DOI -10.21276/obgyn.2023.10.1.12 *ISSN Print – 2454-2334; ISSN Online – 2454-2342*

RESEARCH ARTICLE

A study of association of uric acid with the development of gestational diabetes mellitus

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ABSTRACT

Objectives: To evaluate the value of serum uric acid in early pregnancy to predict the development of gestational diabetes mellitus (GDM). **Methods:** This prospective observational cohort study included 336 women in their first trimester of pregnancy (<13 weeks of gestation). Uric acid was measured using colorimetric assay with a detection limit of 10 mg/dl. GDM was diagnosed using DIPSI recommended method at 24-28 weeks of gestation. The primary outcome of the study was the association of serum uric acid levels with occurrence of GDM and secondary outcomes were the correlation of age, body mass index (BMI), and high risk factors with the development of GDM. P - value <0.05 was considered statistically significant. **Results**: Total 336 antenatal women were studied. Most were in 21-25 years age group (51.49%), primigravida (65.18%) and had BMI <25kg/m^2 (86.01%). High-risk factors were present in 40(11.9%) patients. Serum uric acid level was >3.5 mg/dl in 54 (16.07%) participants. The prevalence of GDM was 27(7.71%) among which 24 cases had higher serum uric acid. Higher age carried a significantly higher odds of occurrence of GDM with odds ratio of 8.125 (P=0.0004). Presence of higher-risk factors and increased uric acid carried significantly higher odds of 11.722 and 74.4, respectively for occurrence of GDM (P<0.0001). ROC curve showed that serum uric acid level with a criteria of >3.5 carried a sensitivity of 88.9% and specificity of 90.3% for predicting GDM. **Conclusion**: Antenatal women without the known high-risk factors of DM developed GDM when the serum uric acid level was > 3.5 mg/dl. In conclusion, higher serum uric acid levels in the early pregnancy can serve as a novel marker for predicting the development of GDM.

Keywords: First trimester, fetomaternal complications, gestational diabetes mellitus, uric acid.

Gestational diabetes (GD) is defined as a certain amount of glucose intolerance which arises or is first recognized at the time of pregnancy [1, 2]. GDM is one of the most important complications during pregnancy which is associated with both maternal and fetal morbidity and mortality [3].

The range of prevalence of GDM is between 1% and 14% of all the pregnancies. A variation is reported in rates of GDM prevalence in India, which varies from <4% to 18% [4, 5]. National statistics on the total prevalence of type 2 diabetes in the Indian population is emerging [6, 7]. The overall prevalence is at 7%, with rates higher in urban than rural areas, in older age groups, and in those with higher socioeconomic status (SES) [6].

The prevalence of GDM is rising, in part reflecting the changing demographics of women of childbearing age, with an increasing incidence of both obesity and advanced maternal age. The prevalence of pre-gestational diabetes (diabetes that was present before pregnancy) has increased in the past decade, especially as a result of the increase in type 2 diabetes. In a recent Indian study, Swaminathan et al [3] reported that based on fourth National Family Health Survey, the weighted age-adjusted prevalence of GDM was 1.3% (95% CI, 1.1%-1.5%), with the prevalence being 2.4% (95% CI, 1.0%-3.8%) at age ≥35 years and 1.8% in women with BMI of ≥27.5 kg/m^2.

GDM or even slight degree of intolerance to

Received: 6th November 2021, **Peer review completed**: **26th March 2022**, **Accepted: 6th April 2022**.

Sharma N, Jha S, Pundir S, Sahu C. A study of association of uric acid with the development of gestational diabetes mellitus. The New Indian Journal of OBGYN. 2023; 10(1): 71 -6.

carbohydrates has been found to increase the complications during pregnancy for both mother and the fetus [8]. A large body of evidence supports the fact that uric acid could be an important risk factor for development of type 2 diabetes, especially in women [9]. This evidence is more important in the first trimester of pregnancy since during that period, there is a natural decline in the uric acid by 25-35% value on account of increased glomerular filtration rate. So, if some women have high uric acid values in the first trimester, they show a heightened risk of development of GDM in the second or third trimester of pregnancy [10]. However not many studies have conducted to prove this among Indian women and this warrant future investigations and management of patients.

So, we intended this study to assess the relationship between maternal serum uric acid concentration in early pregnancy and development of gestational diabetes mellitus (GDM), so that early steps can be taken for the management of the patients and deleterious effects of the disease on the mother and the fetus can be prevented.

