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ASSOCIATION OF ELEVATED FIRST TRIMESTER URIC ACID WITH DEVELOPMENT OF GESTATIONAL DIABETES MELLITUS: A PROSPECTIVE STUDY

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is one of the most common metabolic disorders encountered during pregnancy and is associated with significant short- and long-term complications for both mother and fetus. Early identification of women at risk is crucial for timely intervention. Serum uric acid, a marker commonly linked with metabolic syndrome and insulin resistance, has been proposed as a potential early biomarker for GDM. **Objectives:** This study aimed to investigate the association between elevated first-trimester serum uric acid levels and the subsequent development of GDM in pregnant women attending a tertiary care center in South India. **Methods:** A prospective observational study was conducted among 323 pregnant women with gestational age less than 12 weeks. Serum uric acid levels were measured during the first trimester. All participants underwent screening for GDM using the Diabetes in Pregnancy Study Group India (DIPSI) method at 24–28 weeks of gestation. Data on maternal age, body mass index (BMI), parity, and family history of diabetes mellitus were also collected. Statistical analysis was performed to determine the association between elevated uric acid levels and GDM incidence. **Results:** Of the 323 participants, 17.34% exhibited elevated serum uric acid levels (>3.6 mg/dL), and 20.12% were diagnosed with GDM based on DIPSI criteria. Notably, all women with uric acid levels above 3.6 mg/dL had DIPSI values exceeding 140 mg/dL, revealing a statistically significant association between high uric acid levels and GDM development ($p<0.00001$). Additionally, a significant positive correlation was observed between higher BMI and both uric acid and DIPSI levels ($p<0.0004$). However, maternal age and parity did not show a significant association with uric acid levels. **Conclusion:** First-trimester serum uric acid elevation is significantly associated with the development of GDM, independent of maternal BMI and parity. These findings support the utility of uric acid as a simple, cost-effective biomarker for early GDM risk assessment. Integrating uric acid testing into routine early antenatal screening could facilitate earlier diagnosis and preventive strategies in high-risk populations.

KEYWORDS

Gestational Diabetes Mellitus (gdm), Uric Acid, First Trimester, Dipsi Test, Early Pregnancy Screening, Biomarker

INTRODUCTION

Gestational diabetes mellitus (GDM) is recognized as a common and complex metabolic disorder that arises during pregnancy. It is defined as any degree of carbohydrate intolerance first detected during pregnancy, irrespective of the requirement for insulin therapy[1]. GDM is linked with considerable maternal and fetal risks, making its early detection and management crucial. The rising incidence of GDM worldwide highlights the importance of identifying relevant risk factors, early predictors, and targeted preventive measures. Among emerging biochemical markers, serum uric acid has gained attention for its potential role in predicting GDM[2].

Uric acid is the final product of purine metabolism, generated through enzymatic activity involving xanthine oxidase and dehydrogenase. In non-pregnant populations, elevated uric acid levels—or hyperuricemia—are closely related to components of metabolic syndrome, such as insulin resistance, obesity, and abnormal lipid profiles[3]. Additionally, elevated uric acid has been identified as an independent predictor of type 2 diabetes mellitus (T2DM) within ten years, with a stronger predictive value noted in women. These associations suggest that uric acid may be directly involved in glucose dysregulation and insulin sensitivity, thereby contributing to the underlying mechanisms of GDM[4].

During pregnancy, uric acid levels exhibit a distinct trajectory. Compared to pre-pregnancy values, there is a significant reduction in serum uric acid by around the eighth week of gestation, attributed primarily to increased renal clearance. This decrease generally persists until the 24th week[5]. Nevertheless, elevated uric acid concentrations during gestation have been associated with various complications, including gestational hypertension and GDM. Furthermore, women with a prior history of GDM have been shown to maintain higher serum uric acid levels even outside of pregnancy, indicating persistent metabolic alterations that may predispose them to long-term insulin resistance and development of T2DM[6].

In pregnant women diagnosed with GDM, uric acid levels measured at 24-28 weeks are frequently higher compared to those in normoglycemic pregnancies. This suggests that uric acid could serve as an early biochemical marker for GDM. The proposed mechanisms through which uric acid contributes to insulin resistance are multifactorial[7]. One of the key hypotheses is that uric acid impairs endothelial function by reducing the bioavailability of nitric oxide, which is essential for insulin-mediated glucose uptake in muscle and adipose tissues. This impairment may result in decreased glucose utilization and enhanced insulin resistance[8].

