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Original Research Article

Assessment of gestational diabetes mellitus development in correlation with elevated first trimester serum uric acid levels

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ABSTRACT

Background: More than 10% of pregnancies in the world are affected with gestational diabetes mellitus (GDM), making it a prevalent pregnancy complication. The goal of this research was to examine whether or not higher serum uric acid levels in the first trimester of pregnancy are associated with an increased risk of developing GDM.
Methods: The study was conducted on 56 first-trimester pregnant females at risk of GDM attending the outpatient clinic of the S. S. institute of medical sciences, Davanagere. All cases underwent estimation of uric acid levels <15 weeks, 24 to 28 weeks, and oral glucose challenge test (OGCT) at 24 to 28 weeks.
Results: In our study, among 56 pregnant women, 17 (30.3%) developed GDM. Of these 12 women (70.6%) with GDM had higher uric acid levels and 5 women (29.4%) with GDM had normal uric acid levels. Uric acid levels were higher in women with a higher BMI.
Conclusions: GDM development is significantly correlated with elevated serum uric acid levels in the first trimester. Early interventions by dietary and exercise regimes in these patients can reduce the maternal and neonatal complications.

Keywords: Hyperuricemia, OGCT, Serum uric acid, Diabetes in pregnancy study group India, GDM

INTRODUCTION

Diabetes complicating pregnancy has become more common worldwide, around 3-10% of pregnancies. The reason for this rise in the prevalence of diabetes is mainly change in the lifestyle, dietary habits, older age at first conception polycystic ovarian disease and obesity.[1] American diabetes association and world health organization define GDM as "any degree of glucose intolerance with onset or first recognition during pregnancy."[2,3] Uric acid in the first trimester is most likely comparable to preconception uric acid levels. Elevated uric acid levels may identify women at risk of developing GDM who are prone to metabolic syndrome.[1]

In pregnancy, uric acid is correlated with insulin resistance in women with gestational hypertension and GDM.[1] Women with hypertensive disorders of pregnancy had greater uric acid levels, and at 24-28 weeks of pregnancy, women with GDM have higher uric acid levels than women without GDM.[3] Increased expression of xanthine oxidase and subsequent generation of uric acid and reactive oxygen species is induced by placental hypoxia, ischemia, and cytokines like interferon[4]. Serum uric acid levels typically decrease significantly during pregnancy from the eighth to the twenty-fourth week due to increased glomerular filtration rate and reduced reabsorption of uric acid from the renal tubules. Elevated levels may indicate women who are predisposed to metabolic syndrome and have an increased risk of developing GDM. It most likely closely resembles preconception uric acid levels in the first trimester.[3] A rate of 79.4 million cases, or a 15.1% increase

from 2000, is anticipated in 2030 in India, where the frequency of GDM was 2.5% in 1982, 7.62% in 1991, and 16.5% in 2003. South Asian females, particularly Indian females, have an 11-fold increased risk of GDM when compared to European females.[5] GDM is associated with various maternal complications like pre-eclampsia, preterm deliveries, polyhydramnios, still births, increased rates of LSCS and in fetus CNS, cardiac and genitourinary anomalies and NTD, macrosomia, still birth, birth injuries, hypoglycemic episodes post-delivery, hyperbilirubinemia and RDS.[5] High levels of uric acid in the early stages of pregnancy may be a sign of a metabolic disturbance that will impede the physiological adaptations that pregnant women typically experience, making them more susceptible to the development of GDM.[5]

Table 1: Pregnancy status.

Pregnancy status	Uric acid (mg/dl)
Non-pregnant adult	2.5-5.6
First trimester	2.0-4.2
Second trimester	2.4-4.9
Third trimester	3.1-6.3

Various studies have shown that serum uric acid is related to obesity, hypertension, dyslipidemia, and hyperinsulinemia, indicating that it may be one of the many factors that contribute to the metabolic syndrome.[6] GDM is a relatively common pregnancy disorder. Pregnancy outcomes and the health of the mother after delivery are greatly influenced by the ability to anticipate and diagnose GDM.[7] Preeclampsia and cesarean section are short-term maternal consequences of GDM, and long-term risk of T2DM is increased. If GDM is not treated, mothers are more likely to develop preeclampsia and require a cesarean section. While GDM in and of itself is not an indication for cesarean section, complications associated with GDM, such as preeclampsia and macrosomia, may indicate it.[8] The purpose of this research is to ascertain whether or not maternal serum uric acid levels in the first trimester can reliably and clinically useful to predict the occurrence of gestational diabetes in the succeeding trimester.

