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Original Research Article

First trimester serum uric acid as an early predictor of gestational diabetes mellitus

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ABSTRACT

Background: First identified during pregnancy, GDM (Gestational diabetes mellitus) is referred by reduced glucose tolerance that results in varied degrees of hyper-glycemia. Usually, the diagnosis is made between twenty four to twenty eight weeks period of gestation. Compared to European women, South Asian, and especially Indian women have an 11 times elevated chance of developing GDM. GDM women are more prone to operative vaginal deliveries, cesarean sections, and complications such as shoulder dystocia during vaginal delivery due to the fetus having macrosomia or large for gestation. Screening and diagnostic methods for GDM depend largely on historical data, clinical examination, and laboratory tests like DIPSI and IADPSG. Early detection and prevention methods for GDM are limited. The purpose of this study was to evaluate the predictive value of serum uric acid levels in the first trimester for GDM in low-risk pregnant women.

Materials and Methods: Following obtaining permission, the level of serum uric acid had been measured from blood samples obtained from low-risk pregnant women. DIPSI testing was done twice, once between the weeks of gestation of 24 and 28 and then again between 28 and 32 weeks of gestation. Regression analysis employing receiver operating characteristic (ROC) curves and logistic regression was used to evaluate serum uric acid's capacity to predict GDM. The Youden index was utilized to establish the cut-off values. A statistically significant result was defined as having a p-value of <0.05.

Results: 106 patients who met the study's inclusion criteria were included. The level of Serum uric acid in the 1^{st} trimester had an AU-ROC of 0.8316 with a cut-off > 3.4 mg/dl, meaning 74.70% sensitivity and 82.61% specificity for GDM prediction. Serum uric acid and GDM showed a significant correlation ($p < 0.001$), according to logistic regression. Individuals whose level of serum uric acid is >3.4mg/dl had 14.02 times greater odds of suffering from GDM (95% CI: 4.28 - 45.92) than those with serum uric acid ≤ 3.4.

Conclusion: A one-year observational study conducted at the Dr. Prabhakar Kore Charitable Hospital and Research Centre, Belgaum, on behalf of KAHER revealed that the improvement of GDM can be predicted early with a 1^{st} trimester serum uric acid cutoff of higher than 3.4 mg/dl.

1. Introduction

Globally, pregnant women are at the risk of developing GDM. It has variable prevalence rates in India, ranging from 0.53% in 2015-16 to 0.80% in 2019-21 with Goa recording the highest unadjusted prevalence at 4.88%, followed by Karnataka at 1.81%.[1] Both predicting and diagnosing GDM are crucial for preventing and managing high risk pregnancies and have long-term health implications for mothers. Research indicates that although pregnant GDM patients generally have a lower cardiovascular risk profile than pregnant GDM patients,[2,3] GDM is known to be linked to the eventual development of type II diabetes.

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The American Diabetes Association recommends universal testing b/w the 24^{th} & 28^{th} week of pregnancy, but there is still debate over the diagnostic criteria and screening techniques for GDM, including the move away from risk-dependent screening.[4] This modification was brought about by doubts regarding the efficacy of previous risk assessment techniques. The advantages of universal screening haven't been proven beyond a reasonable doubt, though. Despite increased GDM cases and the widespread use of glucose-challenge tests and induced labor, current research, like one by Koivunen et al.,[5] have shown no significant impact on cesarean section rates or birth weights. Therefore, there is a need for improved risk assessment strategies until the advantages of comprehensive screening are validated.

Numerous research have investigated at uric acid as a possible risk factor for the development of type II diabetes and have discovered a connection b/w uric acid levels along with GDM.[6] Based on an analysis done in 2021, there are new novel biomarkers to diagnose GDM which include BNP, Afamin, FGF21, ANGPTL8, Placental Lactogen, Galanin, VAP1, FABP4, Fetuin A, PGCD59, Extracellular vesicles and PlGF to name a few.[7–10] The real challenge lies in implementing these in daily practice for early diagnosis of GDM due to the cost and unavailability even at tertiary centres. This study looked at a low-risk group of pregnant women to see if there was a correlation b/w the development of GDM as wel as the level of uric acid at the time of 1^{st} trimester of pregnancy.

2. Materials and Methods

From March 2022 to February 2023, all pregnant women enrolled in the ANC clinic at KLE's Dr. Prabhakar Kore Hospital and Medical Research Centre had been involved in this prospective longitudinal study.