The observed association between elevated uric acid and GDM carries considerable clinical significance. Since GDM is a known precursor to T2DM in later life, recognizing uric acid as an early marker may facilitate preventive healthcare strategies and better long-term outcomes for both mother and child[9].

Despite growing interest in this field, the clinical utility of uric acid as a routine screening marker for GDM remains debated. While some studies have demonstrated a statistically significant link between elevated uric acid in early pregnancy and GDM onset, others report inconsistent results. These differences may be attributed to variability in study methodologies, population demographics, and the diagnostic thresholds used for GDM. This prospective study seeks to bridge this gap by exploring the relationship between first-trimester serum uric acid levels and the subsequent diagnosis of GDM. By focusing specifically on women in early pregnancy, the study aims to determine whether uric acid can function as a reliable early screening tool, enabling timely interventions. A better understanding of uric acid's role in GDM development could also provide broader insights into pregnancy-induced metabolic changes, ultimately guiding future diagnostic and therapeutic advancements.

OBJECTIVES OF THE STUDY

- To assess the association between elevated uric acid levels in the first trimester of pregnancy with Gestational Diabetes Mellitus.

- To assess the predictive value of Serum Uric acid in first trimester.

MATERIALS AND METHODS

Study Population: All antenatal mothers <12 weeks of gestation attending regular antenatal care (ANC) at the OBG outpatient department (OPD) or those admitted to obstetrics wards at AJIMS and the attached hospitals.

Study Design: Hospital-Based Prospective Observational Study
Sample Size: 323

Inclusion Criteria:
- Pregnant women <12 weeks of gestation
- Antenatal mothers attending regular ANC at the OBG OPD or admitted to the OBG wards at AJ Institute of Medical Sciences, Mangaluru and the attached hospitals

Exclusion Criteria:
- Pregnant women >12 weeks
- Gestational Diabetes mellitus in previous pregnancy
- Women with Overt Diabetes Mellitus
- Women receiving any form of steroids
- Women diagnosed with hyperuricemia or other endocrine disorders and chronic renal disorders

Sample Size Calculation: Based on the study conducted by Suvarna Jyothi Ganta[10], assuming a prevalence (p) of 28% (elevated uric acid and development of Gestational Diabetes Mellitus), a 95% confidence interval, and a 5% absolute allowable error (L), the estimated sample size for the study is 322.56, approximately equal to 323.

Sampling Technique: Purposive sampling was adopted to select the study subjects. Categorical data was expressed in terms of percentages.

Method of Data Collection: Ethical clearance was obtained from the institutional ethical committee. An informed written consent was taken from each participant before recruitment into the study. Participants were provided with detailed information regarding the study, its benefits, and their right to participate voluntarily or withdraw at any time without any consequences.

Data Collection Procedure: Pregnant women fulfilling the inclusion criteria were recruited for the study. A detailed history was taken, and clinical examination performed. Information regarding demographic data, obstetrical history, medical history, and family history were collected. Height, weight, and BMI were measured. Gestational age was calculated from the last menstrual period (LMP) and confirmed by ultrasonography. After obtaining informed consent, blood samples were collected for serum uric acid estimation along with other routine serological investigations during the first trimester. Serum uric acid was repeated along with DIPSI during 24-28 weeks of gestation. Serum uric acid levels were assessed using the enzymatic uricase method. Normal range: 1.5 to 6 mg/dl; values >3.5 mg/dl was considered as elevated uric acid in this study.

DIPSI Test: At 24 to 28 weeks of gestation, a one-step test (DIPSI) was conducted to detect GDM using a 75g oral glucose load, irrespective of the last meal. The test is performed because insulin resistance increases during the second trimester, leading to elevated glucose levels in women who are unable to produce sufficient insulin to compensate for this resistance. Antenatal mothers with plasma glucose levels >140 mg/dl after 2 hours were considered high risk.

Statistical analysis: Statistical analysis was performed using SPSS software version 16. Descriptive statistics were used to summarize baseline characteristics, with continuous variables expressed as mean ± standard deviation and categorical variables as percentages. The independent t-test or Mann-Whitney U test was applied for comparing continuous variables, while the chi-square test was used for categorical data. Logistic regression analysis was conducted to evaluate the association between elevated first trimester uric acid levels and the development of gestational diabetes mellitus (GDM). A p-value <0.05 was considered statistically significant.

