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First trimester Serum Uric Acid levels in predicting Gestational Diabetes Mellitus: A hospital based longitudinal follow-up study

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KEYWORDS

Serum uric acid, Gestational diabetes mellitus, Diagnostic accuracy, India, Pregnancy, Maternal complications

ABSTRACT:

Background: Elevated serum uric acid levels have been associated with insulin resistance, hypertension, and metabolic syndrome, conditions that share common pathophysiological mechanisms with gestational diabetes mellitus (GDM).

Objectives: To determine the diagnostic accuracy of first trimester serum uric acid levels in predicting Gestational Diabetes Mellitus.

Methods: This was a longitudinal follow-up study conducted in the Department of Biochemistry and Obstetrics & Gynaecology, of a tertiary teaching healthcare facility in South India.

Results: The study enrolled 400 women with single live intrauterine pregnancy up to 14 weeks of gestation; 74.5% were between 21 and 30 years of age. Nearly two third patients were multigravida (62.5%); 36.7% were overweight, and 14.5% were obese. The mean (SD) levels of uric acid was 3.3 (0.9); 47.7% had serum uric acid levels >3.2 mg/dl. Serum uric acid levels were significantly ($p<0.05$) elevated among overweight and obese women. Of the 400 women, 149 women (37.3%) had GDM on follow-up. Patients with gestational diabetes mellitus (GDM) had significantly higher mean uric acid levels (3.8 mg/dl) compared to those without GDM (2.9 mg/dl). 65.8% of GDM patients had uric acid levels ≥3.2 mg/dl, versus 37.1% without GDM, a statistically significant difference. Serum uric acid levels showed a mild to moderate positive correlation with fasting, one-hour, and two-hour postprandial blood glucose in both first and second OGTT. First-trimester serum uric acid levels predicted GDM with 68.4% sensitivity, 74.2% specificity, 53.5% positive predictive value, 84.4% negative predictive value, and 72.4% overall diagnostic accuracy at a cutoff of ≥3.2 mg/dl.

Conclusion: Early pregnancy serum uric acid levels could potentially serve as a valuable biomarker for identifying women at higher risk for GDM, thereby allowing for earlier interventions and improved management of pregnancy outcomes.

Introduction

Gestational diabetes mellitus (GDM) is a condition characterized by glucose intolerance that is first recognized during pregnancy. It affects approximately 7-10% of pregnancies worldwide, with significant variations across different populations and ethnic groups.[1,2] GDM is associated with adverse maternal and fetal outcomes, including preeclampsia, caesarean delivery, macrosomia, and an increased risk of developing type 2 diabetes mellitus later in life for both the mother and child.[3-5] Early identification and management of GDM are crucial to mitigate these risks. The oral glucose tolerance test (OGTT) is the standard diagnostic tool for GDM, typically conducted between 24 and 28 weeks of gestation.[6] However, there is growing interest in identifying predictive markers that can indicate the risk of GDM earlier in pregnancy, allowing for proactive interventions.[7,8]

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Serum uric acid, a product of purine metabolism, has been investigated as a potential early marker for various metabolic disorders, including GDM. Elevated serum uric acid levels have been associated with insulin resistance, hypertension, and metabolic syndrome, conditions that share common pathophysiological mechanisms with GDM.[9,10] Previous studies have suggested a correlation between elevated serum uric acid levels in early pregnancy and the subsequent development of GDM.[11-14] Despite these findings, the diagnostic accuracy and clinical utility of serum uric acid as a predictor for GDM remain underexplored. Most studies have focused on the correlation between serum uric acid and GDM, but comprehensive evaluations of its sensitivity, specificity, and predictive values are limited.[15,16] Additionally, there is a need to investigate whether serum uric acid levels can serve as a reliable screening tool that complements existing diagnostic methods.

The present study aims to address these gaps by evaluating the diagnostic accuracy of first trimester serum uric acid levels in predicting GDM among a cohort of pregnant women in South India. By examining the sensitivity, specificity, and predictive values of serum uric acid, this study seeks to determine its potential role in early GDM screening. Furthermore, the study investigates the correlation between serum uric acid levels and blood glucose measurements obtained from OGTTs conducted at different stages of pregnancy.