We were able to recruit any antenatal woman who gave informed consent and was in her 1^{st} trimester of pregnancy (<12 weeks gestation). Pre-gestational diabetes mellitus, gestational hypertension, chronic hypertension, gout, arthritis, renal disease, chronic liver disease, eclampsia, and the use of drugs known to raise the level of serum uric acid (example diuretics, aspirin, phenothiazines, anti-tubercular drugs like Ethambutol, Pyrazinamide, and niacin) were among the exclusion criteria.

2.1. Methods

1. Women in their 1^{st} trimester had venous blood samples taken.
2. After centrifuging the samples, an enzymatic colorimetric test with a detection limit of 0.2–25 mg/dl was used to quantify the amounts of uric acid in the serum.
3. DIPSI readings were taken during follow-up visits, which were planned at 24-28 weeks along with 28-32 weeks of gestation.
4. Patients had been administered 75g of glucose regardless of fasting status. After 2 hours, venous samples were collected, and a DIPSI value > 140 mg/dl was indicative of GDM.

The study's objective was to evaluate the relationship b/w high uric acid levels in the 1^{st} trimester and the onset of gestational diabetes mellitus.

2.2. Data processing and statistical analysis

Data were analyzed using R version 4.3.2 and Microsoft Excel.

1. Frequency tables were used to display categorical variables.
2. The continuous variables had been presented as median (Max, Min) or mean ± SD.
3. The Chi-square test examined associations between categorical variables and GDM.
4. Normality of variables had been evaluated by using the Shapiro-Wilk test.
5. The two-sample t-test compared means across GDM groups.
6. The Mann-Whitney U test assessed variable distributions b/w GDM groups.
7. Logistic regression and ROC curves had been used to evaluate the predictive ability of serum uric acid for GDM.
8. Cut-off values were determined using the Youden index, with statistical significance set at $p \leq 0.05$.

3. Results

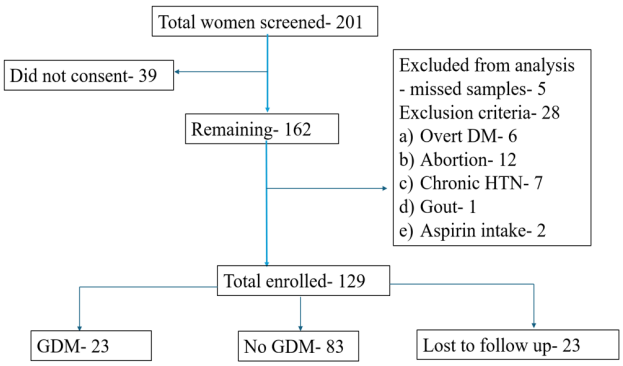

Figure 1:

With 106 participants, the study's mean age was 25.64 ± 3.91 years, with participants ranging in age from 19-42. 150.61 ± 5.52 cm, 54.23 ± 7.34 kg, and 23.87 ± 2.63 kg/m2

were the average height, weight, and BMI, respectively. At enrollment, the average gestational age was 8.91 ± 1.9 weeks. The diastolic blood pressure (DBP) was 74.3 ± 6.64 mmHg and the mean systolic blood pressure (SBP) was 115.28 ± 8.8 mmHg. Of the individuals, 43 (40.57%) were primigravida and 63 (59.43%) were multigravida. Two (3.17%) of the multigravida participants had previously been diagnosed with GDM.

Based on their serum uric acid levels in the 1^{st} trimester, the subjects' distribution is displayed in the Table 1.

Table 1: Serum uric acid distribution in participants

Serum Uric Acid (mg/dl)	Number of subjects (%)
1-2	5 (4.72%)
2-3	38 (35.85%)
3-4	36 (33.96%)
>4	27 (25.47%)
Mean ± SD	3.41 ± 1.03
Median (Min, Max)	3.2 (1.4, 7.6)

Uric acid levels were divided among the 106 participants as follows: 5 (4.72%) had levels between 1-2 mg/dl, 38 (35.85%) between 2-3 mg/dl, 36 (33.96%) between 3-4 mg/dl, and 27 (25.47%) had levels over 4 mg/dl. Serum uric acid levels ranged from 1.4-7.6 mg/dl, with an average of 3.41 ± 1.03 mg/dl.