Aims and objectives

The only aim and objective of the study is to study the association between serum uric acid levels in the first trimester and the development of GDM.

METHODS

The prospective observational study was conducted in S.S. institute of medical sciences and research hospital, Davangere from Aug 2021 to July 2022. Pregnant women of gestational age less than 15 weeks who attended the OBG outpatient department for regular antenatal check-up were enrolled in the study with prior consent taken for study after ethical and scientific committee approval.

Demographic information, obstetrical, family and medical history was obtained. Weight, height and BMI were calculated. Gestational age was calculated from the LMP and further confirmed by ultrasonography.

Method of serum uric acid level estimation by uricase-peroxidase system. Blood samples were taken in order to estimate serum uric acid levels at less than 15 weeks in addition to other basic investigations. At 24-28 weeks of gestation, a one-step test (DIPSI) was performed to detect GDM using 75g of oral glucose load, regardless of the patient's last meal, and a blood sample also collected to estimate S. uric acid levels.

Those pregnant women with plasma glucose level >140 mg/dl at 2 hours were considered high risk and were subjected to oral glucose tolerance test (OGTT). Serum uric acid was again measured at 24-28 weeks and any changes were noted.

Follow-up of the patient until delivery to know whether they got GDM or not.

Method of collection of data: (including sampling method if any)

Duration of study was from August 2021 to July 2022 and sample size was 56.

Inclusion criteria

Pregnant women with a gestational age less than 15 weeks were included in the study.

Exclusion criteria

Pregnant women>15 weeks', multiple pregnancies, presentational diabetes, H/O thromboembolism, smoking, connective tissue disorder, overt DM, patients on steroids, gout, chronic renal disease, liver disease, cardiovascular disease were excluded from the study.

Statistical analysis

SPSS (Statistical package for social sciences) version 20. (IBM SPASS statistics [IBM corp. released 2011] was used to perform the statistical analysis. Data was entered in the excel spread sheet. Descriptive statistics of the explanatory and outcome variables were calculated by mean, standard deviation for quantitative variables, frequency and proportions for qualitative variables. Inferential statistics like-Chi-square test was applied for qualitative variables. Independent sample t test was applied to compare the quantitative variables between the groups. The level of significance is set at 5%,

RESULTS

After meeting our criteria, a total of 56 antenatal women with a gestational age of less than 15 weeks were recruited

in the study. Table 1-4 shows demographic variables in which the majority of the subjects are in the age group of 25–29 years, and of all subjects, primigravida's were 57.1%. Out of all the subjects, 25% have a positive family history. The serum uric acid level was between 1.4 and 5.7 mg/dl at less than 15 weeks of gestation, and the mean uric acid value was 3.38 mg/dl, with 21 subjects having a uric acid value greater than 3.38 mg/dl. The value of one step test ranged between 98 and 192 mg/dl at 24 to 28 weeks of gestation, with an average value of 131.48 mg/dl. Out of those, 17 subjects had values greater than 140 mg/dL. Table 6 shows the significant increase in one-step values with increased values of serum uric acid at <15 weeks of gestation with a p=0.00. But the correlation between serum uric acid value at 24 to 28 weeks and the one-step test at 24 to 28 weeks was not significant as only 4 subjects had a high uric acid value when compared to 12 subjects at <15 weeks. This showed that the correlation of serum uric acid levels at <15 weeks of gestation with a one-step test is more significant than serum uric acid levels at 24-28 weeks of gestation (Table 6 and 7). While comparison of baseline variables (age, parity, BMI, and family history) with serum uric acid levels at <15 weeks of gestation showed a moderately significant correlation between family history of DM, advanced maternal age, obese and overweight women, it did not show any significant correlation with parity (Figure 1 and Table 8).

In Table 2 the study population had a mean age of 26.16 years.

Table 2: distribution of the subjects based on age.

Age groups (Years)	Frequency	Percentage (%)	Mean	SD
18-24	18	32.14		
25-29	28	50		
30-34	9	16.07		
>35	1	1.79	26.16	4.067
Total	56	100.0		

In Table 3 shows that primigravida's constituted 57.1% and multigravidas constituted about 42.9% of our study population.

Table 3: Distribution of the subjects based on parity.

Parity	Frequency	Percentage (%)
Primi	32	57.1
Multi	24	42.9
Total	56	100.0

In Table 4, out of 56 women, 14 (25%) had positive family history.

