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INTRODUCTION

Gestational diabetes mellitus (GDM) is a metabolic disorder of glucose intolerance and hyperglycemia first time diagnosed during gestation.¹ Onset of GDM is common in the middle to late trimester but continues till term.¹ Prevalence of GDM is estimated at 1-14%. Occurrence of GDM is reported in 7% of pregnancies, and this accounts for >0.2 million diseased cases each year.¹⁻² In majority of GDM cases, the glucose intolerance returns to normality within 6 weeks of parturition.¹ Pregnant women of GDM are at increased risk of developing type 2 DM in post partum period.^{2,3} Currently, many biomarkers have been reported for the prediction of GDM in normal pregnancy and serum uric acid (SUA) is one of them.

Predictive significance of first trimester serum uric acid as risk factor for the gestational diabetes mellitus.

Anjum Rehman¹, Sadia Saeed², Syeda Fariha Hasny³, Nathumal Maheshwari⁴, Urooj Tabassum⁵, Arshad Ali⁶

ABSTRACT... Objective: Determining the predictive significance of first trimester serum uric acid for the development of gestational diabetes mellitus (GDM) in pregnant women. **Study Design:** Case Control study. **Setting:** Department Gynecology and Obstetrics, Shaheed Muhtrama Benazir Bhutto Medical College Layari General Hospital Karachi. **Period:** March 2017 to December 2018. **Material & Methods:** Sample of 172 pregnant women in first trimester (<14 weeks gestation) were divided into; 72 controls and 72 cases through purposive sampling. Pregnant women with fasting blood glucose (FBG) ≥ 100 mg/dl were defined as GDM. FBG was estimated by hexokinase and uric acid by enzymatic method (uricase) using commercial colorimetric assay (Nikken Seal Co., Ltd, Japan). Data was analyzed on SPSS software 21.0 (IBM, Inc USA) at 95% CI. **Results:** Maternal age of control and cases was noted 30.23 ± 1.47 and 30.14 ± 1.41 years. Gestational age in controls was 9.80 ± 2.23 weeks compared to 10.37 ± 2.34 weeks in cases. Serum Uric acid in control was 3.19 ± 0.49 mg/dl compared to 3.73 ± 0.43 mg/dl in cases ($P=0.0001$). Logistic regression analysis model generated ROC curve shows excellent area under the curve (AUC) of 0.92 [95% CI (0.87-0.97)] with a diagnostic threshold of 3.91 mg/dl for uric acid. At this Uric acid threshold, the specificity and sensitivity was 96.4% and 69.7% respectively ($P=0.0001$). **Conclusion:** It is concluded first trimester serum uric acid may be used for predicting the future development of gestational diabetes mellitus.

Key words: First Trimester, Gestational Diabetes Mellitus, Predictive Significance, Serum Uric Acid.

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The SUA is being investigated and reported as a possible risk factor for the future development of GDM. Previous researchers^{4,5} have linked the association of SUA with the development of GDM. Uric acid (UA) is a xanthine derivative of purine catabolism. A previous study⁶ reported uric acid is a pro-oxidant hence may be used as a biomarker of oxidative stress, but it also showed antioxidant potential.⁶ Soluble form of uric acid; the urate is a potent scavenger of superoxide (O_2^-) and hydroxide ($-OH$) radicals and is capable of chelating the transition metals.⁷ Elevated serum uric acid level is termed the hyperuricemia that has been linked metabolic syndrome of insulin resistance, hyperinsulinemia,

diabetes mellitus, etc.⁸ Hyperinsulinemia may contribute to hyperuricemia through activation of sympathetic nervous system that reduces the urinary excretion of uric acid. Hyperuricemia in GDM reflects the metabolic syndrome of insulin resistance.⁴ Hyperuricemia has been closely correlated with obesity, hyperlipidemia and dyslipidemia and DM.⁹ Gestational hyperuricemia is associated with materno-fetal complications of proteinuria and systemic hypertension.¹⁰ Keeping in view the current scenario of rising incidence of DM in Pakistan, metabolic syndrome and hyperuricemia, it is essential to conduct related research particularly for the neglected topic of GDM that will be important for the maternal and fetal outcome. The present study was planned to measure the serum uric acid during first trimester of pregnancy and determining its predictive significance for the future development of gestational diabetes mellitus (GDM) in pregnant women reporting at our tertiary care hospital.