The distribution of patients with and without GDM in terms of BMI, age, gestational age, diastolic blood pressure (DBP), and systolic blood pressure (SBP) did not differ significantly, according to the findings of the Mann-Whitney U test. Nonetheless, a notable variation in the mean weight was found between patients with and without GDM according to the two-sample t-test. In particular, the mean weight of those with GDM was higher than that of those without GDM. Between the two groups, there was no appreciable difference in mean height.

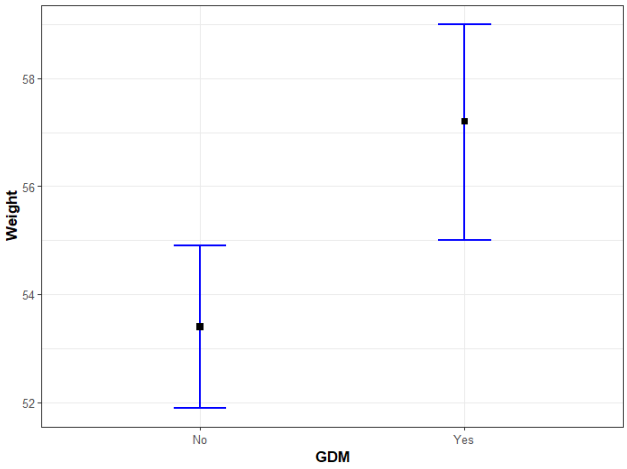

Figure 2: Mean plot of weight over GDM

The comparison b/w GDM and serum uric acid is shown in the Table 2.

Table 2: Comparison of serum uric acid and development of GDM

Serum Uric Acid (mg/dl)	GDM		p-value
	No	Yes	
1-2	5 (6.02%)	0	
2-3	36 (43.37%)	2 (8.7%)	< 0.001*
3-4	29 (34.94%)	7 (30.43%)	
>4	13 (15.66%)	14 (60.87%)	
Mean ± SD	3.15 ± 0.86	4.33 ± 1.06	< 0.001*
Median (Min, Max)	3.1 (1.4, 6.4)	4.1 (3, 7.6)	

The results of the Chi-square test and the Mann Whitney U test show that there is significant variation in the distribution of serum uric acid over GDM.(Table 3)

Table 3: Diagnostic analysis of serum uric acid for predicting GDM

	Serum uric acid
Cut off	> 3.4
Sensitivity (95% CI)	74.70% (63.96%, 83.61%)
Specificity (95% CI)	82.61% (61.22%, 95.05%)
PPV (95% CI)	93.94% (83.74%, 96.40%)
NPV (95% CI)	47.50% (35.23%, 78.53%)
LR +	4.29 (1.75, 10.56)
LR -	0.31 (0.20, 0.46)
AU-ROC (95% CI)	0.8316 (0.7494, 0.9138)
p-value	**<0.001***

When predicting GDM, the serum uric acid AU-ROC is 0.8316 at cutoff > 3.4, indicating 74.70% sensitivity and 82.61% specificity. Serum uric acid is strongly predicting GDM (p-value < 0.001), according to logistic regression.

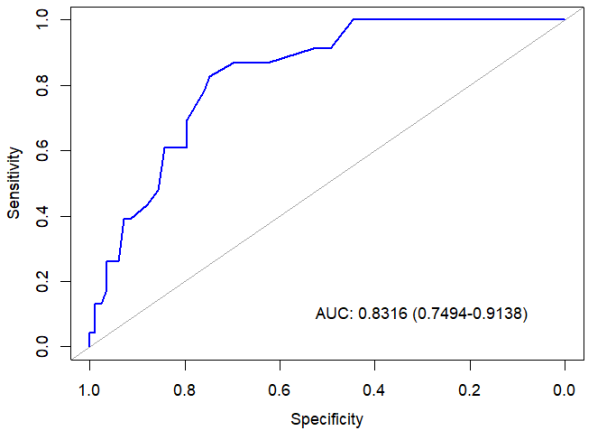

Figure 3: ROC curve of serum uric acid to predict GDM

The Chi square test result showed a strong relationship b/w serum uric acid & GDM. The results show that patients with blood uric acid levels over 3.4 have a 14.02 (95% CI: 4.28 - 45.92) times higher chance of having GDM than persons with levels ≤ 3.4.

