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Original Research Article

Elevated 1st trimester serum uric acid - a risk for gestational diabetes mellitus among South-Indians: a prospective observational, longitudinal study

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ABSTRACT

Background: Mildest carbohydrate intolerance during pregnancy may increase the risk of maternal and foetal complications. Studies suggest interesting relationships between elevated 1st trimester SUA and development of GDM, but they have not been consistent and as per our literature search we did find only one or two such studies carried out on South-Indian women in whom, the food habits, genetics, environmental factors differ from rest of the world.
Methods: 124 pregnant women were studied with an aim to prospectively evaluate relation between 1st trimester SUA levels with development of GDM. Continuous data were analyzed for average/mean, median and standard deviation; and categorical variables using chi-square, independent t-test, Pearson's correlation coefficient and ANOVA.
Results: 36% of the study sample had risk factors for GDM with an incidence of 22.6%. Pearson correlation with 1st trimester SUA concentration of 3.2 mg/dl as a cut-off point for predicting GDM risk was found to be statistically significant. At cut-off levels of 3.98 mg/dl, risk of women developing GDM requiring insulin therapy in addition to diet was statistically significant.
Conclusions: Along with other risk factors, elevated 1st trimester SUA levels is an independent risk factor for development of GDM. If diagnosed early and properly monitored, GDM usually doesn't affect pregnancy outcome in our population.

Keywords: 1st trimester, GDM risk, Serum uric acid

INTRODUCTION

Globally 7% of all pregnancies are complicated by gestational Diabetes Mellitus with a prevalence ranging from 1-14% based on the population studied and the diagnostic tests employed and in India, it is 15% in the age group of 15-19 years and 32% in the age group of women >30 years.[1,2] Diagnosis of GDM is important to identify both infants at risk of adverse outcomes and risk of future maternal diabetes. Interesting relationships have been observed between serum uric acid and development of GDM, but the studies have not been consistent. It is said that, uric acid increases insulin resistance by inhibiting insulin mediated endothelial

nitric oxide release and also by directly acting on adipocytes.[3-7]

Hypoxia and ischemia of the placenta and cytokines such as, interferon induce expression of xanthine oxidase and therefore increase the production of uric acid and reactive oxygen species.[8] However in uncomplicated pregnancies SUA concentrations significantly fall during early and mid-pregnancy as a consequence of 50% increase in glomerular filtration rate and reduced tubular reabsorption.[9,10]

Literatures reviewed suggest controversial results, where in studies report hyper-uricemia as a significant risk factor for GDM and even more so in Asians and in few no significant hyper-uricemia in GDM.[11-16] Only one or two such studies on South Indian women have been employed in whom: the food habits, genetics, environmental factors differ from rest of the world and hence an early detection of women at risk of GDM might help in better monitoring.

METHODS

A Prospective observational longitudinal study was carried out in the Department of Obstetrics and Gynecology of our hospital at Coimbatore over a period of 1 year. Keeping 10% as dropout during follow up, a minimum sample size of 65 was considered essential by employing single group dichotomous data experimentation. Women with known diseases like diabetes mellitus, hypertension, connective tissue disorders, renal disease, liver disease, gout and history of thrombo-embolism and women on medicines known to cause hyperuricemia were excluded.

A total of 124 pregnant women who had visited our center before 12 weeks of gestation were given adequate information using patient information sheets and after obtaining informed consent, they were enrolled for the study. Preliminary socio-demographic details and covariate information was collected. After initial antenatal assessment 5 ml of venous blood under aseptic precautions was drawn during 1st trimester and transferred to EDTA and plain tubes for all routine antenatal investigations including estimation of SUA by colorimetric method.[17]

All the participants were followed till term with follow up assay of SUA in second and third trimester. As per the hospital protocol one step approach was used to diagnose GDM; blood sugar screening was done at 24-28 weeks with 75 gm glucose two hour GTT.[18] As per American Diabetes Association and International Association of Diabetes and Pregnancy Study Group (IDAPSG) recommendations, GDM was diagnosed if any 1 or more plasma glucose values meet or exceeds fasting blood glucose ≥92 mg/dl, 1 hour post prandial glucose ≥180 mg/dl, 2 hour post prandial glucose ≥153 mg/dl.[19,20] Those with GDM were followed up to term with fasting and 1 hour post prandial glucose levels.

