

## Predictive Value of First Trimester Uric Acid in Development of Gestational Diabetes

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### ABSTRACT

**Background:** Gestational diabetes mellitus (GDM) is considered a common complication in pregnancy, affecting greater than 10% pregnancies worldwide. However, the definitive underlying causes still not fully explained.

**Objectives:** This study aimed to detect the predictive value of uric acid level at first trimester in development of GDM.

**Patients and Methods:** The study was conducted on 300 first trimester pregnant females attending the Outpatient Clinic of Al-Azhar University Hospital. All cases underwent measurement of first trimester serum uric acid level. Between 24 and 28 weeks of gestation glucose challenge test was done. Positive cases underwent confirmation by 3 h glucose tolerance test. **Results:** The Pearson's test showed that there was a highly significant correlation between serum uric acid at first trimester and plasma glucose levels at 24-28 weeks.

**Conclusion:** There is increased risk in development of GDM with the increase in uric acid level at the first trimester.

**Keywords:** GDM, Uric acid, First trimester.

### INTRODUCTION

Pregnancy is associated with insulin resistance, caused primarily by diabetogenic hormones secreted from placenta mainly progesterone, corticotropin-releasing hormone, placental lactogen and growth hormone. GDM develops during pregnancy in women whose pancreatic function is not sufficient to cope with the insulin resistance associated with the pregnant state<sup>(1)</sup>. Prediction and diagnosis of GDM is important for ongoing pregnancy and has important implications for subsequent health of the mother. GDM is considered a significant risk factor for subsequent development of type II diabetes and is associated with a poorer cardiovascular risk profile compared to women without GDM<sup>(2)</sup>. Uric acid is formed from xanthine by the effect of xanthine oxidase. It is considered the main product of purine metabolism. Normal serum uric acid levels are generally 3.5 – 7.2 mg/100 ml for men and 2.6 – 6.0 mg/100 ml for women. The reason is that uric acid excretion is enhanced by estrogen during the productive period. In extracellular fluids, the limit of uric acid solubility is 7.0 mg/dL and patients with greater serum concentrations are considered hyperuricemic<sup>(3)</sup>.

Recent studies have showed that increased serum uric acid level is accompanied by hyperinsulinemia, hypertension, dyslipidemia and obesity, supporting that it could be a member of the group of factors of the metabolic syndrome<sup>(4)</sup>.

Early in pregnancy, the level of serum uric acid falls 25-35% due to an enhancement of renal clearance secondary to increased glomerular filtration rate or reduced proximal tubular reabsorption and due to changes in its production rate<sup>(5)</sup>.

As pregnancy proceeds, the level of uric acid increases may be due to increased fetal production, reduced albumin binding and a reduction in clearance of uric acid until near the pregnancy end when it approaches non-pregnant value<sup>(6)</sup>.

### PATIENTS AND METHODS

This study was conducted at Bab Al Shaarya University Hospital from January 2018 to December 2018. It is a prospective observational study which included 300 pregnant women in their first trimester who regularly attended the Outpatient Clinic for routine antenatal care. Measurement of serum uric acid was done for all women between 9-13 weeks. They underwent a screening test for GDM at 24-28 weeks. The aim was to detect if serum uric acid had a predictive value in development of gestational diabetes.

#### *Inclusion criteria*

- Pregnant not exceeding 13weeks gestation.

#### *Exclusion criteria*

- Gestational age >13 week.
- Pregestational DM.
- Gout or other endocrine disorders.
- Chronic renal diseases.
- Drugs known to increase uric acid level in the blood such as aspirin, caffeine, diuretics and phenothiazines

All patients were fully counselled for their approval to be included in this study and they all signed written informed consent.

