FIRST-TRIMESTER SERUM URIC ACID CONCENTRATIONS AS A PREDICTOR FOR GESTATIONAL DIABETES MELLITUS

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Abstract

Objective: To evaluate first trimester serum uric acid level as a predictor for gestational diabetes mellitus.

Patients and method: A prospective observational study at obstetrics and Gynecology Department of Suez Canal University Hospital during the period from March 2011 to March 2012. A total of 850 pregnant women with gestational age 10 – 13 weeks at presentation were recruited into the study. All women were subjected to complete history, full general and obstetric examination and routine obstetric ultrasonography evaluation. Serum uric acid was measured at time of presentation screening for diabetes was done at 24 - 28 weeks of gestation using 50gm oral glucose-loading test if >140mg/dl, subsequent 3hrs oral 100g glucose tolerance test (OGTT) was done, diagnosis of GDM was done when at least two of the following plasma glucose values was high.

Results: A total of 37 /813women were diagnosed to have GDM. Women with GDM have higher mean BMI (29.02 kg/m2) than women without GDM (26.04 kg/m2) with p-value < 0.05. Median serum uric acid at 10 - 13 weeks of gestation was significantly higher among women with GDM (3.5 mg/dl versus 2.9 mg/dl among women without GDM, p-value < 0.05). The adjusted odds of gestational diabetes increased with increasing first trimester uric acid quartile (p=0.003 for trend). ROC curve showed that best cutoff value was set at ≥ 3.05mg/dl with 75.7% sensitivity, 57.8% specificity, 7.5% positive predictive value and 89.1% negative predictive value. Risk estimate showed increased risk of GDM with serum uric acid ≥ 3.05 mg/dl with risk ratio =4.02.

Conclusion: first trimester serum uric acid concentration is a significant predictor for development of GDM.

Keywords: Uric acid, Gestational Diabetes Mellitus, Hyperuricemia.

Introduction

Gestational diabetes mellitus (GDM) is defined as "any degree of glucose intolerance with onset or first recognition during pregnancy". The definition has applied whether or not insulin is used for treatment or hyperglycemia persists after pregnancy [1]. There is increasing prevalence of Gestational diabetes mellitus (GDM) all over the world [2] and several large studied have shown GDM occurring in 2.2- 8.8% of pregnancies [3].

GDM carries considerable health risks for both the fetus and the mother, for the infants; they include an increased risk of macrosomia, birth injuries such as (shoulder dystocia, bone fracture and nerve palsies), hypoglycemia and hyperbilirubinaemia [4]. Women with GDM are at increased risk of developing preeclampsia with an increased chance of need for induction of labor and caesarean section, gestational diabetes is also a strong risk factor for later development of type 2 diabetes [5].

Uric acid is the end product of purine catabolism catalyzed by the enzyme

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xanthine oxidase/dehydrogenase [6]. In non-pregnant women, uric acid is associated with insulin resistance and is an independent risk factor for development type 2 diabetes within 10 years [7]. In pregnancy, uric acid is correlated with insulin resistance in women with gestational hypertension and is higher at 24-28 weeks gestation in women diagnosed with GDM compared to women without diabetes [8].

Two mechanisms have been hypothesized by which uric acid can cause insulin resistance; the first proposed that uric acid causes endothelial dysfunction and decrease nitric oxide production by the endothelial cell [9]. The second mechanism by which uric acid may induce insulin resistance may be that uric acid causes inflammation and oxidative stress in adipocytes, which is a contributor to the development of metabolic syndrome in mice [10]. The aim of the present study was to measure serum uric acid level in first trimester of pregnancy as a predictor for development of gestational diabetes mellitus.

Patients and method

After approval of ethics committee of faculty of medicine, Suez Canal University, this prospective observational study was performed at Obstetric and Gynecology Department of Suez Canal University Hospital during the period from March 2011 to March 2012 among pregnant women regularly attending outpatient clinic of Obstetric and Gynecology department for routine antenatal care.