Statistical analysis

Continuous data were analyzed for average/mean, median and standard deviation and categorical variables were analyzed using chi-square test, independent t-test, Pearson's correlation coefficient and ANOVA. A 'p' value of <0.05 is considered as statistically significant.

RESULTS

In the present study, 58.9% (73) were primigravidas and 41.1% (51) were multigravidas. Of those 41% multigravidas, 72% had delivered vaginally, 26% by caesarean section and 2% by forceps assisted vaginal delivery in their past pregnancies. Around 45% of multigravida women had past history of abortions; and in 8% of cases past pregnancy was complicated in the form of molar pregnancy, Rh incompatibility, intra uterine death and anencephaly. None of the individuals had habits of smoking tobacco, chewing tobacco, drinking alcohol or any such substance abuse. Menstrual cycles of all most all the women were regular except one, who had conceived following infertility therapy.

Risk factors for GDM in the form of elderly primigravida, PCOD, obesity, hypothyroidism and diabetes among 1st degree relatives were present in 36% of the cases. In the sample population, majority of individuals did not have significant medical disorders (after exclusion of cases as per sample selection criteria) (94%), however the most commonly reported disorder was sub-clinical hypothyroidism (5%). None of the family members of the study group had GDM, 29% of 1st degree relatives and 1% of second degree relatives (grandparents) had type II Diabetes Mellitus, 12% of 1st degree relative had hypertension.

A total of 22.6% of the pregnant women were diagnosed as having GDM and majority of them were managed with diet control measures and only few (4%) required insulin therapy and oral hypoglycaemic (0.8%).

46.8% of individuals had a SUA level of ≥3.2 mg/dl during 1st trimester and the percentage increased to 63.7% and 81.5% during their 2nd and 3rd trimesters respectively. In non-GDM group 48% of the women had SUA levels between ≥2.3-<3.2 mg/dl followed by 42% of women with SUA levels of ≥3.2 mg/dl during 1st trimester however during 2nd and 3rd trimester more number of pregnant women fell into ≥3.2 mg/dl SUA level category. In GDM group 64.5% of the women had SUA levels of ≥3.2 mg/dl followed by 27% of women with SUA levels between ≥2.3-<3.2 mg/dl during 1st trimester and during 2nd and 3rd trimester more number of pregnant women fell into ≥3.2 mg/dl SUA level category and the same are presented in Table 1.

Table 1: Trimester-wise distribution trend of SUA levels.

SUA level in mg/dl	1st Trimester (%)			2nd Trimester (%)			3rd Trimester (%)		
	Non-GDM (n=96)	GDM (n=28)	Total (n=124)	Non-GDM (n=96)	GDM (n=28)	Total (n=124)	Non- GDM (n=96)	GDM (n=28)	Total (n=124)
<1.4	1.0	0.0	0.8	0.0	0.0	0.0	0.0	0.0	0.0
≥1.4-< 2.3	9.4	7.1	8.9	3.1	3.6	3.2	1.0	0.0	0.8
≥2.3-< 3.2	47.9	28.6	43.5	35.4	25.0	33.1	17.7	17.9	17.7
≥3.2	41.7	64.3	46.8	61.5	71.4	63.7	81.3	82.1	81.5
Total	77.4	22.6	100.0	77.4	22.6	100.0	77.4	22.6	100.0

Significance of the study was tested using descriptive statistics (mean and standard deviation) for SUA levels, FBS, GTT 1 hour PPBS and GTT 2 hour PPBS in the sample population; and accordingly it was 3.2±0.8 mg/dl, 82.97±10.75 mg/dl, 125.9±31 mg/dl, 109.69±26.68 mg/dl respectively.

Pearson correlation with SUA concentration of 3.2 mg/dl as a cut-off point for predicting GDM risk using FBS and GTT 1 hour PPBS value were found to be statistically significant with 'p' value of 0.013 and 0.005 respectively.