Materials and Methods

This was a longitudinal follow-up study conducted in the Department of Biochemistry and Obstetrics & Gynaecology, of a tertiary teaching healthcare facility in South India. The study was approved by the Institutional Human Ethics Committee (IHEC). The participants were given the Participant Information Sheet (PIS) in their native language, and its contents were verbally explained to ensure their understanding and satisfaction. Enrolment into the study proceeded upon receipt of written informed consent. All women more than or equal to 18 years of age with single live intrauterine pregnancy up to 14 weeks of gestation were enrolled in the present study. However, women with overt diabetes mellitus, women diagnosed with gestational diabetes mellitus by oral glucose tolerance test (OGTT) before 14 weeks period of gestation, women on chronic steroids/steroid treatment, women with gout, chronic renal disease, connective tissue disorders, liver diseases and cardiovascular diseases were excluded from the present study.

We computed sample size considering sensitivity to be 80%, specificity to be 70%, alpha error to be 5%, beta error to be 20%, absolute precision to be 5%, and non-response rate to be 10%. The minimum estimated sample size was rounded off to 400 women. We used nonprobability sampling – convenient sampling technique – complete enumeration of patients in line with prespecified inclusion and exclusion criteria. We used a purpose predesigned, semi structured, pretested questionnaire to capture the detailed history (including age, parity, obstetric history, family history, past history and presence of other comorbidities) general physical examination, clinical examination (including antenatal), anthropometry, and laboratory investigations (including serum uric acid in early pregnancy (less than 14 weeks of gestation) and OGTT done between 24-28 weeks and 32-34 weeks of gestation). Blood sugar levels were measured using the hexokinase method.[17] The obtained blood sugar values were analysed against the standards established by the International Association of the Diabetes and Pregnancy Study Groups (IADPSG). The criteria for diagnosis included a fasting blood glucose level of ≥92 mg/dL, a 1-hour blood glucose level of ≥180 mg/dL, and a 2-hour blood glucose level of ≥153 mg/dL. If any of these values met or exceeded the IADPSG thresholds, the women were diagnosed with gestational diabetes mellitus (GDM).[18] These patients were subsequently monitored and managed according to the department's protocol.

Statistical analysis: The data obtained was manually entered into Microsoft Excel and analysed using Statistical Package for Social Sciences (SPSS) v23. All the categorical variables were summarised using frequencies and percentages. Continuous variables were summarized using mean (standard deviation) and/or median (interquartile range) (based on the results of data normality, tested using Kolmogorov–Smirnov test and the Shapiro–Wilk test). To test for statistical significance, Chi square test or Fisher exact test (for categorical variables) and independent “t” test or Mann Whitney U test (for continuous variables) was used. Statistical significance was considered at p value less than 0.05.

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Results

The present study enrolled a total of 400 women more than or equal to 18 years of age with single live intrauterine pregnancy up to 14 weeks of gestation. The distribution of patients by age showed that nearly three in four patients (74.5%) were between 21 and 30 years of age, followed by 16.2% patients more than 30 years and 9.3% patients less than or equal to 20 years of age. Nearly two third patients were multigravida (62.5%) and 37.5% were primigravida. Based on body mass index, the results showed that 10.0% patients were underweight, 36.7% were overweight, and 14.5% were obese; on the other hand, 38.8% patients had normal body mass index. The mean (SD) levels of uric acid was 3.3 (0.9); 209 patients (52.3%) had serum uric acid levels less than 3.2 mg/dl and 191 patients (47.7%) had serum uric acid levels more than or equal to 3.2 mg/dl.