Pregnant women were recruited into the study if they were presented to outpatient clinic at gestational age 10 – 13 weeks at the first antenatal visit. Women with pre-gestational Diabetes Mellitus, renal diseases, liver diseases, cardiovascular diseases, gout, smoking, or on drugs known to increase uric acid level in the blood such as phenothiazines, some diuretics, vitamin C (ascorbic acid), lower doses of aspirin (75 to 100 mg daily), niacin, warfarin (such as oumadin), cyclosporine, levodopa, and some medicines used to treat leukemia, lymphoma, or tuberculosis were excluded from the study. After applying our inclusion and exclusion criteria a total of 850 pregnant women were recruited into the study. The required sample size was estimated depending on data from previous study [11], setting power of the study at 80% and alpha error at 0.05 [12].

An informed written consent was obtained from all participants. All of the studied pregnant women were subjected to complete medical and obstetric history assessment, full general and obstetric examination, and routine obstetric ultrasonographic assessment. Peripheral venous blood samples were obtained from all participants between 10-13 weeks gestation after 4-hours fasting. The blood samples were centrifuged to separate the serum and were stored at -70°C till examined. Uric acid was measured using a colorimetric assay (Kit U7581-120; Pointe scientific Inc, Canton, MI) with a detection limit of 10mg/dl. Adult female's normal uric acid level is 2.0 - 6.5 mg/dl. Any value above that is considered hyperuricemia [13].

All participants (n=850) were screened for gestational DM with 50gm oral glucose-loading test (GLT) between 24-28 weeks gestation [14]. When blood glucose level after 1hr was >140mg/dl, the patient was considered to be at increased risk for developing GDM and underwent 3hrs oral glucose tolerance test (OGTT). The diagnostic criteria of American Diabetes Association [1] consider diagnosis of GDM when 3-hours 100g glucose OGTT showed at least two of the following plasma glucose values: 1) Fasting blood glucose level ≥95mg/dl (5.33mmol/L), 2) one-hour blood glucose level ≥180 mg/dl (10mmol/L), 3) two-hours blood glucose level ≥155 mg/dl (8.6mmol/L), and/or 4) three-hours blood glucose level ≥140 mg/dl (7.8mmol/L) [1]. Based on results of 3 hours 100g OGTT, a total of 37 pregnant women were diagnosed to have GDM versus 813 women in whom GDM were excluded (Figure 1).

Statistical analysis

Data were processed using SPSS version 15 (SPSS Inc., Chicago, IL, USA). Quantities data were expressed as means ±SD and qualitative data were expressed as numbers and percentages. Unpaired T-test was used to test significance of difference for quantitative variables while Chi-square and fisher's exact tests were used to test significance for qualitative variables. Mann Whitney test was used to compare two groups as regard non parametric data. ROC (Receiver Operator Characteristic) curve was used to find out the overall productivity of serum uric acid to predict GDM and to find out the best cut of value with detection of sensitivity, specificity at this cut off value. A probability value (p-value) < 0.05 was considered statistically significant.

Results

Women were recruited into the study at GA 10 – 13 weeks with mean gestational age at time of recruitment 11.01 weeks. Participants were assessed for GDM at GA 24 – 28 weeks with mean GA at time of screening for GDM 25.9 weeks. At time of presentation serum uric acid values of all 850 women showed median of 2.9 mg/dl with inter-quartile range (IQR) of 2.4 – 3.5 mg/dl and minimum value of 0.4 mg/dl and maximum value of 8.2 mg/dl.

No statistically significant difference was found between women whom were diagnosed to have GDM at those without GDM regarding age (27.4 years versus 27.55 years respectively, p-value > 0.05) and parity. Women with GDM showed higher mean BMI (29.02 kg/m2) compared to women without GDM (26.04 kg/m2) with statistically significant difference. The median serum uric acid at recruitment was significantly higher in women who developed GDM when compared to women who did not develop GDM [3.5 mg/dl (range: 1.2 – 7.3 mg/dl; interquartile range: 3.05 – 4.7 mg/dl) vs. 2.9 mg/dl (range: 0.4 – 8.2 mg/dl; interquartile range: 2.35 – 3.5 mg/dl), respectively, p<0.001] (Table 1).