RESULTS

Baseline Demographics

Table 1 summarizes the baseline demographic characteristics of the 323 participants. The majority of women (55.42%) were aged 20–24 years, followed by 29.72% in the 25–29 age group and 9.91% aged 18–19 years; only 4.95% were aged 30–34 years. Primigravida constituted 64.71% of the study population, while multigravida accounted for 35.29%. Regarding body mass index (BMI), 54.49% had normal BMI (18.5–24.9 kg/m²), 20.43% were overweight (25–29.9 kg/m²), 17.96% were underweight (<18.5 kg/m²), and 7.12% were obese (>30 kg/m²). The mean BMI was 22.69±4.25 kg/m².

Table 1: Baseline demographic characteristics of study participants (N=323)

Characteristic	Category	Number	Percentage
Age (years)	18–19	32	9.91
	20–24	179	55.42
	25–29	96	29.72
	30–34	16	4.95
Parity	Primigravida	209	64.71
	Multigravida	114	35.29
BMI (kg/m²)	<18.5	58	17.96
	18.5–24.9	176	54.49
	25–29.9	66	20.43
	>30	23	7.12

Mean±SD: Age 24.43±4.13 years, BMI 22.69±4.25 kg/m²

Serum Uric Acid and DIPSI Distribution

Table 2 presents the distribution of serum uric acid levels in the first and second trimesters along with DIPSI test results. In the first trimester, 34.05% had uric acid 1.5–2.5 mg/dL, 48.61% had 2.6–3.5 mg/dL, and 17.34% had elevated levels >3.6 mg/dL (mean 2.66±0.73 mg/dL). In the second trimester, 85.14% had levels <3.5 mg/dL and 14.86% had >3.5 mg/dL (mean 2.62±0.71 mg/dL); the difference between trimesters was not significant (p=0.42). GDM was diagnosed in 20.12% of participants based on DIPSI values >140 mg/dL (mean DIPSI 136.24±23.36 mg/dL).

Table 2: Distribution of serum uric acid and DIPSI values

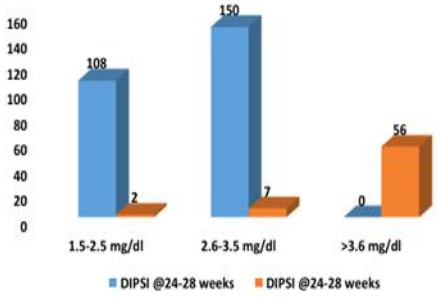
Parameter	Category	Number	Percentage	Mean±SD
First-trimester uric acid (mg/dL)	1.5–2.5	110	34.05	2.66±0.73
	2.6–3.5	157	48.61	
	>3.6	56	17.34	
Second-trimester uric acid (mg/dL)	<3.5	275	85.14	2.62±0.71
	>3.5	48	14.86	
DIPSI test (mg/dL)	<140	258	79.88	136.24±23.36
	>140	65	20.12	

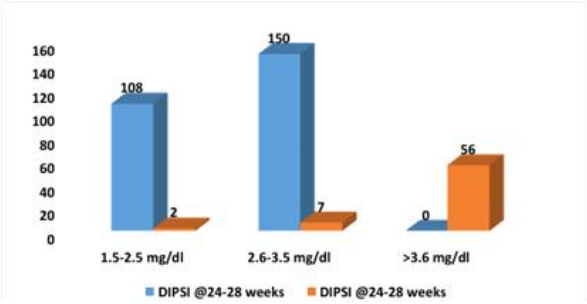
Primary Correlation: First-Trimester Uric Acid and GDM

Table 3 shows the correlation between first-trimester serum uric acid levels and DIPSI results at 24–28 weeks. Nearly all women with uric acid levels of 1.5–2.5 mg/dL and 2.6–3.5 mg/dL had DIPSI values below 140 mg/dL, whereas **all 56 women (100%) with uric acid >3.6 mg/dL had DIPSI values above 140 mg/dL**. The mean DIPSI level in the >3.6 mg/dL group was 175.27±14.33 mg/dL, compared to 126.66±14.57 mg/dL and 128.00±14.16 mg/dL in the lower uric acid groups. This association was highly significant (p<0.00001).