Methods

This prospective observational cohort study was conducted at department of obstetrics and gynaecology from October 2016 to May 2017, after approval by ethical and scientific committee. The study population included 350 women during the first trimester of pregnancy (<13 weeks of gestation). Those with pre-existing diabetes mellitus, any medical disorder, on medications causing hyperuricemia, and those with history of smoking/alcohol intake were excluded. All the participants were provided adequate information in relation to the study and a duly informed written consent was obtained.

The sample size for the present study was based on the study findings of Kappaganthu A et al [11] who observed that serum uric acid cut-off value 3.4mg/dl had a sensitivity of 90%, specificity of 95% and a negative predictive value of 99% for predicting subsequent development of GDM. These values were used as reference and the sample size derived for the present study was 350 with 15% precision and 5% alpha error.

All routine antenatal investigations (ANC profile) along with serum uric acid concentration were carried out. Uric acid was measured using calorimetric assay with a detection limit of 10 mg/dl. GDM was diagnosed using DIPSI recommended method at 24-28 weeks of gestation [12]. 75 gm glucose was given to patients irrespective of the fasting state and if after 2 hours blood glucose was ≥ 140mg/dl, patient was diagnosed as gestational diabetes mellitus.

Information was collected on other covariates like maternal socio-demographic, behavioral and medical characteristics, using structured questionnaires. Covariate information included maternal age, pre-pregnancy weight, height, reproductive and personal and family medical history. Pre-pregnancy body mass index (BMI) was used as an index of maternal adiposity (weight/ height^2, units of kg/m^2). The primary outcome of the study was the association of serum uric acid levels with occurrence of GDM and secondary outcomes were the correlation of age, BMI, and high risk factors with the development of GDM.

Statistical analysis: The data presentation is done in the tables and graphs after entering into "Microsoft EXCEL spreadsheet". Qualitative variables like gravida and high risk factors were analysed using Chi-Square test. For cell value <5 like age, body mass index and serum uric acid levels then Fisher's exact test was used. Odds ratio with 95% CI for occurrence of GDM was calculated. Receiver operating characteristic curve determined the cut off for serum uric acid which helped in predicting GDM. Sensitivity, specificity, positive predictive value, and negative predictive value was calculated.

The final analysis was done by "Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, version 21.0". For statistical significance, "p value of less than 0.05" was considered statistically significant.

Results

In the our study, total 350 antenatal women were enrolled in the study, out of which 11(3.14%) were lost to follow up and 3 (0.86%) aborted. 336 antenatal women remained for analysis out of which 27(7.71%) women developed GDM on follow up.

Most of the women were in 21-25 years age group (51.49%). Most of the women were primigravida (65.18%) and had BMI <25kg/m^2 (86.01%). High-risk factors were present in 40(11.9%) patients. Serum uric acid level was >3.5mg/dl in 54(16.01%) participants (table 1). The prevalence of GDM was 27(7.71%) among which 24 cases had higher serum uric acid.

Higher age carried a significantly higher odds of occurrence of GDM with odds ratio of 8.125 (P=0.0004). Gravida showed no significant association with GDM (OR=0.760, P=0.501). BMI (≥30 kg/m^2) also showed no significant association with GDM (OR=0.756, P=0.663).

Presence of higher-risk factors carried significantly higher odds of 11.722 for occurrence of GDM (P<0.0001). Increased uric acid also carried significantly higher odds occurrence of GDM (r=74.4, P<0.0001) (table 2). ROC curve showed that serum uric acid level with a criteria of >3.5 carried a sensitivity of 88.9% and specificity of 90.3% for predicting GDM (figure 1).

Table 1: Distribution of baseline demographics

Baseline demographic	Frequency (N %)
Age group (in years)	
≤ 20	31(9.23)
21-25	173(51.49)
26-30	71(21.13)
>30	61(18.15)
Gravida	
Multigravida	117(34.82)
Primigravida	219(65.18)
BMI(Kg/m^2)	
<25	289(86.01)
25-29.9	40(11.9)
≥ 30	7(2.08)
High risk factors	
Absent	296(88.1)
Present	40(11.9)
Serum uric acid level(mg/dl)	
>3.5	54(16.07)
≤ 3.5	282(83.93)