Factors associated with serum uric acid levels: Age distribution revealed that patients younger than 20 years constituted 7.7% in the <3.2 mg/dl group and 11.0% in the ≥3.2 mg/dl group. Participants aged 21 to 30 years comprised 77.5% of the <3.2 mg/dl group and 71.2% of the ≥3.2 mg/dl group. Those older than 30 years accounted for 14.8% in the <3.2 mg/dl group and 17.8% in the ≥3.2 mg/dl group. The serum uric acid levels did not vary significantly by age ($p>0.05$). Regarding gravida status, 39.2% patients of the <3.2 mg/dl group were primigravida, compared to 35.6% in the ≥3.2 mg/dl group. Multigravida patients made up 60.8% of the <3.2 mg/dl group and 64.4% of the ≥3.2 mg/dl group. The serum uric acid levels did not vary significantly by gravida ($p>0.05$). BMI analysis showed a significant difference between the groups ($p<0.05$). Among those with uric acid levels <3.2 mg/dl, 7.2% were underweight, compared to 13.1% in the ≥3.2 mg/dl group. Normal BMI was observed in 47.4% of the <3.2 mg/dl group and 29.3% of the ≥3.2 mg/dl group. Overweight individuals comprised 32.5% of the <3.2 mg/dl group and 41.4% of the ≥3.2 mg/dl group. Obesity was noted in 12.9% of the <3.2 mg/dl group and 16.2% of the ≥3.2 mg/dl group.

Of the 400 women, 149 women (37.3%) were found to have gestational diabetes mellitus on follow-up. Of the 149 women diagnosed with gestational diabetes mellitus, 117 patients were diagnosed during the first OGTT (between 24-28 weeks) and the other 32 patients were diagnosed during the second OGTT (between 32-34 weeks).

The mean (SD) uric acid levels were 3.8 (1.1) among patients with gestational diabetes mellitus and 2.9 (0.8) among patients without gestational diabetes mellitus. The difference was found to be statistically significant ($p<0.05$). Similarly, among patients with gestational diabetes mellitus, 65.8% patients had serum uric acid levels more than or equal to 3.2 mg/dl compared to 37.1% patients without GDM having uric acid levels more than or equal to 3.2 mg/dl. This difference (higher proportion of patients with gestational diabetes mellitus had serum uric acid levels greater than or equal to 3.2 mg/dl) was found to be statistically significant ($p<0.05$).

Correlation analysis: The results showed that the levels of serum uric acid had mild to moderate positive significant correlation with fasting blood glucose ($r_p=0.322$; $p<0.05$), one-hour postprandial blood glucose ($r_p=0.243$; $p<0.05$), and 2-hour postprandial blood glucose ($r_p=0.217$; $p<0.05$) in first OGTT (between 24-28 weeks); mild to moderate positive significant correlation with fasting blood glucose ($r_p=0.463$; $p<0.05$), one-hour postprandial blood glucose ($r_p=0.448$; $p<0.05$), and 2-hour postprandial blood glucose ($r_p=0.262$; $p<0.05$) in second OGTT (between 32-34 weeks).

Diagnostic accuracy of first trimester serum uric acid levels in predicting gestational diabetes mellitus: The results showed that serum uric acid levels had a sensitivity of 68.4%, specificity of 74.2%, positive predictive value of 53.5%, negative predictive value of 84.4%, and an overall diagnostic accuracy of 72.4% in predicting gestational diabetes mellitus at cut off of more than or equal to 3.2 mg/dl.

Discussion

The present study aimed to investigate the diagnostic accuracy of first trimester serum uric acid levels in predicting Gestational Diabetes Mellitus (GDM). The study enrolled 400 pregnant women. The majority of participants in this study were between 21 and 30 years old, which aligns with the reproductive age range typically seen in other similar studies (Agha-Jaffar et al., 2016).[19] The lack of significant variation in serum uric acid levels by age suggests that age alone may not be a determinant of uric acid levels in early pregnancy. This is consistent with findings from other studies which have shown that age is not a strong independent predictor of hyperuricemia (Thangaratinam et al., 2011).[20] The distribution of primigravida and

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multigravida participants was relatively balanced across the different serum uric acid levels, indicating no significant association between gravida status and uric acid levels. Previous research has similarly found that gravida status does not significantly impact serum uric acid levels during pregnancy (Duo et al., 2023).[21] This suggests that the number of previous pregnancies does not alter the metabolic profile of uric acid significantly in early pregnancy. The study found a significant association between BMI and serum uric acid levels, with higher uric acid levels observed in overweight and obese individuals. This is in line with existing literature which highlights that elevated BMI is strongly associated with increased serum uric acid levels (Perichart-Perera et al., 2017).[22] Obesity and overweight conditions are known to contribute to insulin resistance and metabolic syndrome, which are risk factors for GDM (Kampmann et al., 2015).[23] The significant difference in BMI categories between the <3.2 mg/dl and ≥3.2 mg/dl uric acid groups underscores the importance of considering BMI as a confounding factor when evaluating the risk of GDM based on serum uric acid levels (Chu et al., 2007).[24]