Table 3: Correlation between first-trimester serum uric acid and DIPSI values at 24–28 weeks

First-trimester uric acid (mg/dL)	Number	DIPSI <140 mg/dL	DIPSI >140 mg/dL	Mean DIPSI (mg/dL)	P value
1.5–2.5	110	108	2	126.66±14.57	<0.0000
2.6–3.5	157	150	7	128.00±14.16	1
>3.6	56	0	56	175.27±14.33	
Total	**323**	**258**	**65**	**136.24±23.36**	





Graph1: Correlation between OGTT values (DIPSI) @24-28 weeks and Serum Uric acid level at first trimester

Secondary Associations

Table 4 summarizes the associations between BMI, age, family history of diabetes mellitus, and both uric acid levels and DIPSI results.

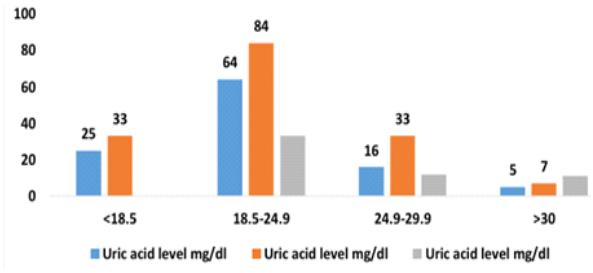
BMI: Women with lower BMI (<18.5 kg/m²) predominantly had uric acid levels below 3.6 mg/dL, while those with BMI >30 kg/m² had a higher proportion of elevated uric acid (>3.6 mg/dL) (p<0.0001). Regarding DIPSI, no woman with BMI <18.5 kg/m² had DIPSI >140 mg/dL, whereas 38.89% of those with BMI >30 kg/m² had abnormal DIPSI values. The association between higher BMI and elevated DIPSI was statistically significant (p=0.0004).

Age: Advanced maternal age (≥25 years) was significantly associated with abnormal DIPSI results (p=0.0001). However, age showed no significant association with uric acid levels (p=0.397).

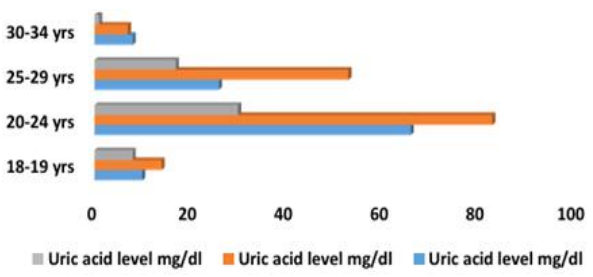
Family history of diabetes: A positive family history was present in 92.26% of participants. Family history was significantly associated with both elevated uric acid levels (p=0.0007) and abnormal DIPSI values (p=0.001). Notably, a higher proportion (19.64%) of women without a family history had uric acid >3.6 mg/dL compared to those with a family history.

Table 4: Secondary associations with uric acid and DIPSI

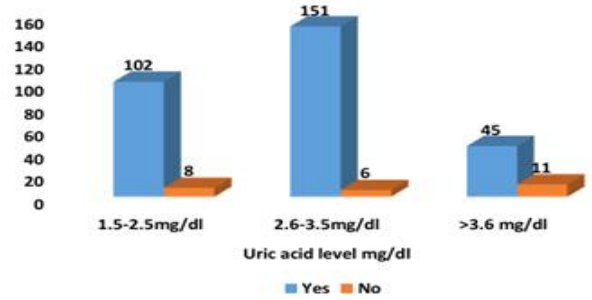
Variable	Category	Association with uric acid (p value)	Association with DIPSI (p value)
BMI (kg/m²)	<18.5, 18.5–24.9, 25–29.9, >30	<0.0001	0.0004
Age (years)	18–19, 20–24, 25–29, 30–34	0.397	0.0001
Family history of DM	Yes / No	0.0007	0.001



Graph 2:BMI and Serum Uric acid levels



Graph 3:Serum Uric acid levels in different age group



Graph 4: Association between Family History of DM and Serum Uric acid levels

Other Findings

Parity did not show a significant correlation with either serum uric acid levels (p=0.833) or DIPSI results (p=0.37). First-trimester random blood glucose levels were <100 mg/dL in 85.45% of participants (mean 85.41±19.67 mg/dL). Detailed data on age-specific uric acid distribution, parity-wise comparisons, and complete family history analyses are provided in **Supplementary Tables S1–S16**.

