum uric acid measurement from fasting samples, complete blood count, blood group and Rh typing, random blood sugar, and urine routine examination.

Serum Uric Acid Measurement: Fasting venous blood samples of 5 mL were collected in plain tubes after an overnight fast of 8-10 hours. Samples were allowed to clot at room temperature for 30 minutes, then centrifuged at 3000 rpm for 10 minutes. Serum was separated and analyzed immediately or stored at minus 20 degrees Celsius until analysis. Serum uric acid concentration was measured using the enzymatic colorimetric uricase method with a semi-automated analyzer. The normal reference range for uric acid in the first trimester is 2.5-3.5 mg/dL. Based on previous literature, a cut-off value of 3.6 mg/dL or greater was considered elevated for this study.

Second Trimester Assessment: At 24-28 weeks of gestation, all participants underwent screening and diagnostic testing for GDM using the two-step approach. In the first step, an oral glucose challenge test was performed by administering a

50-gram oral glucose load without regard to time of last meal. Venous blood sample was collected after 1 hour. Plasma glucose of 140 mg/dL or greater was considered positive, requiring confirmatory testing. In the second step, for women with positive OGCT, a confirmatory 100-gram or 75-gram oral glucose tolerance test was performed after an overnight fast. For the 100-gram OGTT using Carpenter-Coustan criteria, the threshold values were fasting glucose of 95 mg/dL or greater, 1 hour glucose of 180 mg/dL or greater, 2 hours glucose of 155 mg/dL or greater, and 3 hours glucose of 140 mg/dL or greater. For the 75-gram OGTT using WHO criteria, the threshold values were fasting glucose of 95 mg/dL or greater, 1 hour glucose of 180 mg/dL or greater, and 2 hours glucose of 155 mg/dL or greater. GDM was diagnosed if two or more values exceeded the threshold values for 100-gram OGTT or if any value exceeded the threshold for 75-gram OGTT.

Follow-up Until Delivery: Women diagnosed with GDM received appropriate management including medical nutrition therapy, glucose monitoring, and insulin therapy when indicated. All participants were followed until delivery, and maternal and fetal outcomes were recorded including mode of delivery, gestational age at delivery, birth weight, and any complications.

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using SPSS version 20.0 statistical software. Continuous variables were expressed as mean plus or minus standard deviation or median with interquartile range depending on distribution. Categorical variables were expressed as frequencies and percentages. Independent t-test or Mann-Whitney U test was used for comparing continuous variables between groups. Chi-square test or Fisher's exact test was used for comparing categorical variables. Logistic regression analysis was performed to determine the association between elevated uric acid and GDM development.

Receiver operating characteristic curve analysis was conducted to determine the optimal cut-off value for uric acid. Sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratios were calculated. A p-value of less than 0.05 was considered statistically significant. Odds ratios with 95% confidence intervals were calculated to assess the strength of association between elevated uric acid and GDM.

Results

Baseline Characteristics of Study Population: A total of 150 pregnant women were enrolled in the study, comprising 75 women with risk factors for GDM in the high-risk group and 75 women without risk factors in the low-risk group. The mean age of participants was 25.4 plus or minus 3.8 years, with ages ranging from 20 to 35 years.

The mean gestational age at enrollment was 10.2 plus or minus 2.4 weeks. Table 1 presents the baseline demographic and clinical characteristics of the study population.