MATERIAL & METHODS

This case control study was conducted at the Department Gynecology and Obstetrics, Shaheed Muhtrama Benazir Bhutto Medical College Layari General Hospital Karachi, Sindh, Pakistan from March 2017 to December 2018. Study protocol was applied for approval by ethical review committee of institute for conducting the study. Sample size was calculated as the 'sampling for proportions'. Sample size was 172 pregnant women. It was calculated by using 5% type-I error (α -level of significance) (2-tailed) and power of test (90%) at an expected% of serum uric acid in GDM cases as 50% and without GDM as 20.9%.¹ GDM was defined according to the American Diabetes Association (ADA) criteria of 75g OGTT.¹¹ GDM was defined as pregnant women with fasting blood glucose levels ≥ 100 mg/dL.¹¹ Study subjects were enrolled by purposive sampling technique through inclusion and exclusion criteria. Pregnant volunteer women in first trimester (gestational age <14 weeks) and fasting blood glucose (FBG) (<92 mg/dl) attending the outpatients were included. Serum uric acid was estimated and subjects were followed up by 24 to 28 weeks gestations for GDM screening with OGTT (75g glucose challenge) as per American

Diabetes Association (ADA) criteria.¹¹

Other inclusion criteria for GDM cases were; maternal age of age 25 - 40 years, and LMP date known. Those with diabetes mellitus, systemic hypertension, metformin intake, pregnant women in 2nd and 3rd trimester of pregnancy, history of tuberculosis, chronic pancreatic disease, chronic kidney disease, valvular heart disease, vegans and chronic liver disease were excluded. Pregnant female using multivitamin pills since beginning of first trimester were strictly excluded. Volunteers were informed of no harm by the researcher and no financial expenditure. Consent form was signed by volunteers or legal heirs. Data was noted in a pre- structured proforma. Confidentiality of patient's data and clinical findings was secured. Clinical history, age, gravidity, gestational age (GA), body mass index (BMI) and physical examination findings were noted in proforma. Volunteers were informed of blood sampling will be used only for blood testing. Volunteers were examined on patient examination couch. Blood samples were collected from ante-cubital fossa after aseptic measures. Disposable syringe (BD, USA) was used for venesection. 3ml blood was taken into Sodium fluoride tubes for full blood counts. 2ml blood was centrifuged to get sera for the serum uric acid. Fasting blood glucose (FBG) was detected by "hexokinase method". Serum uric acid was measured by enzymatic method (uricase) using commercial colorimetric assay (Nikken Seal Co., Ltd, Japan). Data was analyzed on SPSS software 21.0 (IBM, Inc USA). Students t-test was employed for the analysis of age, gestational age (weeks), gravida, BMI, systolic and diastolic blood pressure, fasting blood glucose (FBG) and serum uric acid. Pearson's correlation model was designed for the association of uric acid and FBG. Logistic regression analysis was run to generate ROC curve for serum uric acid as predictor of GDM. Statistical analysis was performed at 5% α -level of significance (2-tailed) defined 95% confidence interval ($P \leq 0.05$).

RESULTS

Age of control and cases was noted 30.23 ± 1.47 and 30.14 ± 1.41 years. Demographic, physical

and laboratory findings of controls and cases are shown in Table-I. Gestational age in controls was 9.80 ± 2.23 weeks compared to 10.37 ± 2.34 weeks in cases. Majority of GDM women were Primigravida in both control and cases (Table-III). Serum Uric acid in control was 3.19 ± 0.49 mg/dl compared to 3.73 ± 0.43 mg/dl in cases. Serum Uric acid in control and cases revealed statistically significant difference ($P=0.0001$) as shown in Table-I and II. Table-IV (IVa, IVb & IVc) show

the Logistic regression analysis model results. The ROC curve was obtained by the Predicted probability of the first trimester serum uric acid levels to detect GDM (Figure-1). The area under the curve was 0.92 [95% CI (0.87-0.97)] with a diagnostic threshold of 3.91 mg/dl. Specificity and sensitivity of first trimester serum uric acid levels was found as 96.4% and 69.7% respectively for the prediction of GDM ($P=0.0001$).

