Section: Obstetrics & Gynecology

Original Research Article

FIRST-TRIMESTER SERUM URIC ACID AS AN EARLY PREDICTOR OF GESTATIONAL DIABETES MELLITUS: A PROSPECTIVE OBSERVATIONAL STUDY

Harishkumar S[1], A.Narmadhapriya[2], R.Selvi[2]

[1]*Postgraduate, Department of Obstetrics and Gynaecology, Government Vellore medical college, Vellore, Tamil Nadu, India*
[2]*Assistant Professor, Department of Obstetrics and Gynaecology, Government Vellore Medical College Vellore, Tamil Nadu, India*

Received *: 12/07/2026*
Received in revised form *: 15/08/2026*
Accepted *: 27/08/2026*

Corresponding Author:
Dr. R. Selvi,
Assistant Professor,Department of Obstetrics and Gynaecology, Government Vellore Medical College
Email: drselvi84@gmail.com

DOI: 10.70034/ijmedph.2026.4.372

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2026; 16 (4); 2478-2483

ABSTRACT

Background: Gestational diabetes mellitus (GDM) is one of the most common metabolic complications of pregnancy and, if undetected, predisposes both mother and offspring to significant short- and long-term morbidity. Serum uric acid, an inexpensive and widely available biochemical test, has been implicated in insulin resistance and may permit earlier risk stratification than the conventional oral glucose tolerance test (OGTT) performed at 24–28 weeks. Objectve of our study is to evaluate whether serum uric acid levels measured in the first trimester predict the subsequent development of GDM, and to determine an optimal predictive cut-off value.

Materials and Methods: A prospective observational cohort study was conducted on 210 pregnant women recruited during the first trimester (≤13 weeks + 6 days) of gestation at a tertiary care antenatal clinic over one year. Maternal age, body mass index (BMI), fasting blood sugar, and serum uric acid were recorded at recruitment. All participants underwent a 75 g OGTT as per DIPSI criteria between 24 and 28 weeks of gestation to diagnose GDM. Data were analysed using independent t-tests, chi-square tests, multivariate logistic regression, and receiver operating characteristic (ROC) curve analysis.

Results: Fifty-nine of the 210 women (28.1%) developed GDM. Women who developed GDM were significantly older (29.6 ± 3.2 vs 27.1 ± 3.5 years, $p<0.001$), had higher BMI (28.4 ± 2.8 vs 24.7 ± 3.1 kg/m², $p<0.001$), and had markedly higher first-trimester serum uric acid (5.8 ± 0.6 vs 4.1 ± 0.5 mg/dL, $p<0.001$) than women who remained normoglycemic. Uric acid ≥4.5 mg/dL was strongly associated with subsequent GDM (55/94 vs 4/116, $p<0.001$). ROC analysis showed an area under the curve of 0.86 (95% CI 0.80–0.91); a cut-off of 4.9 mg/dL yielded 83.1% sensitivity and 78.8% specificity. On multivariate logistic regression, serum uric acid remained an independent predictor of GDM (odds ratio 3.8, 95% CI 2.4–6.1, $p<0.001$) after adjustment for age and BMI.

Conclusion: Elevated first-trimester serum uric acid is independently and strongly associated with subsequent GDM and shows good discriminatory performance. Given its low cost and wide availability, serum uric acid estimation may serve as a practical adjunctive early screening tool for GDM, particularly in resource-limited antenatal care settings, pending validation in larger multicentric cohorts.

Keywords: Gestational diabetes mellitus; serum uric acid; first trimester; insulin resistance; predictive marker; oral glucose tolerance test; pregnancy screening.

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy and represents one of the most common metabolic complications encountered in obstetric practice worldwide. It affects an estimated 7–10% of pregnancies globally,

though the reported prevalence varies considerably depending on the population studied, ethnicity, prevailing lifestyle factors, and the diagnostic criteria applied.[1,2] When GDM remains undetected or inadequately managed, it can result in a spectrum of maternal and fetal complications. Maternal risks include preeclampsia, pregnancy-induced hypertension, higher rates of operative delivery, and an increased lifetime risk of developing overt type 2 diabetes mellitus.[3,4] Fetal and neonatal risks include macrosomia, shoulder dystocia, neonatal hypoglycaemia, respiratory distress syndrome, and a heightened long-term predisposition to obesity and metabolic disease.[5] Because of this considerable burden of morbidity, early identification and timely management of GDM have become central priorities in contemporary antenatal care.[6]