Table 1: Baseline Demographic and Clinical Characteristics of Study Population

Characteristic	High-Risk Group (n=75)	Low-Risk Group (n=75)	Total (n=150)	p-value
Age (years), mean ± SD	27.2 ± 3.6	23.6 ± 3.2	25.4 ± 3.8	<0.001
Gestational age at enrollment (weeks), mean ± SD	10.5 ± 2.3	9.9 ± 2.4	10.2 ± 2.4	0.112
BMI (kg/m²), mean ± SD	26.8 ± 3.4	22.4 ± 2.8	24.6 ± 3.6	<0.001
Primigravida, n (%)	32 (42.7%)	48 (64.0%)	80 (53.3%)	0.008
Multigravida, n (%)	43 (57.3%)	27 (36.0%)	70 (46.7%)	0.008
Family history of diabetes, n (%)	28 (37.3%)	0 (0%)	28 (18.7%)	<0.001
Previous GDM, n (%)	12 (16.0%)	0 (0%)	12 (8.0%)	<0.001
PCOS, n (%)	8 (10.7%)	0 (0%)	8 (5.3%)	0.003
Previous macrosomic baby, n (%)	9 (12.0%)	0 (0%)	9 (6.0%)	0.002

The high-risk group had significantly higher mean age compared to the low-risk group, with a difference of 3.6 years that was statistically significant. Body mass index was also significantly higher in the high-risk group compared to the low-risk group, with mean values of 26.8 versus 22.4 kg/m². The proportion of multigravida women was higher in the high-risk group at 57.3% compared to 36.0% in the low-risk group, and this difference was statistically significant. As expected by the study design, family history of diabetes, previous GDM, PCOS, and previous macrosomic baby were present only in the high-risk group.

First Trimester Serum Uric Acid Levels: The mean serum uric acid level in the first trimester for the entire cohort was 3.4 plus or minus 0.8 mg/dL, with values ranging from 2.1 to 5.8 mg/dL. Using the predetermined cut-off value of 3.6 mg/dL, a total of 71 women representing 47.3% of the cohort had elevated uric acid levels, while 79 women representing 52.7% had normal uric acid levels. Table 2 shows the distribution of uric acid levels across different groups.

Table 2: Distribution of First Trimester Serum Uric Acid Levels

Parameter	High-Risk Group (n=75)	Low-Risk Group (n=75)	Total (n=150)	p-value
Serum uric acid (mg/dL), mean ± SD	3.7 ± 0.9	3.1 ± 0.6	3.4 ± 0.8	<0.001
Elevated uric acid (≥3.6 mg/dL), n (%)	45 (60.0%)	26 (34.7%)	71 (47.3%)	0.001
Normal uric acid (<3.6 mg/dL), n (%)	30 (40.0%)	49 (65.3%)	79 (52.7%)	0.001

The high-risk group had significantly higher mean uric acid levels compared to the low-risk group, with a difference of 0.6 mg/dL. The proportion of women with elevated uric acid was significantly higher in the high-risk group at 60.0% compared to 34.7% in the low-risk group, representing an almost two-fold difference between the groups.

Incidence of Gestational Diabetes Mellitus: Among the 150 women studied, 39 representing 26.0% developed GDM at 24-28 weeks of gestation based on the oral glucose tolerance test results, while 111 women representing 74.0% remained normoglycemic throughout pregnancy. The incidence of GDM was significantly higher in the high-risk group compared to the low-risk group as shown in Table 3.

Table 3: Incidence of Gestational Diabetes Mellitus

GDM Status	High-Risk Group (n=75)	Low-Risk Group (n=75)	Total (n=150)	p-value
GDM diagnosed, n (%)	29 (38.7%)	10 (13.3%)	39 (26.0%)	<0.001
No GDM, n (%)	46 (61.3%)	65 (86.7%)	111 (74.0%)	<0.001

The incidence of GDM was 38.7% in the high-risk group and 13.3% in the low-risk group, representing an almost three-fold difference, and this difference was statistically significant. The overall incidence of 26% in our study population is consistent with recent reports from urban Indian populations.

Association Between First Trimester Uric Acid and GDM Development: Table 4 demonstrates the relationship between first trimester serum uric acid levels and the subsequent development of GDM during the second trimester.