	Control	Cases	P-Value
Maternal Age (years)	30.23 ± 1.47	30.14 ± 1.41	0.69
BMI (Kg/m ²)	26.35 ± 4.19	26.45 ± 3.92	0.87
Systolic BP (mmHg)	120.1 ± 6.14	120.5 ± 6.18	0.85
Diastolic BP (mmHg)	68.25 ± 4.58	67.73 ± 4.76	0.46
Gestational age	9.80 ± 2.23	10.37 ± 2.34	0.10
Gravida	2.40 ± 1.47	2.43 ± 0.48	0.75
Hematocrit (Hct.) (%)	38.05 ± 3.25	36.58 ± 2.93	0.002
Hemoglobin (g/dl)	10.89 ± 0.61	10.75 ± 0.49	0.094
Fasting Glucose (mg/dl)	88.7 ± 8.28	150.38 ± 39.79	0.0001
Uric acid (mg/dl)	3.19 ± 0.49	3.73 ± 0.43	0.0001

Table-I. Demographic characteristics and blood findings (n=172).

	Serum Uric Acid (mg/dl)	Range (mg/dl)	SEM	T-Value	P-Value
Control	3.19 ± 0.49	2.30 – 4.51	0.052	12.67	0.0001
Cases	3.73 ± 0.43	2.71 – 4.51	0.047		

Table-II. Serum uric acid in control and cases (n=172).

Gravida	Control	Cases	X ² -value	P-Value
Primigravida	67 (39%)	69 (40.1%)	0.7	0.071
Multigravida	19 (11%)	17 (9.9%)		
Total	86	86		

Table-III. Gravida status of control and cases (n=172).

	Observed	Predicted		% Correct
		GDM		
		No	Yes	
Step 1	GDM	No	134	96.4
		Yes	10	69.7
	Overall Percentage			91.3

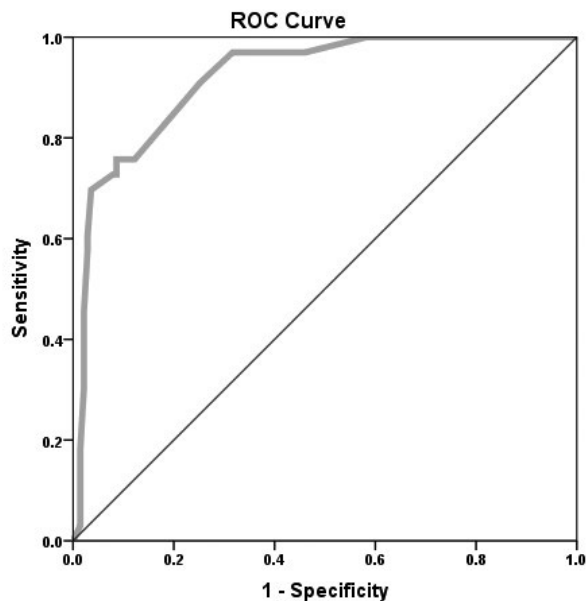
Table-IV A. Logistic regression analysis - classification table.

Step 1	-2 Log likelihood	Cox & Snell R ²	Nagelkerke R ²
	94.882	0.347	0.556

Table-IV B. Model summary.

		B	S.E.	Wald	df	P-Value	Exp (B)
Step 1	SUA	5.17	0.922	31.423	1	0.0001	176.016
	Constant	-20.949	3.626	33.371	1	0.0001	0.0001

Table-IV C. Variables in the Equation.



Prediction Model- Uric Acid Predicting the GDM ROC - AUC 0.92

Figure-1. ROC curve showing AUC (area under the curve) was 0.92, Specificity (96.4%) and Sensitivity (69.7%).