The adjusted odds of gestational diabetes increased with increasing first trimester uric acid quartile (p=0.003 for trend). Women with early pregnancy uric acid concentrations in the highest (4th) quartile had a three-fold increased risk for developing GDM compared to those in the lowest quartile. Of the 37 women who developed gestational diabetes mellitus, 18 (48.6%) had uric acid in the 4th quartile (Figure 2).

Receiver operator characteristics (ROC) curve was constructed for serum uric acid as predictor of GDM and showed a significant predictability with AUC = 0.725 (95%CI: 0.638-0.801; p<0.001) (Figure 3). ROC curve showed that best cutoff value was set at ≥ 3.05mg/dl with 75.7% sensitivity, 57.8% specificity, 7.5% positive predictive value and 89.1% negative predictive value. 28 women out of 371 women with serum uric acid ≥ 3.05 mg/dl were diagnosed to have GDM versus 9 out of 479 of women without GDM. Risk estimate showed increased risk of GDM with serum uric acid ≥ 3.05 mg/dl with risk ratio =4.02 (table 2).

Discussion

Gestational diabetes mellitus (GDM) is one of the most common medical disorders found in pregnancy. Rates can range from 2 to >10%, and sometimes much higher, depending on the population being tested and the diagnostic criteria being used [2]. Hyperuricemia is associated with components of metabolic syndrome and it has been debated for a while to be a component of it [15]. Historically, the elevated level of uric acid observed in the metabolic syndrome has been attributed to hyperinsulinaemia, since insulin reduces renal excretion of uric acid [16]. Hyperuricemia however, often precedes the development of hyperinsulinaemia [17], obesity [18], and diabetes [7].

The present study was done to determine if the uric acid level in the first trimester of pregnancy can be used as a predictor of subsequent GDM. Prevalence of GDM was estimated to be 4.4% among the studied pregnant women. Gestational diabetes mellitus (GDM) is one of the most common medical disorders found in pregnancy. Rates can range from 2 to >10%, and sometimes much higher, depending on the population being tested and the diagnostic criteria being used [2].

In the present study, there was no statistically significant relationship between age and development of GDM. In contrast Lao et al., [19] have found that the risk of GDM becomes significantly and progressively increased from 25 years onwards. In the present study, the mean BMI was significantly higher in women who developed GDM when compared to women who did not develop GDM. This is supported by findings of Jenny et al., [20] who

concluded that pre-pregnancy body mass index BMI) is a strong predictor for development of GDM. This is also consistent with findings of Ogonowski et al., [21].

The present study has shown significantly higher serum uric acid among women with GDM versus women without GDM. These results were consistent with previous reports [10,22,23] who have found that serum uric acid was significantly correlated with insulin resistance. Also the present study have found that women with early pregnancy uric acid concentrations in the highest (4th) quartile had a three-fold increased risk for developing GDM compared to those in the lowest quartile. This coincides with the result of Laughon et al., [11] who have reported that women with uric acid in the highest quartile had a 3.25-fold increased risk (95% confidence interval, 1.35–7.83) of developing GDM after adjustment for body mass index and age.

In contrast, Gunger et al., [8] have found that single estimations of serum uric acid concentration were not significantly different between a normal pregnant group and a GDM group. Receiver operator characteristics (ROC) curve was constructed for serum uric acid as predictor of GDM and showed a significant good predictability [AUC =0.725, 95% CI (0.638 to 0.801), p<0.001] (figure III). The best cutoff point for serum uric acid as predictor of GDM was ≥ 3.05 mg/dl, sensitivity 75.7%, specificity 57.8%, PPV 7.5%, NPV 89.1%, positive likelihood ratio 1.8 and negative likelihood ratio 0.42]. This obviously low PPV is explained by the low prevalence of women who developed GDM among included women [37/850 (4.4%)] (table VII). The relatively high sensitivity and NPV (75.7% and 89.1%, respectively) makes serum uric acid useful as a 'screening' test for GDM.