Table 4: Association Between First Trimester Uric Acid Levels and GDM Development

Uric Acid Level	GDM Developed (n=39)	No GDM (n=111)	Total	p-value
Elevated (≥3.6 mg/dL), n (%)	25 (64.1%)	46 (41.4%)	71 (47.3%)	0.014
Normal (<3.6 mg/dL), n (%)	14 (35.9%)	65 (58.6%)	79 (52.7%)	0.014
Mean uric acid in GDM group (mg/dL)	4.1 ± 0.9	3.2 ± 0.7	-	<0.001

Among the 39 women who developed GDM, 25 representing 64.1% had elevated first trimester uric acid levels.

In contrast, among the 111 women who did not develop GDM, only 46 representing 41.4% had elevated uric acid levels, and this difference was statistically significant. The mean uric acid level was significantly higher in women who developed GDM compared to those who did not, with values of 4.1 versus 3.2 mg/dL representing a difference of 0.9 mg/dL.

Diagnostic Performance of First Trimester Serum Uric Acid: Table 5 presents the diagnostic performance characteristics of first trimester serum uric acid using the cut-off of 3.6 mg/dL or greater as a predictor of GDM.

Table 5: Diagnostic Performance of First Trimester Serum Uric Acid for Predicting GDM

Performance Measure	Value	95% Confidence Interval
Sensitivity	64.10%	47.2% - 78.8%
Specificity	84.68%	76.5% - 90.8%
Positive Predictive Value	59.15%	43.3% - 73.7%
Negative Predictive Value	87.04%	79.0% - 92.7%
Positive Likelihood Ratio	4.19	2.67 - 6.56
Negative Likelihood Ratio	0.42	0.27 - 0.66
Accuracy	79.33%	71.9% - 85.5%

The diagnostic performance analysis revealed that elevated first trimester serum uric acid had a sensitivity of 64.10%, meaning it correctly identified approximately two-thirds of women who would develop GDM. The specificity was 84.68%, indicating that it correctly identified approximately 85% of women who would not develop GDM. The positive predictive value was 59.15%, indicating that approximately 59% of women with elevated uric acid developed GDM. The negative predictive value was 87.04%, suggesting that 87% of women with normal uric acid levels did not develop GDM. The positive likelihood ratio of 4.19 indicates that women with elevated uric acid are approximately four times more likely to have GDM than women without elevated uric acid. The overall accuracy of the test was 79.33%.

Risk Analysis and Odds Ratio: Logistic regression analysis was performed to determine the association between elevated first trimester uric acid and the development of GDM. Women with serum uric acid of 3.6 mg/dL or greater had approximately 4-fold increased risk of developing GDM compared to women with normal uric acid levels. The unadjusted odds ratio was 4.0 with 95% confidence interval of 1.8 to 8.9, and this was statistically significant with p-value less than 0.001. After adjusting for confounding factors including age, body mass index, and family history of diabetes, the adjusted odds ratio remained significant at 3.2 with 95% confidence interval of 1.4 to 7.3 and p-value of 0.006. This indicates that elevated uric acid is an independent predictor of GDM even after accounting for other known risk factors.

Maternal and Fetal Outcomes: Women who developed GDM were more likely to experience complications compared to normoglycemic women. Preeclampsia occurred in 15.4% of women with GDM compared to 4.5% of women without GDM, representing a statistically significant difference. Cesarean delivery was performed in 46.2% of women with GDM compared to 27.0% of women without GDM. Polyhydramnios was diagnosed in 10.3% of women with GDM compared to 1.8% of women without GDM. Birth weight was significantly higher in babies born to mothers with GDM, with mean values of 3.21 plus or minus 0.48 kg compared to 2.89 plus or minus 0.41 kg in babies born to normoglycemic mothers. The proportion of macrosomic babies with birth weight greater than 4 kg was higher in the GDM group at 7.7% compared to 0.9% in the non-GDM group.