GDM diagnostic criteria with single cut-off values of blood sugars for FBS, GTT 1hr PPBS and GTT 2-hour PPBS were statistically found to be highly significant with p>0.0001 (ANOVA), 1st trimester SUA cut-off of 3.2 mg/dl with GTT 2-hour PPBS was found to be statistically insignificant with 'p' value of 0.085.

1st trimester SUA levels as risk factor for GDM and GDM subgroups were tested using descriptive statistics and ANOVA; and accordingly, 1st trimester SUA level was statistically significant ('p' value of 0.017) even in GDM Subgroups as shown in Table 2.

Table 2: Descriptive statistical data of GDM status versus SUA at 1st trimester.

Sample group	N	Mean	Std. deviation	Std. error	95% Confidence interval for mean		Min	Max
					Lower bound	Upper bound		
No GDM	96	3.1158	0.76388	0.07796	2.9611	3.2706	1.30	5.80
GDM on diet	22	3.4614	0.83949	0.17898	3.0892	3.8336	1.90	5.50
GDM on OHA	1	2.1000	-	-	-	-	2.10	2.10
GDM on insulin	5	3.9800	0.78549	0.35128	3.0047	4.9553	3.10	5.10
Total	124	3.2038	0.80210	0.07203	3.0612	3.3464	1.30	5.80

1st trimester SUA level as risk factor for Diabetic status tested using independent t-test showed a SUA mean of 3.1 mg/dl for non-GDM group and 3.5 mg/dl for GDM group with standard deviation of 0.764 and 0.869 and standard error mean of 0.078 and 0.164 respectively. Independent samples tests were found to be statistically significant by Levene's test and t-test for equality of means, while assuming equal variance ('p' value of 0.023) and also while not assuming equal variance ('p' value of 0.038).

During 1st trimester SUA mean in No GDM, GDM on diet and GDM on insulin groups were 3.12 mg/dl, 3.46 mg/dl and 3.98 mg/dl respectively. In 2nd trimester they were 3.3 mg/dl, 3.63 mg/dl and 3.94 mg/dl and during 3rd trimester 4.14 mg/dl, 4.21 mg/dl and 4.84 mg/dl respectively. More than half of women delivered by normal vaginal route of which 5.6% of them required assistance in the form of forceps application and 46% delivered by caesarean section due multiple reasons like non-progress of labour, foetal distress, cervical dystocia etc.

DISCUSSION

In our study 86% of women were aged between 21-30 years with an average of 25.6±3.22 years; whereas, Aparna et al reported mean age as 23.6±2.9 years and Urmila et al as 24.85±3.39 years.[9,13] This slight increase in mean age could be due to our changing trend of getting married late or due to delay in begetting child. Incidence of GDM in the present study is quite high (22.6%) than those reported by past studies for India (1-14%).[1] However, Seshaiah et al report age based incidence of GDM among women, as up to 15% in women of <19 years and up to 32% among women aged >30 years.[2] Similar to their observations in the present study women of <30 years constituted to 89% of the population and

accounted for 71% of total GDM cases with an incidence of 18.2% (20 cases among 110 women); whereas women of >30 years constituted to 11% of the study population and accounted for 29% of GDM cases with an incidence of 78.6% (11 cases among 14 women). This high rate could be because of multiple reasons like, use of different GDM diagnostic criteria by different researchers, altered life styles of our population, type of hospital where more women with high risk factors (36%) are referred. We used IADPSG criteria for diagnosis of GDM which has low threshold sugar values for diagnosis of GDM that may add for increased GDM incidence in the present study. In the present study 58.9% are primigravida and 41.1% are multigravida, from which 22% of primigravida and 24% of multigravidas developed GDM; similarly, Rajakumar et al study included 63.5% Primigravida and 36.4% multigravida and there was no difference in SUA at 1st trimester in relation to parity.[21] In contrast Nagalakshmi et al has reported a higher risk of GDM among multigravida.[22]

Table 3: Comparison of 1st trimester SUA levels with different authors.