The oral glucose tolerance test (OGTT), performed between 24 and 28 weeks of gestation, remains the standard diagnostic method for GDM.[5] However, mounting evidence suggests that the underlying metabolic derangements of GDM — principally progressive insulin resistance — may begin considerably earlier in pregnancy, well before hyperglycaemia becomes clinically overt. This has generated substantial research interest in first-trimester biochemical markers capable of identifying at-risk women before the conventional screening window, thereby permitting earlier dietary counselling, lifestyle modification, and closer surveillance.[6]

Serum uric acid, the terminal product of purine metabolism, has attracted growing attention as one such candidate marker. It is closely linked to insulin resistance, obesity, hypertension, metabolic syndrome, and cardiovascular disease in the non-pregnant population.[7] Mechanistically, elevated uric acid promotes oxidative stress, impairs endothelial nitric oxide bioavailability, and triggers low-grade chronic inflammation, all of which are believed to contribute to impaired glucose homeostasis.[8] Several earlier reports have suggested that women with elevated first-trimester uric acid levels are more likely to subsequently develop GDM.[9,10] Nevertheless, existing evidence on the diagnostic performance of serum uric acid — specifically its sensitivity, specificity, and an appropriate clinical cut-off — remains comparatively limited, and its feasibility as a routine adjunct to antenatal screening protocols warrants further prospective evaluation, particularly in South Asian populations known to have a heightened predisposition to insulin resistance.[11]

The present study was therefore undertaken to evaluate the predictive value of first-trimester serum uric acid for the later development of GDM among pregnant women attending a tertiary-care antenatal clinic in South India.

The primary objective of the study was to assess serum uric acid measured during the first trimester as a predictor of, and to determine its association with, the subsequent development of GDM. The secondary objectives were: to determine an optimal cut-off value of serum uric acid for prediction of GDM risk; to assess the correlation between first-trimester serum uric acid, body mass index, and maternal age; and to evaluate the potential scope for early lifestyle intervention in women identified as being at increased biochemical risk.

MATERIALS AND METHODS

This was a prospective observational cohort study conducted over a period of one year in the Department of Obstetrics and Gynaecology of a tertiary-care government medical college. The study population comprised pregnant women attending the antenatal clinic during the first trimester of pregnancy, defined as gestational age of 13 weeks and 6 days or less, confirmed by the last menstrual period and corroborated by first-trimester ultrasonography. A total of 210 women who satisfied the eligibility criteria were enrolled after obtaining written informed consent; the minimum calculated sample size based on the anticipated proportion of women developing GDM and standard formulae for prospective cohort studies was 202.

Women aged 18–35 years with a singleton pregnancy, gestational age ≤13 weeks + 6 days, and willingness to undergo regular antenatal follow-up including OGTT were included. Women were excluded if they were older than 35 years, had pre-existing type 1 or type 2 diabetes mellitus, chronic hypertension, renal disease or deranged renal function tests, a history of gout or hyperuricaemia, twin pregnancy, any chronic systemic illness such as autoimmune or hepatic disease, or were unable or unwilling to complete follow-up and undergo OGTT.

At enrolment, a detailed history was obtained and a general physical and systemic examination performed. Baseline investigations included complete blood count, random blood sugar, and serum uric acid, along with urine routine and microscopy. Obstetric ultrasonography was performed to confirm gestational age. Serum uric acid was estimated using the standard uricase-peroxidase colorimetric method on an autoanalyser in the institutional biochemistry laboratory. Maternal age, BMI (calculated from height and weight recorded at the first antenatal visit), gestational age, fasting blood sugar, and first-trimester serum uric acid constituted the principal variables of interest. All participants were followed up prospectively and underwent a 75 g oral glucose tolerance test between 24 and 28 weeks of gestation, with GDM diagnosed according to Diabetes in Pregnancy Study Group India (DIPSI) criteria — a single-step test in which a 2-hour post-glucose plasma value of ≥140 mg/dL was taken as diagnostic of GDM.