DISCUSSION

Gestational diabetes mellitus (GDM) is increasingly recognized as a major public health issue due to its association with adverse maternal and fetal outcomes. Early identification of at-risk women is essential for timely intervention and improved prognosis. Uric acid, an end product of purine metabolism, has emerged as a potential early marker of metabolic disturbances during pregnancy. Elevated serum uric acid (SUA) levels in the first trimester have been implicated in insulin resistance and impaired glucose tolerance. Several studies have reported a relationship between hyperuricemia and subsequent development of GDM, although findings remain variable across different populations. The current study aims to explore this association in a South Indian cohort, providing insight into whether elevated SUA in early pregnancy is predictive of GDM. Conducted as a prospective observational study at AJ Institute of Medical Sciences (AJIMS), Mangalore, and its affiliated hospitals, the study included 323 antenatal women with gestational age less than 12 weeks.

In terms of age distribution, the majority of participants (55.42%) were aged between 20 and 24 years, followed by 29.72% in the 25-29 age range, and 9.91% under the age of 20. These findings contrast with data from Sivasarupa et al[6], where the most prevalent age group was 26-30 years. Similarly, larger studies by Laughon et al[11] and Wolak et al[12] have also reported a higher proportion of women in the slightly older age group during the first trimester. Most participants in the current study were assessed at 10 weeks (26.63%), followed by 9 weeks (24.46%) and 12 weeks (17.65%), with the mean gestational age at first assessment of 9.67±1.47 weeks.

Regarding parity, 64.71% of participants were primigravida, while 35.29% were multigravida. This distribution is consistent with previous studies, such as Sivasarupa et al[13] (53.8% primigravida), Rasika C et al[14] (51.4%), and Ganta SJ et al[10] (55.8%), reflecting a predominance of first-time mothers. In contrast, El-Gharib et al[15] reported a lower proportion of primigravidas (24.8%).

The BMI profile of the study population revealed that 54.49% of participants had normal BMI (18.5-24.9 kg/m²), while 20.43% were overweight (25-29.9 kg/m²), 17.96% were underweight (<18.5 kg/m²), and 7.12% were obese (BMI >30 kg/m²). The mean BMI was 22.69±4.25 kg/m². A statistically significant association (p=0.001) was found between BMI and the risk of developing GDM. Importantly, even women with normal BMI but elevated SUA levels before 15 weeks showed higher glucose levels at 24-28 weeks, indicating that SUA may serve as an independent predictor for GDM regardless of BMI. This observation is consistent with findings from Laughon KS et al[16]., who reported that while SUA levels correlated with BMI, high SUA in early pregnancy was independently associated with an increased risk of GDM.

The majority of the study population (85.14%) had serum uric acid levels below 3.5 mg/dL, while 14.86% had levels above 3.5 mg/dL. The mean serum uric acid level was 2.62±0.71 mg/dL. When compared with other studies, the mean UA level observed in the

present research appears slightly lower. For example, in the study conducted by Sivasarupa et al the mean uric acid level was higher at 3.81 mg/dL. Aker SS et al[17] also reported a similar mean UA level of 3.72±1.14 mg/dL. The study by Laughon SK et al[16] showed a mean uric acid level of 3.08±0.85 mg/dL. On the other hand, findings from the study by Baliga et al. reported a mean UA level of 2.83 mg/dL closely aligning with the present study's results.

In this study, 79.88% of participants had DIPSI results below 140 mg/dL, while 20.12% showed values above this threshold. When uric acid levels were analyzed in conjunction with DIPSI outcomes, a clear pattern emerged. Nearly all women with uric acid levels in the 1.5-2.5 mg/dL and 2.6-3.5 mg/dL ranges had DIPSI values below 140 mg/dL. In contrast, all 56 women with uric acid levels exceeding 3.6 mg/dL had DIPSI values above 140 mg/dL. Notably, the mean DIPSI level in this group was 175.27±14.33 mg/dL, with a highly significant p-value (<0.00001), suggesting a strong association between elevated first-trimester uric acid levels and impaired glucose metabolism during pregnancy.