There is a strong correlation b/w serum uric acid and GDM, according to the Chi square test results. Blood uric acid levels above 3.4 were found to be associated with a 14.02 (95% CI: 4.28 - 45.92) times higher risk of developing GDM compared to subjects with levels below 3.4. (Table 4)

Table 4: Comparison of serum uric acid based on the cutoff obtained with GDM

Serum uric acid	GDM		p-value
	No	Yes	
No (≤ 3.4)	62 (74.7%)	4 (17.39%)	**< 0.001**^{C}
Yes (> 3.4)	21 (25.3%)	19 (82.61%)	*

Abbreviation: C – Chi square test, * indicates statistical significance

4. Discussion

Because GDM poses significant health risks to the fetus as well as the mother, early detection & treatment of GDM at the time of pregnancy are essential. The purpose of this study is to evaluate the predictive accuracy of 1^{st} trimester serum uric acid levels in a real-world clinical setting at a quaternary care hospital in Karnataka. Despite the growing interest in identifying early markers for GDM, the purpose of this study is to examine the prognostic significance of uric acid levels. The study assesses uric acid's predictive power in relation to established risk factors and clarifies the connection b/w uric acid levels and the onset of GDM.

We discovered a clear connection between elevated levels of uric acid at the time of the 1^{st} trimester of pregnancy along with the onset of GDM. Many studies have pursued a focus on relationship between High Uric acid in pregnancy and insulin resistance and the disturbed metabolism of glucose in this scenario. Insulin dysfunction leading to the outcome of hampered glucose metabolism has been postulated to occur due to hyperuricemia induced oxidative stress and pro-inflammatory cytokines, leading to insulin resistance.[10,11]

The odds ratio among those with uric acid levels above 4.0mg/dL & those with levels below 4.0 mg/dL were 1.82 (95% confidence interval: 1.51-2.21), indicating a significantly increased risk of GDM development in those with b/w 4.0&4.5 mg/dL. This result is consistent with earlier research by Hemaswapnika et al.,[12] Zhu et al., Dheghan et al., and Fieg et al. that also found a link b/w elevated uric acid levels along with GDM.[7–9] Lou et al, who performed a large cohort in China stated that hyperuricemia had the ability to behave as a factor that predisposes for insulin resistance and development of diabetes, especially in the female population, in a time span of a decade.[13] There was also a trial done by Pleskacova and collegues, which was based on uric acid and xanthine levels and their associations with GDM, came to a result of high levels of the above complicating pregnancy with DM.[14]

With an AU-ROC of 0.8316 and a threshold value of 3.4, the current study found that serum uric acid levels had a 74.70% sensitivity and an 82.61% specificity in predicting GDM. Serum uric acid was found to be a significant predictor of GDM ($p < 0.001$) by logistic regression.

Hemaswapnika et al.[12] found that values above 4.5 mg/dL demonstrated an 85% sensitivity & a 68% specificity for identifying GDM in their study on uric acid levels. Even though elevated uric acid levels appear to be a sensitive sign for GDM detection, more specificity is needed. Thus, to increase the accuracy of the predictive models, it becomes imperative to combine uric acid with traditional risk factors.

The distribution of subjects with and without GDM in terms of age, gestational age, BMI, SBP, and DBP did not differ statistically significantly over the course of the research period, according to the current study.

A statistically Important difference in mean weight had been found b/w those with & without GDM based on the results of a two-sample t-test. In particular, the average weight of those with GDM was higher than that of those without GDM. We also took into account known risk variables including body mass index (BMI) and maternal age in our study.

It's noteworthy that the sensitivity and specificity in predicting GDM varied notably among participants aged over 30 years and those with a BMI over 25 kg/m2. These results emphasize the difficulty of precisely predicting GDM and show the possible advantages of including uric acid levels in addition to conventional risk factors in a multifactorial predictive model.

5. Conclusion

According to the study's findings, the onset of GDM can be predicted using serum uric acid levels in the 1^{st} trimester. It can be implemented as 1^{st} trimester screening method for mothers below 12 weeks of gestation. Early detection and treatment can improve a woman's and her unborn child's status and prevent short- and long-term complications in a world where GDM is becoming more common and has many associated complications.

There is growing desperation to find newer methods to predict development of gestational diabetes mellitus due to the high burden it has on the outcome of pregnant women and the neonates born to them based on fascinating studies like the one done by Riis, J.L et al in 2022, on serum uric acid and salivary uric acid being a new mode of predicting development of diabetes in pregnancy.[15]

The goal of implementing an antenatal 1^{st} trimester screening test for GDM is to focus on pre-symptomatic women as well as to hasten management to avoid adverse

pregnancy outcomes like GDM, which was the subject of this study.

6. Source of Funding

None.

7. Conflict of Interest

None.

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