In Table 5, mean BMI, S. UA<15 weeks, S. UA at 24-28 weeks and OGCT is 23.73, 3.38, 3.63 and 131.48 respectively.

Table 4: Distribution of the subjects based on family history.

Family history	Frequency	Percentage (%)
Present	14	25.0
Absent	42	75.0
Total	56	100.0

Table 5: Mean BMI, serum uric acid levels and OGCT.

Variables	N	Min	Max	Mean	SD
BMI	56	18	32	23.73	3.606
S. UA and<15 weeks	56	1.4	5.70	3.38	0.89
Serum UA at 24 to 28 weeks	56	2.5	5.9	3.63	0.75
OGCT	56	98	192	131.48	25.945

In Table 6, out of 17 women who developed GDM 12 women had high uric acid levels. This shows a positive correlation between GDM as well as the 1st trimester uric acid levels.

Table 6: Cross-tabulation of uric acid levels at <15 weeks and OGCT.

UA levels < 15 weeks		OGCT-classified		Total
		<140	**> 140**	
High	Count	0	12	12
	%	0	70.6	21.4
Low	Count	1	0	1
	%	2.6	0.	1.8
Normal	Count	38	5	43
	%	97.4	29.4	76.8
Total	Count	39	17	56
	%	69.64	30.36	100

Significant, Chi-square value=35.10, p=0.00

In Table 7, out of 17 women who developed GDM only 4 women had high uric acid levels and 13 women had normal uric acid levels at 24-28 weeks.

Table 7: Cross-tabulation of uric acid levels at 24 to 28 weeks and OGCT.

UA levels at 24 to 28 weeks		OGCT-classified		Total
		<140	**>140**	
High	Count	0	4	4
	%	0	23.5	7.1
Normal	Count	39	13	52
	%	100	76.5	92.9
Total	Count	39	17	56
	%	100	100	100

Significant, Chi-square value=9.88, p=0.002

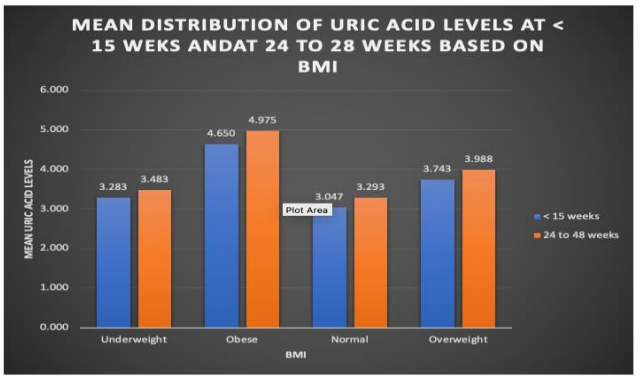

Figure 1: Mean distribution of uric acid levels at <15 weeks' and at 24 to 28 weeks based on BMI.

In, Figure 1 overweight and obese women had high UA levels.

In Table 8, age wise differences in serum uric acid levels were statistically significant. Serum uric acid level increased with age.

Parity wise differences in serum uric acid at less than fifteen (<15) weeks of gestation is statistically not significant.

Overweight as well as obese are those with the family history of diabetes had significantly higher serum uric acid at less than fifteen weeks when compared to their counter parts.

Table 8: Comparison of the serum uric acid levels at less than 15 weeks' with baseline variables.

Variables			Serum uric acid levels at <15 weeks			Total	Chi-square value	P value
			High	Low	Normal			
Age groups (Years)	18 to 25	Count	3	0	16	19	1.14	0.56
		%	25	0	37.2	33.9		
	26 to 35	Count	9	1	27	37		
		%	75	100	62.8	66.1		
Obstetric history	Multi	Count	6	0	18	24	1.01	0.60
		%	50	0	41.9	42.9		
	Primi	Count	6	1	25	32		
		%	50	100	58.1	57.1		
Family history	-	Count	2	1	39	42	27.76	0.00*
		%	16.7	100	90.7	75		
	+	Count	10	0	4	14		
		%	83.3	0	9.3	25		