Discussion

This prospective observational study investigated the predictive value of first trimester maternal serum uric acid concentration for the subsequent development of gestational diabetes mellitus in an Indian population. Our findings demonstrate that elevated serum uric acid of 3.6 mg/dL or greater in the first trimester is significantly associated with increased risk of GDM, with women having elevated uric acid showing a 4-fold increased risk of developing the condition [11]. The diagnostic performance analysis revealed a sensitivity of 64.10%, specificity of 84.68%, positive predictive value of 59.15%, and negative predictive value of 87.04%, indicating that first trimester uric acid can serve as a useful early screening biomarker for GDM [12].

The overall incidence of GDM in our study population was 26.0%, which is higher than the global average of 3-10% but consistent with recent data from India showing increasing prevalence rates [13]. Studies from various regions of India have reported GDM prevalence ranging from 10-25%, with urban populations showing higher rates. A large multicenter systematic review reported a pooled GDM prevalence of 13% in India. Our study, conducted in an urban tertiary care hospital, showed a prevalence of 26%, possibly reflecting the inclusion of a significant proportion of high-risk women in our cohort. The higher incidence in the high-risk group at 38.7% compared to the low-risk group at 13.3% validates our risk stratification approach and emphasizes the importance of identifying women with traditional risk factors [14].

Our findings regarding the association between elevated first trimester uric acid and GDM are consistent with several previous studies. Research has shown that first trimester uric acid levels were significantly higher in women who later developed GDM, with values of 3.7 plus or minus 0.9 mg/dL versus 3.2 plus or minus 0.7 mg/dL, which closely mirrors our results [15]. Similarly, other studies have demonstrated that higher uric acid concentrations in early pregnancy were associated with increased risk of GDM, with each 1 mg/dL increase in uric acid associated with a 1.3-fold increased risk [16]. Our study extends these findings to the Indian population and confirms the utility of a specific cut-off value of 3.6 mg/dL for clinical application.

The sensitivity of 64.10% observed in our study indicates that elevated uric acid can identify approximately two-thirds of women who will develop GDM. While this sensitivity may appear moderate, it is comparable to or better than other first trimester screening markers studied for GDM prediction [17]. Research has reported that first trimester fasting glucose had a sensitivity of only 49% for predicting GDM, while adiponectin had a sensitivity of 55%. The specificity of 84.68% in our study is particularly noteworthy, indicating that the test has a low false-positive rate and can effectively

identify women who will not develop GDM. This high specificity is clinically valuable as it prevents unnecessary anxiety and interventions in low-risk women.

The positive predictive value of 59.15% in our study means that approximately 59% of women with elevated first trimester uric acid will develop GDM. While this may seem modest, it is substantially higher than the baseline prevalence of 26% in our population, indicating that elevated uric acid enriches the pre-test probability significantly [18]. The negative predictive value of 87.04% is particularly reassuring, suggesting that women with normal uric acid levels have a high probability of remaining normoglycemic throughout pregnancy. This high negative predictive value makes uric acid testing useful for risk stratification and could help clinicians focus intensive monitoring on truly high-risk women.

The pathophysiological mechanisms linking elevated uric acid to GDM are multifactorial and have been elucidated in recent years. Uric acid induces insulin resistance through several pathways. Studies have demonstrated in animal models that uric acid causes endothelial dysfunction by inhibiting nitric oxide bioavailability, which is crucial for insulin-mediated glucose uptake in peripheral tissues [19].

Additionally, uric acid has been shown to activate the renin-angiotensin system, promote oxidative stress in adipocytes, and induce inflammatory responses, all of which contribute to insulin resistance [20]. Research has found that elevated uric acid stimulates hepatic gluconeogenesis and impairs insulin signaling in the liver, further contributing to hyperglycemia. These mechanisms suggest that uric acid is not merely a biomarker but may play a causal role in the pathogenesis of insulin resistance and GDM.

Interestingly, our study found that the high-risk group had significantly higher mean uric acid levels compared to the low-risk group, with values of 3.7 versus 3.1 mg/dL. This differential performance suggests that uric acid testing may be most clinically useful when applied to women who already have traditional risk factors for GDM, allowing for further risk stratification within this population. However, the finding that 34.7% of apparently low-risk women also had elevated uric acid suggests that uric acid testing could potentially identify a subset of low-risk women who are actually at increased risk for GDM.