Comparative analysis with the study by Sivasarupa et al [13], which utilized IADPSG-ADA criteria for diagnosing GDM, shows consistency in prevalence. Using these criteria, 11 women (10.4%) in the present study were diagnosed with GDM. This rate is similar to that reported by Wolak T et al[12]., who found a GDM prevalence of 7.6%. However, lower rates were noted in studies by Laughon SK et al[16]. (4.6%) and Baliga P et al. (2.28%)[18].

When age was evaluated in relation to uric acid levels, the highest SUA levels (>3.6 mg/dL) were more frequently observed in older women, particularly in the 25-29 year group, although the majority of participants were from the 20-24 year group (55.42%). Despite this trend, the p-value (0.397) indicates no statistically significant association between age and uric acid levels. Similarly, parity did not show a significant correlation with SUA levels. These findings align with Rasika C et al., who found no significant link between parity and GDM incidence (p=0.870), even when assessing SUA[14].

In terms of BMI, women with lower BMI (<18.5 kg/m²) predominantly had uric acid levels below 3.6 mg/dL. Conversely, women with BMI >30 kg/m² had a higher proportion of uric acid levels above 3.6 mg/dL. The p-value (<0.0001) confirms a statistically significant association between BMI and uric acid. These results parallel findings by Rasika C et al., who observed a similar proportional trend in SUA with increasing BMI, although not statistically significant in their study[14]. However, they did find a significant relationship between BMI and GDM risk (p=0.001), reinforcing the dual impact of elevated BMI and uric acid in disturbed glucose metabolism.

In evaluating family history, 92.26% of women reported a positive family history of diabetes. Among women without a family history, a higher percentage (19.64%) had uric acid levels exceeding 3.6 mg/dL compared to those with a family history (80.36%). This yielded a statistically significant p-value (0.0007), indicating an unexpected inverse association. These findings are in line with Laughon SK et al, who emphasized uric acid's role as an independent predictor of GDM—one not necessarily tied to traditional risk markers such as BMI or family history[16].

The majority of women were in the 20-24 age group (55.42%), with a higher proportion having DIPSI values below 140 mg/dL. However, the percentage of women with elevated DIPSI levels (>140 mg/dL) was higher in the older age groups, particularly among those aged 25-29 years. The p-value (0.0001) indicates a statistically significant association between age and DIPSI results. These findings are consistent with existing literature, where advanced maternal age is recognized as a risk factor for GDM.

In examining family history, 16.92% of women with a positive family history of diabetes had DIPSI >140 mg/dL, compared to just 5.43% with DIPSI <140 mg/dL. A p-value of 0.001 confirms a statistically significant relationship between family history and abnormal glucose tolerance during pregnancy. These findings support the well-established role of genetic predisposition in GDM development, similar associations have been observed in previous research, including studies by Singh U et al. and Laughon SK et al[16].

In terms of biochemical correlation, 56 women in this study were found to have SUA levels >3.5 mg/dL, and 65 women were diagnosed with GDM. Comparatively, the study by Rasika C et al[14]. reported only 16 women with SUA >3.5 mg/dL, and just 2 were diagnosed with GDM. On the other hand, Ganta SJ et al[10]. observed a higher burden, with 92 women having SUA >3.5 mg/dL and 88 diagnosed with GDM, suggesting a very strong association between elevated SUA and GDM in their population.

CONCLUSION

This prospective study highlights a significant association between elevated first-trimester uric acid levels and the subsequent development of gestational diabetes mellitus (GDM), independent of BMI and parity. Women with higher BMI and advanced maternal age showed a greater risk of elevated uric acid and glucose intolerance. Elevated uric acid levels were also significantly correlated with abnormal DIPSI values, supporting its utility as an early predictive biomarker for GDM. The findings underscore the importance of incorporating uric acid screening in early antenatal care to identify high-risk women. The study highlights the need for targeted screening and early intervention in pregnant women with elevated BMI, as they are at a substantially higher risk of developing GDM and related complications. Early detection can guide timely interventions and potentially reduce the burden of GDM-related complications.

LIMITATIONS

1. Limited gestational age range: Our study only followed participants up to 28 weeks of gestation, which may not capture the development of gestational diabetes mellitus (GDM) beyond this period. Future studies should consider longer follow-up periods to assess the association between elevated serum uric acid and GDM development throughout pregnancy.

2. Lack of neonatal outcome data: This study did not measure neonatal outcomes, which could provide valuable insights into the impact of elevated serum uric acid on fetal health. Further research should prioritize collecting neonatal outcome data to better understand the implications of our findings.

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