The dependent variable was the development of GDM (yes/no) as diagnosed on OGTT. The principal independent variable was first-trimester serum uric acid; maternal age, BMI, parity, family history of

diabetes, prior history of GDM or macrosomia, blood pressure, fasting blood glucose, and lifestyle factors were considered as covariates and potential confounders. Statistical analysis was performed using SPSS software. Continuous variables were expressed as mean ± standard deviation and compared between the GDM and non-GDM groups using the independent-samples t-test; categorical variables were expressed as frequencies and percentages and compared using the chi-square test. Multivariate logistic regression analysis was performed to identify independent predictors of GDM after adjustment for potential confounders, with results expressed as adjusted odds ratios (OR) and 95% confidence intervals (CI). The predictive performance of serum uric acid for GDM was assessed using receiver operating characteristic (ROC) curve analysis, with calculation of the area under the curve (AUC), and the optimal cut-off value was derived using the Youden index, from which sensitivity and specificity were computed. A p-value <0.05 was considered statistically significant throughout. The study was approved by the Institutional Ethics Committee, and confidentiality of participant data was maintained throughout.

RESULTS

A total of 210 pregnant women in the first trimester were enrolled and followed prospectively to the point of GDM screening. Of these, 59 women (28.1%) subsequently developed GDM on OGTT performed at 24–28 weeks of gestation, while the remaining 151 women (71.9%) remained normoglycemic throughout the screening window. The baseline demographic, clinical, and biochemical characteristics of the two groups, along with the results of the association, receiver operating characteristic, and multivariate regression analyses, are summarised in [Table 1] through 5 below.

Table 1: Baseline demographic and clinical characteristics of the study population (n = 210)

Variable	Total (n=210)	GDM (n=59)	Non-GDM (n=151)	p-value
Age (years), mean ± SD	28.5 ± 3.7	29.6 ± 3.2	27.1 ± 3.5	<0.001
BMI (kg/m²), mean ± SD	25.8 ± 3.4	28.4 ± 2.8	24.7 ± 3.1	<0.001
Gestational age at recruitment (weeks), mean ± SD	10.5 ± 1.1	10.6 ± 1.0	10.4 ± 1.2	0.312

Women who subsequently developed GDM were, on average, significantly older and had a significantly higher BMI at the time of first-trimester recruitment than women who remained normoglycemic [Table 1]. Gestational age at recruitment, however, was comparable between the two groups, confirming that both cohorts were assessed at an equivalent stage of early pregnancy and that timing of sampling did not confound the biochemical comparisons that follow.

Table 2: Comparison of first-trimester biochemical parameters between women with and without gestational diabetes mellitus

Parameter	GDM (n=59)	Non-GDM (n=151)	p-value
Serum uric acid (mg/dL), mean ± SD	5.8 ± 0.6	4.1 ± 0.5	<0.001
Fasting blood sugar (mg/dL), mean ± SD	105.4 ± 8.2	86.9 ± 6.5	<0.001

Mean first-trimester serum uric acid was markedly and significantly higher in women who later developed GDM compared with those who did not, and a parallel, statistically significant elevation was observed in fasting blood sugar values in the GDM group [Table 2], suggesting that subclinical metabolic dysregulation was already detectable well before the conventional 24–28-week screening window.

Table 3: Association between elevated first-trimester serum uric acid and development of GDM

Uric acid category	GDM	Non-GDM	Total	p-value
< 4.5 mg/dL	4	112	116	<0.001
≥ 4.5 mg/dL	55	39	94	

A markedly disproportionate number of women with first-trimester serum uric acid ≥4.5 mg/dL subsequently developed GDM (55 of 94, 58.5%), compared with only 4 of 116 women (3.4%) whose uric acid remained below this threshold [Table 3]. This strong, statistically significant association indicates that a simple categorical cut-off of serum uric acid can meaningfully discriminate between women who will and will not develop GDM later in pregnancy.

Table 4: Receiver operating characteristic (ROC) curve analysis of serum uric acid for prediction of GDM

Parameter	AUC	95% CI	Optimal cut-off	Sensitivity	Specificity
Serum uric acid	0.86	0.80–0.91	4.9 mg/dL	83.1%	78.8%

ROC curve analysis confirmed good discriminatory performance of first-trimester serum uric acid for prediction of subsequent GDM, with an area under the curve of 0.86 (95% CI 0.80–0.91) [Table 4]. Using the Youden index, the optimal cut-off value was determined to be 4.9 mg/dL, which yielded a

sensitivity of 83.1% and specificity of 78.8%, indicating that serum uric acid at this threshold correctly identified the large majority of women who subsequently developed GDM while also correctly excluding most women who did not.