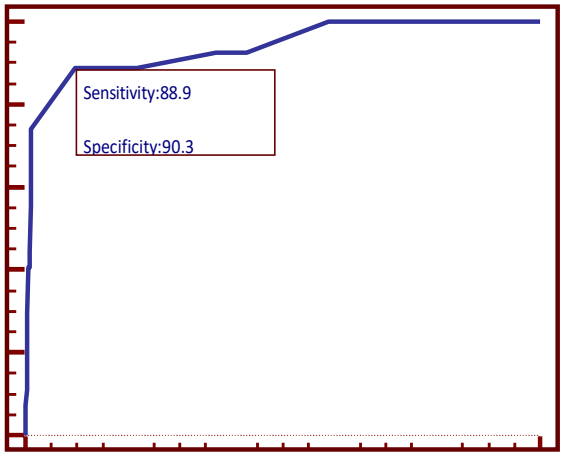

Figure 1: Receiver operating characteristic curve of serum uric acid for predicting GDM

Table 2: Comparison of baseline demographics between patients with and without GDM.

Baseline demographic	GDM No	Yes	Total	P value	Odds ratio (95% CI)
Age(years)					
≤ 20	30(9.71%)	1(3.70%)	31(9.23%)		1
21-25	163(52.75%)	10(37.04%)	173(51.49%)	0.0004*	1.84(0.227 to 14.913)
26-30	68(22.01%)	3(11.11%)	71(21.13%)		1.324(0.132 to 13.249)
>30	48(15.53%)	13(48.15%)	61(18.15%)		8.125(1.011 to 65.331)
Gravida					
Multigravida	106(34.30%)	11(40.74%)	117(34.82%)	0.501†	1
Primigravida	203(65.70%)	16(59.26%)	219(65.18%)		0.760(0.340 to 1.695)
Body mass index (kg/m^2)					
<25	266(86.08%)	23(85.19%)	289(86.01%)		1
25-29.9	36(11.65%)	4(14.81%)	40(11.90%)	0.663*	1.285(0.420 to 3.928)
≥ 30	7(2.27%)	0(0.00%)	7(2.08%)		0.756(0.419 to 13.653)
High risk factors					
Absent	283(91.59%)	13(48.15%)	296(88.10%)	<0.0001†	1
Present	26(8.41%)	14(51.85%)	40(11.90%)		11.722(4.984 to 27.566)
Serum uric acid levels (mg/dl)					
>3.5	30(9.71%)	24(88.89%)	54(16.07%)	<0.0001*	74.4 (21.147 to 261.753)
≤ 3.5	279(90.29%)	3(11.11%)	282(83.93%)		1

Discussion

We found that increase in serum uric acid levels may be a good predictor for the development of gestational diabetes mellitus.

During pregnancy, GDM develops in women whose pancreatic function is inadequate to deal with the insulin resistance that develops with being pregnant. GDM prediction and diagnosis are critical for ongoing pregnancies and have significant ramifications for the mother's long-term health. GDM is a substantial risk factor for the development of type II diabetes and is linked to a worse cardiovascular (CV) risk profile when compared to those without GDM [13].

The metabolism of uric acid rests on the activity of the enzyme "xanthine oxidase" which breaks down xanthine into uric acid during purine metabolism. The normal serum uric acid levels should be between 3.5 and 7.2 mg/100 ml in men, while women's levels are between 2.6 and 6.0 mg/100 ml. The explanation for this is that estrogen increases uric acid excretion during the reproductive period. The solubility limit of uric acid in extracellular fluids is 7.0 mg/dL, and individuals with higher serum levels are considered hyperuricemic [14].

In the present study, the serum uric acid level with a criteria of >3.5 mg/dL demonstrated the sensitivity of 88.9% and specificity of 90.3% for predicting GDM. This corroborates with the previous studies' findings. Aparna et al [15] reported that serum uric acid level at cut-off of 3.4 mg/dL was found to have had sensitivity and specificity of

90% and 95%, respectively for the development of GDM. Amudha P et al [16] declared that a>3.6mg/dl uric acid cut off carries a 92% sensitivity and 99% specificity for predicting the development of GDM. Reason behind this given in their study was that higher serum uric acid levels during the early trimester and mid-trimester causes pre-existing metabolic derangements resulting in poor maternal adaptations in the later months of pregnancy; thereby predisposing the women to GDM.