The study done by Laughon et al., [11] didn›t support assessing uric acid concentration in pregnant wom-

en in the first trimester to predict the development of GDM. The area under the ROC curve was 0.7 for the first trimester uric acid as a predictor of GDM, this value is not sufficiently robust for elevated uric acid to be a clinically relevant predictor of GDM, which had a prevalence of only 4.6% (PPV= 9.0% for a uric acid cutoff of 3.6 mg/dl).

Conclusion

The present study had showed that early serum uric acid at first trimester is a significant predictor of GDM with increased risk of developing GDM in women with first trimester serum uric acid ≥ 3.05 mg/dl. We recommend further larger, multi-center observational studies to evaluate the efficacy of first trimester serum uric acid for development of GDM. Assessment of serum uric acid at first trimester could be used as a significant predictor for GDM.

Table (1) :
Comparison between women with and without GDM regarding baseline characteristics and serum uric acid:

	Women who developed GDM (n=37)	Women who did not develop GDM (n=813)	P
Age (Years) Range: Mean ± SD:	 21 – 39 27.41 ± 4.69	 16 – 43 27.55 ± 5.26	 0.8 NS
BMI (Kg/m2) Range: Mean ± SD:	 22 – 36 29.02 ± 4.39	 18 – 38.5 26.04 ± 4.16	 <0.001* HS
Parity Range: Median (IQR):	 0 – 4 2 (1 – 2)	 0 – 8 1 (1 – 2)	 0.08 NS
Serum Uric Acid at Recruitment (mg/dl) Range: Median (IQR):	 1.2- 7.3 3.5 (3.05 – 4.7)	 0.4 – 8.2 2.9 (2.35 – 3.5)	 <0.001* HS

NS: no statistically significant difference,
*Statistically significant difference
IQR: Inter-quartile range

Table (2) :
Serum uric acid as predictor for women with and without GDM

value	Women with GDM	Women without GDM	Risk difference	Risk ratio	P-
Best cutoff ≥3.05 0.001* value	28 (75.7%) 9 (24.3)	343 (42.2%) 470 (57.8%)	0.06 (0.3-0.09)	4.02 (1.9-8.4)	
Predictive characteristic	Sensitivity Specificity PPV NPV +ve LR -ve LR	 0 – 8 1 (1 – 2)	75.7% 57.8% 7.5% 89.1% 1.8% 0.42%		

* Statistically significant difference versus 6 weeks in the same group
PPV: Positive predictive value NPV: negative predictive value
LR: Likelihood Ratio