Table 5: Multivariate logistic regression analysis of independent predictors of GDM

Variable	Adjusted odds ratio	95% CI	p-value
Serum uric acid (≥4.9 mg/dL)	3.8	2.4–6.1	<0.001
Body mass index	1.6	1.2–2.1	0.002
Maternal age	1.3	1.1–1.6	0.01

On multivariate logistic regression analysis adjusting for maternal age and BMI, serum uric acid remained a strong and statistically significant independent predictor of GDM, conferring an almost fourfold increase in risk (adjusted OR 3.8, 95% CI 2.4–6.1, p<0.001) (Table 5). Higher BMI and increasing maternal age also emerged as significant, though comparatively weaker, independent predictors, with adjusted odds ratios of 1.6 and 1.3 respectively. Taken together, these results indicate that the predictive contribution of first-trimester serum uric acid to GDM risk is not merely a reflection of maternal obesity or advancing age, but represents an independent biochemical signal of early metabolic dysfunction.

DISCUSSION

Gestational diabetes mellitus continues to be recognised as one of the most frequently encountered metabolic complications of pregnancy, and its prevalence has risen steadily over recent decades in association with changing lifestyle patterns, rising maternal age, increasing rates of obesity, and reduced physical activity. GDM is associated with a wide range of maternal and fetal complications, including preeclampsia, polyhydramnios, operative delivery, fetal macrosomia, neonatal hypoglycaemia, respiratory distress syndrome, and an increased long-term risk of type 2 diabetes mellitus in both mother and child.[4,5] Because of this substantial burden, identifying at-risk women as early as possible in pregnancy has become an important clinical priority. Screening for GDM is conventionally performed between 24 and 28 weeks of gestation using the OGTT; however, growing evidence indicates that the metabolic disturbances underlying GDM frequently begin much earlier, often during the first trimester, well before clinical hyperglycaemia becomes apparent.[6] This has prompted increasing interest in early biochemical markers, among which serum uric acid has attracted particular attention because of its established links with insulin resistance, obesity, oxidative stress, inflammation, and endothelial dysfunction.[7,8]

The overall incidence of GDM observed in the present cohort (28.1%) was higher than figures typically reported from Western populations but broadly comparable with rates reported from other Indian and South Asian cohorts.[11] This comparatively high prevalence likely reflects rapid urbanisation, dietary transition, rising obesity, sedentary behaviour, and an inherent genetic predisposition toward insulin resistance and abdominal adiposity among South Asian women, even at relatively lower absolute BMI values.[11]

Maternal age was significantly associated with GDM in the present study, women who developed GDM being on average older than those who remained normoglycemic — a finding consistent with earlier work by Laughon et al. and Hedderson et al., both of whom identified advancing maternal age as an important risk factor for GDM.9 The biological plausibility of this association is supported by the progressive decline in insulin sensitivity, cumulative endothelial dysfunction, reduced pancreatic β-cell reserve, and rising prevalence of obesity and metabolic syndrome that accompany advancing reproductive age.[12,13]

BMI also showed a strong, statistically significant association with GDM in this cohort, corroborating extensive prior literature identifying obesity as one of the most consistent risk factors for GDM.[14,15] Adipose tissue functions as a metabolically active endocrine organ, secreting inflammatory mediators such as tumour necrosis factor-alpha, interleukin-6, leptin, and resistin, all of which interfere with normal insulin signalling; when superimposed on the physiological insulin resistance of pregnancy, excess adiposity substantially amplifies the risk of glucose intolerance.

The central finding of the present study was the markedly elevated first-trimester serum uric acid observed among women who subsequently developed GDM, a difference that was highly statistically significant and persisted as an independent predictor on multivariate analysis. This observation is concordant with the work of Laughon et al., who demonstrated that elevated first-trimester uric acid concentrations were significantly associated with the later development of GDM,[9] and with Wolak et al., who similarly reported that elevated early-pregnancy uric acid predicted subsequent GDM and adverse pregnancy outcomes.[10] Together, these findings reinforce the concept that the metabolic derangements underlying GDM are detectable considerably earlier than the conventional screening period.[16]