Uric acid has been proposed as a potential biomarker for predicting GDM due to its association with insulin resistance and oxidative stress (Retnakaran et al., 2003).[25] Elevated serum uric acid levels in early pregnancy may reflect underlying metabolic disturbances that predispose women to develop GDM later in pregnancy. Several studies have suggested that hyperuricemia in early pregnancy is associated with an increased risk of GDM, supporting the findings of the current study (Laughon et al., 2011).[11]

Among the 400 women studied, 37.3% were diagnosed with GDM, either during the first Oral Glucose Tolerance Test (OGTT) conducted between 24-28 weeks of gestation or during the second OGTT conducted between 32-34 weeks. This prevalence aligns with global trends, which indicate that the incidence of GDM varies widely, but generally affects between 5-20% of pregnancies, depending on the population studied and diagnostic criteria used (Zhu & Zhang, 2016).[26] The study found that the mean uric acid levels were significantly higher in women who developed GDM (3.8 ± 1.1 mg/dl) compared to those who did not (2.9 ± 0.8 mg/dl). This significant difference ($p<0.05$) underscores the potential role of uric acid as a biomarker for GDM. Previous research has consistently shown that higher serum uric acid levels are associated with an increased risk of GDM (Laughon et al., 2011; Nikparast et al., 2023).[11,13]

Elevated uric acid levels may reflect underlying insulin resistance and oxidative stress, both of which are key pathophysiological mechanisms in the development of GDM (Retnakaran et al., 2003).[25]

The study also demonstrated a mild to moderate positive correlation between serum uric acid levels and various blood glucose parameters. Specifically, serum uric acid levels were correlated with fasting blood glucose, one-hour postprandial blood glucose, and two-hour postprandial blood glucose during both the first and second OGTT. These findings suggest that higher uric acid levels may indicate impaired glucose metabolism early in pregnancy, which subsequently leads to GDM. This correlation is supported by studies that have shown similar associations between uric acid levels and glucose metabolism markers (Thangaratinam et al., 2012).[20] The diagnostic accuracy of first trimester serum uric acid levels in predicting GDM was evaluated, revealing a sensitivity of 68.4%, specificity of 74.2%, positive predictive value (PPV) of 53.5%, negative predictive value (NPV) of 84.4%, and an overall diagnostic accuracy of 72.4% at a cutoff of ≥3.2 mg/dl. These metrics indicate that while serum uric acid levels are a useful predictor of GDM, they should be used in conjunction with other risk factors and screening methods to improve diagnostic accuracy. The relatively high NPV suggests that low uric acid levels are quite effective in ruling out GDM, making it a useful initial screening tool (Kampmann et al., 2015).[23]

The findings of this study suggest that measuring serum uric acid levels in the first trimester could help identify women at higher risk for developing GDM, particularly those with elevated BMI. Early identification allows for timely interventions, such as dietary modifications, increased physical activity, and closer monitoring, which can mitigate the adverse outcomes associated with GDM.[19] Incorporating serum uric acid measurements into routine early pregnancy screenings could enhance the current screening protocols for GDM, especially in high-risk populations.

The present study is not without limitations. The study did not account for potential confounding factors such as dietary intake, physical activity, and family history of diabetes, which could influence serum uric acid levels and the risk of GDM. Additionally, the use of a convenience

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sampling technique may limit the generalizability of the findings.