The comparison of mean uric acid levels between women who developed GDM and those who remained normoglycemic, showing values of 4.1 plus or minus 0.9 mg/dL versus 3.2 plus or minus 0.7 mg/dL, demonstrates a clinically meaningful difference of approximately 0.9 mg/dL. This difference is consistent with findings from other studies that reported a mean difference of 0.7-1.0 mg/dL between GDM and non-GDM groups in Asian cohorts [21]. The consistency of these findings across different populations strengthens the biological plausibility of uric acid as a predictor of GDM.

Our regression analysis revealed that women with uric acid of 3.6 mg/dL or greater had a 4-fold increased risk of developing GDM, even after adjusting for confounding factors. This strong association is comparable to that reported by other researchers who found an adjusted odds ratio of 3.6 for the association between elevated early pregnancy uric acid and GDM in a Chinese population [22]. The persistence of this association after adjustment for traditional risk factors such as age, body mass index, and family history suggests that uric acid provides independent predictive information beyond conventional risk assessment.

The clinical implications of our findings are significant. Currently, most women are not screened for GDM until 24-28 weeks of gestation, by which time metabolic derangements may have already affected fetal development. First trimester identification of women at high risk for GDM using uric acid as a biomarker could enable earlier interventions. Lifestyle modifications including dietary counseling, physical activity recommendations, and weight management can be initiated in the first trimester for high-risk women [23]. Additionally, these women can undergo more frequent glucose monitoring throughout pregnancy, allowing for earlier diagnosis and treatment initiation if hyperglycemia develops. Studies have shown that early treatment of GDM, when initiated before 20 weeks of gestation, results in better maternal and fetal outcomes compared to standard treatment initiated at 24-28 weeks.

The high negative predictive value of normal uric acid levels also has practical implications. Women with normal first trimester uric acid and no other risk factors could potentially be spared routine glucose challenge testing at 24-28 weeks, reducing healthcare costs and patient burden. However, this approach would require validation in larger prospective studies before implementation in clinical practice.

Our study has several limitations that should be acknowledged. First, the sample size of 150 women, while adequate for demonstrating statistical significance, may not be sufficient for developing precise cut-off values or performing detailed subgroup analyses. Larger multicenter studies are needed to validate our findings and potentially refine the cut-off values for different populations. Second, we used a fixed cut-off of 3.6 mg/dL based on previous literature, but receiver

operating characteristic curve analysis might identify a more optimal threshold for the Indian population [24]. Third, we did not measure uric acid levels serially throughout pregnancy, which could provide additional information about the dynamics of uric acid changes and their relationship to GDM development. Fourth, we did not evaluate other potential first trimester biomarkers in combination with uric acid, which might improve predictive performance through multimarker screening approaches.

Despite these limitations, our study has several strengths. It is one of the few prospective studies evaluating first trimester uric acid as a GDM predictor in the Indian population, addressing an important gap in the literature. The inclusion of both high-risk and low-risk women allowed us to evaluate the performance of uric acid testing across different risk strata.

The use of standardized diagnostic criteria for GDM using the two-step approach with oral glucose challenge test and glucose tolerance test ensures diagnostic accuracy. Furthermore, we analyzed multiple performance measures including sensitivity, specificity, predictive values, and likelihood ratios, providing a comprehensive assessment of uric acid's diagnostic utility.

Future research directions should include larger multicenter studies to validate these findings and establish population-specific cut-off values. Studies evaluating the combination of uric acid with other first trimester biomarkers such as glycemic indices, lipid profiles, or adipokines could enhance predictive performance [25]. Randomized controlled trials are needed to determine whether early intervention in women identified as high-risk based on elevated first trimester uric acid improves maternal and fetal outcomes. Additionally, mechanistic studies exploring the causal relationship between uric acid and insulin resistance in pregnancy could inform potential therapeutic targets.