Insulin resistance is linked to serum uric acid, and numerous mechanisms have been proposed to explain this link. According to Nakagawa et al, [17] (2007) uric acid inhibits nitric oxide generation and promotes endothelial dysfunction. Nitric oxide is required for "insulin-mediated glucose uptake into cells in skeletal muscles and adipose tissue". As a result, a reduction in nitric oxide causes a reduction in glucose uptake and the development of insulin resistance [18]. Another explanation is that increased uric acid can produce "insulin resistance, inflammation, and oxidative stress" in adipocytes, all of which contribute to metabolic syndrome development [19].

Hyperinsulinemia, hypertension, dyslipidemia, and obesity are all linked to an increase in serum uric acid levels, which indicates that increased uric acid levels are one of the factors of the metabolic syndrome. The serum uric acid levels decrease by 25% to 35% early in pregnancy because of an enhanced renal clearance from increased glomerular filtration rate or lower proximal tubular reabsorption, as well as alterations in its production rate. It probably approximates preconception uric acid levels in the first trimester, and increased levels may recognize women who are susceptible to metabolic syndrome and have a higher chance of developing GDM. [3]

Increased fetal production, decreased albumin binding, and reduced uric acid clearance may cause uric acid levels to rise as pregnancy progresses until it reaches non-pregnant levels at the end of the pregnancy. [3]

Besides increased uric acid, we found that higher age had significantly higher odds of occurrence of GDM with odds ratio of 8.125 (P=0.0004). Thus, increasing age was significantly associated with development of GDM (P<0.05).

This is consistent with the findings by Ali et al, [14] as increasing age was highly-significantly correlated to increasing plasma glucose level at 24 to 28 weeks. Amudha P et al [17] and Aparna K et al [15] also found significant correlation between age and development of GDM in their study. Similar findings are reported in previous studies that also found increase in prevalence of GDM with age in women [20, 21].

Although maternal age is a known risk factor for GDM, there is no consensus on the age at which the risk of GDM increases significantly. The lowest cut-off in the literature is 25 years, as recommended by the American Diabetes Association, but there is little evidence to back this up [22]. Stewart and colleagues discovered that obesity during pregnancy can raise inflammatory levels, and that inflammation is linked to increased maternal age, which is a risk factor for GDM [23, 24]. Previous research has also found that as people get older, their glucose tolerance deteriorates, and obesity is linked to insulin resistance and receptor abnormalities [25, 26].

GDM is amain cause of mortality as well as morbidity for mother and infant around the world [27]. The pregnant women with GDM are at predisposed to increased risk of development of gestational hypertension, pre-eclampsia and caesarean section [28]. In addition, prior history of GDM leads to increased risk of development of T2DM and CV diseases. Consistent with these facts we also found that the presence of high-risk factors increased the odds for development of gestational diabetes mellitus.

There is an increased risk of macrosomia, congenital abnormalities, and development of neonatal hypoglycemia, and subsequently T2DM among infants born to women with GDM. Thus, understanding the burden of GDM is essential for healthcare policy makers for detection and intervention at appropriate time [29].

There is a need of a screening technique that can predict the GDM development in the second trimester when women visit for first antenatal checkup, so that women can be counseled regarding increased risk for development of GDM and requirement of more antenatal visits [14]. Providing intervention and management at appropriate time to women with GDM would help to prevent the adverse maternal as well as perinatal outcomes and subsequently long-term consequences. The aim of timely screening and treatment of GDM is "preventing stillbirths, congenital anomalies, recurrent abortion, pre-eclampsia, intrauterine death and reducing the incidence of macrosomic babies, thus decreasing maternal and perinatal morbidity and mortality" [14]. This study provided the evidence that a simple novel marker like uric acid can be useful enough to predict the development of GDM. This information can be used by practicing obstetricians for a better management in the preventive aspect of GDM.

Limitations: The limitations of the study were a short follow up which was restricted up to 28 weeks of gestation of pregnancy and thus the feto-maternal outcomes could not be recorded and assessed.

Conclusion

In conclusion, the present study showed that increased uric acid levels during the early pregnancy holds the predictive capacity for development of GDM. In view of this, higher serum uric acid levels in the early pregnancy can serve as a novel marker for predicting the development of GDM, however larger follow up studies are needed to label it a baseline screening investigation for prediction of GDM, and so that GDM associated adverse maternal and perinatal complications can be averted.

Conflict of interest: None. **Disclaimer:** Nil.

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