Several biologically plausible mechanisms may explain the observed association. Uric acid is no longer regarded merely as an inert end product of purine metabolism; contemporary evidence indicates that it actively contributes to endothelial dysfunction by inhibiting endothelial nitric oxide synthase and

reducing nitric oxide bioavailability, thereby impairing insulin-mediated glucose uptake in skeletal muscle and adipose tissue.[7,8] In addition, elevated uric acid promotes the generation of reactive oxygen species and activates inflammatory pathways, while also suppressing adiponectin secretion from adipose tissue — an insulin-sensitising adipokine whose deficiency is closely linked to insulin resistance. Through these interconnected pathways of endothelial injury, oxidative stress, chronic low-grade inflammation, and adipocyte dysfunction, elevated serum uric acid may contribute mechanistically, rather than merely serving as an epiphenomenon, to the pathogenesis of GDM.[17]

The ROC analysis in the present study demonstrated good discriminatory performance for serum uric acid, with an AUC of 0.86 and a cut-off of 4.9 mg/dL providing a sensitivity of 83.1% and specificity of 78.8% — findings broadly comparable to those reported by Wolak et al., who similarly found favourable predictive accuracy for early-pregnancy uric acid.[10] The relatively high sensitivity observed suggests particular value as a first-line screening test capable of identifying the majority of women who will go on to develop GDM, allowing them to be prioritised for closer surveillance, dietary counselling, and lifestyle intervention well ahead of the standard 24–28-week OGTT.

An important strength of serum uric acid as a screening tool lies in its simplicity, affordability, and wide availability, including in resource-constrained peripheral healthcare settings where universal early OGTT screening may not be logistically or financially feasible.[18] On multivariate logistic regression, serum uric acid retained independent predictive value even after adjustment for maternal age and BMI, with an odds ratio of 3.8 — appreciably higher than the odds ratios observed for age and BMI in the same model. This suggests that first-trimester uric acid provides predictive information that is not simply a proxy for adiposity or advancing maternal age, but reflects a distinct, biochemically grounded pathway toward glucose intolerance, a conclusion echoed by Hedderson et al.[19]

These findings carry meaningful clinical implications. Early identification of biochemically high-risk women would create an opportunity for timely dietary counselling, structured physical activity, weight management, and more intensive antenatal surveillance, potentially reducing the incidence of downstream complications such as preeclampsia, fetal macrosomia, birth trauma, and neonatal hypoglycaemia. There is, moreover, growing recognition that maternal hyperglycaemia and insulin resistance can influence fetal metabolic programming, predisposing offspring to obesity and type 2 diabetes later in life; early intervention in high-risk pregnancies may therefore confer intergenerational, and not merely immediate, health benefits.[20]

This study has certain limitations that merit acknowledgement. It was conducted at a single tertiary-care centre with a comparatively modest sample size, and the findings, while statistically robust, require confirmation in larger, multicentric, and more ethnically diverse cohorts before serum uric acid can be recommended for universal adoption. Potentially relevant confounders — including detailed dietary intake, physical activity levels, family history of diabetes, socioeconomic status, and fasting insulin — were not comprehensively evaluated and may independently influence both uric acid metabolism and glucose tolerance. Long-term postpartum follow-up was also beyond the scope of the present study and would be valuable in determining whether elevated first-trimester uric acid predicts subsequent development of overt type 2 diabetes mellitus in these women.

CONCLUSION

The present study demonstrates a clear, statistically robust association between elevated first-trimester serum uric acid and the subsequent development of gestational diabetes mellitus. Women who developed GDM had significantly higher serum uric acid, greater BMI, and older age than women who remained normoglycemic, and serum uric acid showed good discriminatory performance on ROC analysis, with a cut-off of 4.9 mg/dL providing acceptable sensitivity and specificity. Serum uric acid remained an independent predictor of GDM even after adjustment for age and BMI, underscoring its value as a distinct biochemical marker rather than a simple surrogate for known demographic risk factors. Because serum uric acid estimation is inexpensive, minimally invasive, and readily available even in resource-limited settings, it holds promise as a practical adjunctive early screening tool that could help identify high-risk women during the first trimester, well before the conventional 24–28-week OGTT, thereby allowing earlier initiation of dietary counselling, lifestyle modification, and closer antenatal monitoring. Larger, multicentric, prospective studies with long-term postpartum follow-up are recommended to validate these findings and to establish standardised reference cut-off values before first-trimester serum uric acid can be incorporated into routine universal antenatal screening protocols for gestational diabetes mellitus.

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