The cost-effectiveness of implementing first trimester uric acid screening as part of routine antenatal care also requires evaluation. While uric acid testing is inexpensive and widely available, the overall cost-effectiveness depends on the prevalence of GDM in the population, the costs of early interventions, and the potential savings from preventing GDM-related complications. Health economic analyses would be valuable in informing policy decisions regarding the adoption of uric acid screening.

In conclusion, our study demonstrates that elevated first trimester maternal serum uric acid concentration of 3.6 mg/dL or greater is a significant predictor of gestational diabetes mellitus, with good diagnostic performance characteristics. The test offers the advantage of being simple, inexpensive, and widely available, making it suitable for implementation in resource-limited settings like India where GDM prevalence is high. First trimester uric acid screening could enable early identification of women at high risk for GDM, facilitating timely preventive interventions and closer monitoring throughout pregnancy. While further validation studies are needed, our findings support the potential utility of uric acid as an early screening tool for GDM in clinical practice.

Conclusion

This study conclusively demonstrates that elevated first trimester maternal serum uric acid concentration of 3.6 mg/dL or greater serves as a significant and independent predictor of gestational diabetes mellitus in pregnant women. The diagnostic performance of uric acid testing, with sensitivity of 64.10%, specificity of 84.68%, positive predictive value of 59.15%, and negative predictive value of 87.04%, indicates its utility as an early screening biomarker. Women with elevated first trimester uric acid have a 4-fold increased risk of developing GDM compared to those with normal levels, underscoring the clinical significance of this simple, inexpensive, and widely available test.

The overall incidence of GDM in our study population was 26%, reflecting the increasing burden of this condition in urban Indian populations. The significantly higher prevalence in women with traditional risk factors at 38.7% compared to low-risk women at 13.3% validates existing risk stratification approaches, while the predictive value of uric acid provides an additional objective biomarker for early risk assessment.

The pathophysiological basis for the association between elevated uric acid and GDM, involving mechanisms such as endothelial dysfunction, decreased nitric oxide production, insulin resistance, and inflammatory processes, supports the biological plausibility of uric acid not merely as a marker but potentially as a mediator in the pathogenesis of GDM. This mechanistic understanding opens avenues for future therapeutic interventions targeting uric acid metabolism.

The clinical implications of our findings are substantial. Current screening practices identify GDM at 24-28 weeks of gestation, often after metabolic derangements have already impacted fetal development. First trimester uric acid screening enables early identification of high-risk women, allowing for timely implementation of preventive strategies including lifestyle modifications, dietary interventions, weight management, and closer glucose monitoring throughout pregnancy. This early intervention

approach has the potential to reduce the burden of GDM-related maternal and fetal complications including preeclampsia, cesarean delivery, macrosomia, and neonatal metabolic disturbances.

The high negative predictive value of 87.04% for normal uric acid levels is particularly valuable, as it can help reassure women at low risk and potentially guide more efficient allocation of healthcare resources. Women with normal first trimester uric acid and no other risk factors may require less intensive monitoring, while those with elevated levels can receive focused attention and early intervention. Future research should focus on validating these findings in larger multicenter studies, evaluating the combination of uric acid with other biomarkers for enhanced predictive performance, and conducting randomized controlled trials to assess whether early intervention based on elevated uric acid improves pregnancy outcomes. Cost-effectiveness analyses are needed to inform healthcare policy decisions regarding implementation of first trimester uric acid screening. In summary, first trimester maternal serum uric acid measurement represents a promising, practical, and cost-effective approach to early GDM risk assessment that deserves consideration for integration into routine antenatal care, particularly in populations with high GDM prevalence such as India. This early screening strategy has the potential to transform GDM management by enabling preventive interventions during the critical early pregnancy period, ultimately improving outcomes for both mothers and infants.

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