Conclusion

The present study aimed to evaluate the diagnostic accuracy of first trimester serum uric acid levels in predicting gestational diabetes mellitus among a cohort of pregnant women. Our findings demonstrate that elevated serum uric acid levels in early pregnancy are significantly associated with an increased risk of developing GDM. Specifically, a serum uric acid cutoff of ≥3.2 mg/dL exhibited a sensitivity of 68.4%, specificity of 74.2%, and an overall diagnostic accuracy of 72.4%. This indicates that serum uric acid is a moderately accurate predictor of GDM. The correlation analysis further supported these findings, showing mild to moderate positive correlations between serum uric acid levels and blood glucose measurements taken during the first and second oral glucose tolerance tests (OGTT). These results suggest that early pregnancy serum uric acid levels could potentially serve as a valuable biomarker for identifying women at higher risk for GDM, thereby allowing for earlier interventions and improved management of pregnancy outcomes.

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Table 1: Comparison of patient characteristics and serum uric acid levels

		Serum uric acid levels (in mg/dl)			**P value**
		<3.2 N = 209	**≥3.2 N = 191**	**Total N = 400**	
		n (%)	**n (%)**	**n (%)**	
Age (in years)	≤20	16 (7.7)	21 (11.0)	37 (9.3)	0.320
	21 to 30	162 (77.5)	136 (71.2)	298 (74.5)	
	More than 30	31 (14.8)	34 (17.8)	65 (16.2)	
Gravida	Primi	82 (39.2)	68 (35.6)	150 (37.5)	0.454
	Multi	127 (60.8)	123 (64.4)	250 (62.5)	
Body mass index (in kg/m2)	Underweight	15 (7.2)	25 (13.1)	40 (10.0)	0002*
	Normal	99 (47.4)	56 (29.3)	155 (38.8)	
	Overweight	68 (32.5)	79 (41.4)	147 (36.7)	
	Obese	27 (12.9)	31 (16.2)	58 (14.5)	
*Statistically significant at p<0.05					

Table 2: Comparison of serum uric acid levels and gestational diabetes mellitus

	Gestational diabetes mellitus			**P value**
	Present N = 149	**Absent N = 251**	**Total N = 400**	
	n (%)	**n (%)**	**n (%)**	
Serum uric acid (in mg/dl)	3.8 (1.1)	2.9 (0.8)	3.3 (0.9)	<0.001*

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Mean (SD)					
Serum uric acid (in mg/dl)	<3.2	51 (34.2)	158 (62.9)	209 (52.3)	<0.001*
	≥3.2	98 (65.8)	93 (37.1)	191 (47.7)	
*Statistically significant at p<0.05					

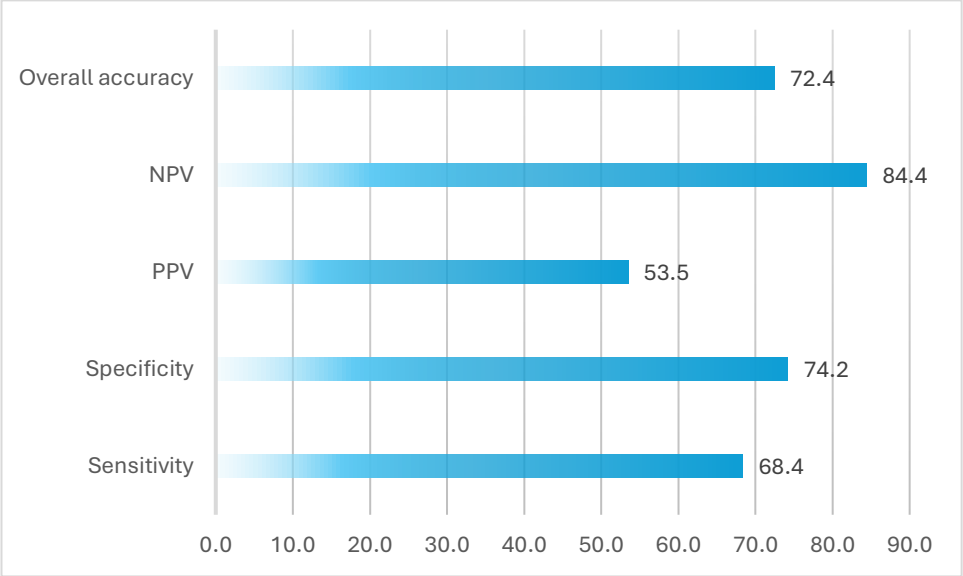

Figure 1: Diagnostic accuracy of first trimester serum uric acid levels in predicting gestational diabetes mellitus