DISCUSSION

The present hospital based study reports the serum uric acid during first trimester of pregnancy predicted the development of gestational diabetes mellitus (GDM) in pregnant women. Noteworthy finding of present study is the AUC of ROC was 0.92 [95% CI (0.87-0.97)] at serum uric acid threshold of 3.91 mg/dl. Specificity and sensitivity of first trimester serum uric acid levels was found as 96.4% and 69.7% for the prediction of GDM ($P=0.0001$).

Uric acid is a metabolic end product of Purine catabolism that has been quoted as a biomarker of metabolic syndrome, insulin resistance and diabetogenesis. Rising prevalence of GDM across the Globe has put populations at danger of losses to both mother and newborn. Broad screening programs of ADA guidelines have not proven helpful for GDM due to materno fetal complications^{12,13} hence there is urgency to evaluate new screening methodology particularly for the developing countries. An inexpensive risk assessment model for GDM may deny unnecessary OGTT screening. In present study, the first trimester serum uric acid showed linear

correlation with development of GDM in future. The findings are in agreement with previous studies.¹⁴⁻¹⁷ A previous study¹⁸ reported no association of serum uric acid and future development of GDM in their previous study this may be because of research bias. Findings of above study are in contrast to present and previous studies.¹⁴⁻¹⁷ In present study, the serum uric acid in control was 3.19 ± 0.49 mg/dl compared to 3.73 ± 0.43 mg/dl in cases. Serum Uric acid in control and cases revealed statistically significant difference ($P=0.0001$). This is in keeping with present and previous studies.^{17,19} However, a previous study²⁰ reported significantly higher mean uric acid levels in women, that is inconsistent with present and previous studies.^{16,17,19}

Majority of GDM women were Primigravida in both control and cases (Table-III). Of 172 pregnant women 80% (39% control and 41% cases) were Primigravida in the present study. The findings are in agreement with Amudha et al¹⁷ that reported 64.6% were Primigravida. Similarly, the Nagalakshmi et al²¹ reported higher incidence of GDM in primigravida that is consistent with present study. However, the Al Rowaily et al²² has reported similar incidence in multiparous pregnant women. The present suggests uric acid levels within high normal range in first trimester of pregnancy are linked to future development of GDM as evidenced by the logistic regression analysis model. The finding is supported by other previous studies.^{5,20} They concluded that the risk of GDM increases with high serum uric acid levels in early pregnancy. They suggested serum uric acid may be exploited as bio marker for subsequent development of GDM. In present study, the first trimester serum uric acid threshold of 3.91 mg/dl showed specificity and sensitivity of 96.4% and 69.7% for the prediction of GDM ($P=0.0001$). This cut off value of 3.91 mg/dl uric acid of present study is in full agreement with Aker et al¹⁶ that reported uric acid 3.95 mg/dL threshold yielding 60% specificity and 100% sensitivity. Amudha et al¹⁷ and Laughton et al⁵ reported cut-off of 3.6 mg/dl threshold of uric acid with sensitivity (92%) and specificity (99%) that cut off point is less than the present study. Another study²⁰ reported serum uric acid threshold of >3.4 mg in first trimester

predicted the future GDM occurrence.

Limitations of present study were; 1st dietary habits, nutritional status, anthropometric data, pre-pregnancy serum uric acid were not known and 2nd small sample size. However strength of study lays in its prospective study design and test sample was sufficiently powered. Future studies are recommended to analyze the predictive value of serum uric acid levels with large sample size combined with other biochemical biomarkers in an effort to develop a cost effective screening model for the Pakistani population.

CONCLUSION

The present study concludes the first trimester serum uric acid may be used for predicting the future development of gestational diabetes mellitus (GDM) in pregnant women. As the diagnosis of gestational diabetes mellitus is made in mid late gestation, till that time the complications become potentially irreversible. Hence, first trimester serum uric acid may be used as simple robust test from the very onset of gestation.




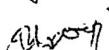
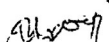
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