*Significant

DISCUSSION

In pregnancy, progressive changes in maternal carbohydrate metabolism is seen. Due to placental hormones, insulin resistance and diabetogenic stress are increased, and when there is no compensation, GDM is developed.[1] So GDM is important to diagnose early and treat effectively to avoid maternal and fetal complications.[5] Incidence rates of GDM range from 17-27%, depending on population and diagnostic criteria, and risk factors may include maternal obesity, advanced maternal age, and a first-degree relative with diabetes and these women will have a higher incidence of developing DM in the next 2 decades.[6] Uric acid levels rise in response to increased protein consumption, alcohol consumption, decreased excretion, or increased endogenous production. The correlation between GDM and diet is an intriguing avenue for future research that we did not pursue in this study. The majority of women should have normal excretion because we did not include women with hypertension, prior diabetes, kidney disease, or other serious medical conditions, so we did not measure creatinine to adjust for glomerular filtration rate (GFR).[9] Normal changes that occur in pregnancy is that uric acid levels falls during early and mid-trimester and to normal value in late pregnancy as stated by the Boyle et al.[10] So, hyperuricemia in early gestation may be associated with pre-existing metabolic derangement which may lead to poor maternal physiological adaptation and causing pregnancy women developing increased risk for GDM and pre-eclampsia.[3] Serum uric acid levels increases with increase in maternal age with mean age of 26.16 similar results were seen in Aparna et al and Nader et al.[11,12] may be due to getting married late or due to delay in becoming pregnant. There is no difference in parity with elevated levels of serum uric acid and it is not significant and similar results are seen in Dunlop et al and Rasika et al in their study.[3,13] Uric acid is strongly associated with BMI and the risk of developing gestational diabetes increases with an increase in 1st trimester uric acid it is independent of BMI similar results were stated in Ramalakshmi et al and El-Gharib et al.[1,6] The byproduct of purine catabolism's oxidation step is uric acid, and it is a significant marker for insulin resistance and the development of metabolic syndrome.[7] In the present study, 17 patients developed GDM, out of which 13 patients had uric acid >3.5 and 4 patients had uric acid < 3.5. In our study, mean uric acid in patients was 3.27 mg/dl and in patients with GDM is 4.2 mg/dl and these is high sensitivity and specificity and the same linear correlation between GDM, and serum uric acid is seen in study conducted by Zhou et al.[14]

A threshold for diagnosis of GDM with a uric acid value of 4.2 mg/dl predicts GDM with 60% sensitivity and 100% specificity and shows a linear association between 1st trimester uric acid and the development of GDM.[7] So current cut off of maternal uric acid of 4.2 mg/dl in 1st trimester was associated with development of GDM. Therefore, we suggest that serum uric acid levels be done as a routine test during the 1st trimester antenatal visit.[6] The risk factor for developing type-2 DM is hyperuricemia, as stated by Dehghan et al and Yoo et al.[15,16] Nakagawa et al have postulated 2 mechanisms by which uric acid causes insulin resistance. A decrease in nitric oxide production by endothelial cells and endothelial dysfunction is caused by uric acid.[4,17] Inflammation and oxidative stress in adipocytes caused by uric acid leads to development of metabolic syndrome.[18] In association with the present study, Katherine study showed that hyperuricemia in the 1st trimester was associated with an increased risk of developing GDM, which is independent of BMI. Katherine found that uric acid ≥3.6 mg/dl in early pregnancy is associated with 3-fold increased risk of developing GDM.[9] In Nagalakshmi et al study showed that increased risk of developing GDM among primigravida.[19] But according to Al-Rowaily et al study increased risk of developing GDM in multigravida by 8.29 times that of primigravida.[20] In the present study there is no much difference in development of GDM with parity. Oral glucose intolerance (p=0.00) though only 30.36% were diagnosed as GDM and the same was stated by Langhonks et al as hyperuricemia in the 1st trimester with a raised risk for developing GDM.[9] Wolak et al also stated the same that elevated uric acid levels in the first 15 weeks of pregnancy was associated with an increased risk of developing GDM and mild pre-eclampsia.[21]

Limitations

The study's sample size was less due to the short time frame. Patients were not monitored after 28 weeks of gestation to see if they later developed GDM in pregnancy.

CONCLUSION

Increased levels of serum uric acid in the first trimester increase the risk of developing GDM. This association is not dependent on parity. But there is association of these variables (advanced maternal age, increased BMI and positive family history) with GDM and increased uric acid levels at <15 weeks. Uric acid levels at less than 15 weeks of gestation are more strongly associated with the risk of developing GDM than levels at 24 to 28 weeks of gestation.

Early interventions by dietary and exercise regimes in these patients can reduce the maternal and neonatal complications. It is our suggestion that serum uric acid level should be done as a routine test during the first antenatal visit itself as a reliable predictor for the development of GDM.

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