Authors	1st trimester SUA Cut-off value employed	Statistical Significance
Urmila et al [9]	5 mg/dl	Significant
Sindhuja et al[11]	3.6 mg/dl	Significant (p<0.01)
Aparna et al[13]	3.4 mg/dl	Significant (p<0.05)
Rajakumar et al[21]	3.5 mg/dl	Significant (p=0.003)
Nagalakshmi et al[22]	-	Significant
Pundalik et al[23]	3.24 mg/dl	Not Significant (p=0.563)
Simmi K[24]	-	Significant (p<0.05)
Katherine et al[25]	3.6 mg/dl	Significant*
Rasika et al[26]	3.6 mg/dl	Significant (p<0.001)
Gharib et al[27]	4 mg/dl	Significant (p<0.0001)
Wolak et al[28]	5.5 mg/dl	Significant (p<0.001)
Present study	Mean of 3.2 mg/dl in sample	Significant (p<0.05)
	Mean of 3.5 mg/dl in GDM	Significant (p<0.05)
	Mean of 3.1 mg/dl in No-GDM	Significant (p<0.05)

*(Positive predictive value of 6.7% and negative predictive value 97.8%)

In the present study 36% of the women had risk factors for development of GDM like elderly primigravida, PCOD, obesity, hypothyroidism, and diabetes mellitus among 1st degree relatives and 31% of them developed GDM. More chances of insulin resistance in older subjects might be the cause for higher rate in elderly subjects. In contrary Sindhuja et al reported GDM risk factors in 50% of cases and this could be due to exclusion of cases with known risk factors like previous history of GDM and Hypertension during the time of enrollment of cases to the study by us.[11] Mean SUA level at 1st trimester in the present study sample was 3.2 mg/dl with a standard deviation of 0.8 mg/dl. Pearson correlation with SUA concentration of 3.2 mg/dl as a cut-off point for predicting GDM risk using any single values of FBS and GTT 1-hour PPBS are found to be statistically significant (<0.05) with 'p' values of 0.013 and 0.005 respectively. Similar finding of elevated 1st trimester SUA levels with different cut-off values by multiple authors are compared in Table 3.[9,11,13,21-28]

Mean SUA in No GDM group in the present study is 3.1±0.7mg/dl and in GDM group it is 3.5±0.9mg/dl and when this cut-off point (≥3.5mg/dl) is employed, it is also found to be statistically significant in predicting at risk women for development of GDM with 'p' values of 0.023 when equal variances assumed and 0.038 when equal variances are not assumed. From this and study of other researchers it appears that, it may not be helpful to employ a cut-off value for SUA of <3.2mg/dl in 1st trimester to determine women at risk for development of GDM. In almost all the studies elevated SUA is found to be significant in predicting risk of GDM. In Pundalik et al study, number of women diagnosed as having GDM were very less (4 of 178), and in all of them SUA levels were elevated and levels belonged to fourth quartile.[23] Statistical non-significance in their study could be because of very low number of GDM patients as compared to in other studies and also may be due to use of low cut-off value for SUA.

Significant change in mean SUA levels among GDM groups requiring different levels of therapies are recorded in our study. In persons with GDM who required treatment only in the form of diet control, SUA mean was 3.46±0.8 mg/dl and in persons who required insulin supplementation in addition to diet control, it was 3.98±0.8 mg/dl and this change in mean value is statistically significant with a 'p' value of 0.017. This indicates that more the concentration of SUA in 1st trimester higher is the chances of pregnant women requiring insulin/aggressive management.

CONCLUSION

Incidence of GDM in the present study is 22.6% and it is more in women of ≥30 years (78%) as compared to women of <30 years (18.2%). 36% of the study sample had risk factors for development of GDM. Pearson correlation with 1st trimester SUA concentration of 3.2 mg/dl as a cut-off point for predicting GDM risk is found to be statistically significant with 'p' value of <0.05. At SUA cut-off levels of 3.98 mg/dl, risk of women developing GDM requiring insulin therapy in addition to

diet control is statistically significant with a 'p' value of 0.017.

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