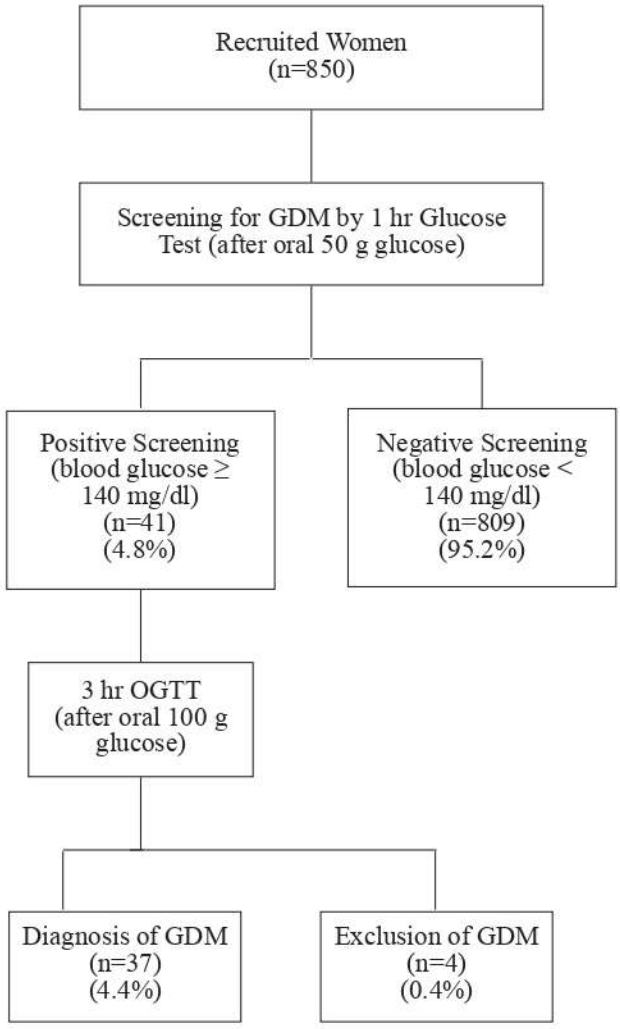

Figure (1):Flow chart of the studied participants for diagnosis of GDM

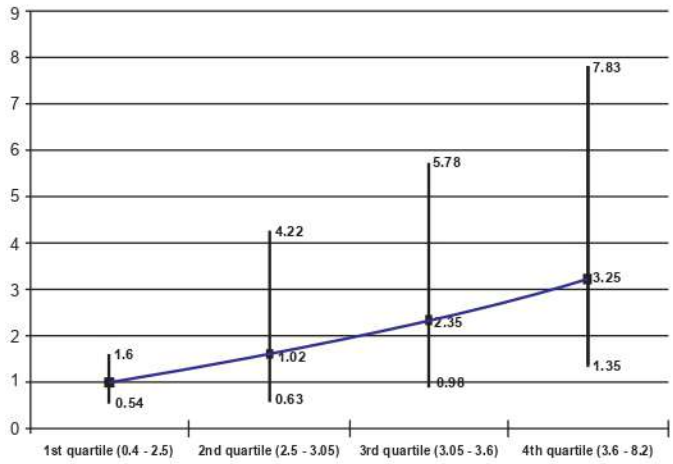

Figure 2: Risk of gestational Diabetes by first trimester uric acid quartile (Figure showed adjusted Odds ration and 95% confidence interval).

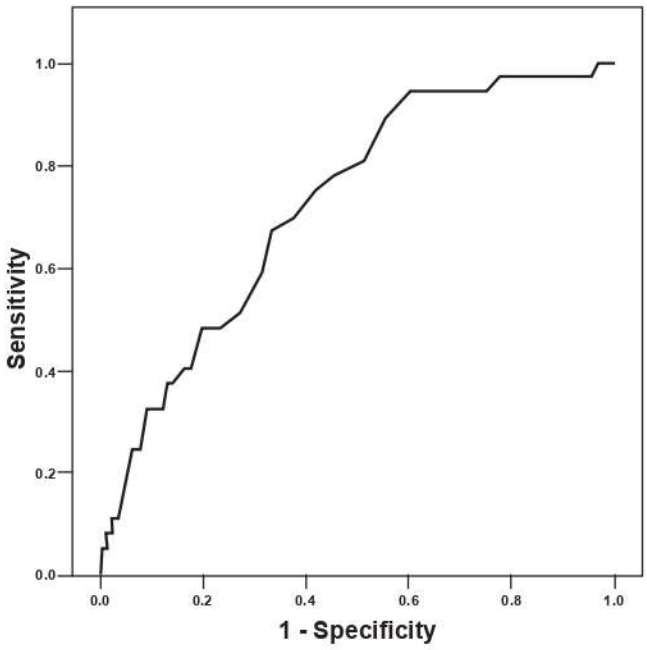

Figure (3): ROC Curve for Serum Uric Acid as Predictor of GDM

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