#### *Methods:*

1. Taking approval consents of patients.

2. History:

- Personal history; including name, age, address, consanguinity and special habits as smoking ...etc.
  - Menstrual history: The 1st day of the last menstrual period (LMP), regularity of menstrual cycles and history of hormonal medications.
  - Obstetric history: Previous deliveries, mode of deliveries, number and sex of living children, date of last delivery, history of abortions, date of last abortion, puerperium and history of complications like macrosomia, preeclampsia, GDM, etc.
  - Past history Of endocrine or systemic diseases as hypertension, DM, renal diseases, hyperthyroidism, etc.
  - Medical history: Especially of hormonal medications and drugs known to elevate uric acid concentration in the blood such as phenothiazines.
  - Family history: Of clinical importance like hypertension, DM, etc.
3. Clinical examination:
- General examination: vital signs (Pulse, temperature, blood pressure, respiratory rate) body weight, body mass index and chest and heart examination, albumin, sugar and acetone in urine using dipsticks.
  - Abdominal examination: Inspection: abdominal distension, scars and pigmentation or stretching marks.
  - Palpation: of the gravid uterus by Leopolds maneuvers as fundal grip, first pelvic grip.
  - Auscultation: Fetal heart sounds.

4. Ultrasonography :

Obstetric ultrasound is used to confirm pregnancy, confirm fetal viability, detect number of fetuses, estimate date of pregnancy, check for other abnormalities, check fetal movement and assess fetal growth.

5. Uric acid: Venous blood samples were collected from all patients between 9-13 weeks. Serum uric acid was measured at clinical laboratories of Bab Al Shaarya University Hospital.

6. Screening and diagnosis of GDM (7).

Between 24-28 weeks all patients underwent 50 gram one-hour glucose screening test with the administration of a 50 g oral glucose solution then after one hour estimation of plasma glucose is done. Women with glucose levels that meet or exceed the screening threshold (140 mg/dl) then underwent a 100 g, 3-hour confirmatory OGTT. GDM is usually diagnosed in women with 2 or more high values on the 3-hour oral glucose tolerance test.

Diagnostic criteria for Gestational Diabetes:

- Fasting blood sugar (8 hours): 95mg/dl or more.
- 1-hour post-prandial blood sugar: 180mg/dl or more.
- 2-hours post-prandial blood sugar: 155mg/dl or more.

3-hours post-prandial blood sugar: 140mg/dl or more.

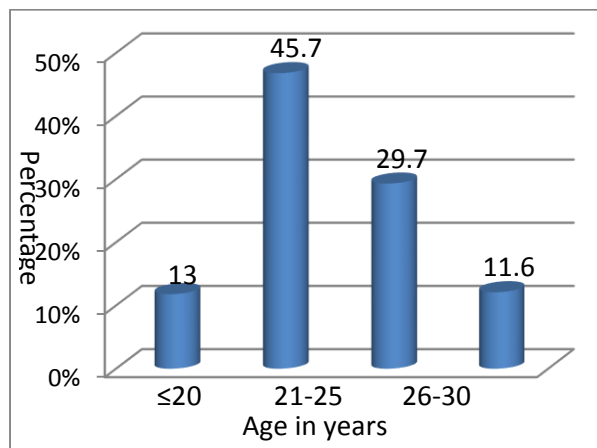
**Statistical methods**

The collected data were analyzed by statistical package for social science (SPSS) version 22 (SPSS Inc., Chicago, USA). For quantitative data, arithmetic mean and standard deviation were calculated. For qualitative data, relative frequency and percent distribution were calculated. For comparison between groups, p value >0.05 was considered insignificant, p value < 0.05 was considered moderately significant, p value < 0.01 was considered highly significant.

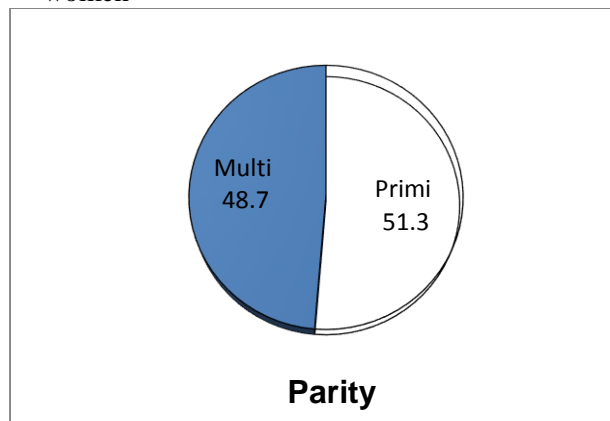
**RESULTS**

A total of 300 pregnant women of gestational age < 15wks were recruited in the study after meeting our criteria. The distributions of age and Parity are demonstrated in Figures (1 and 2).

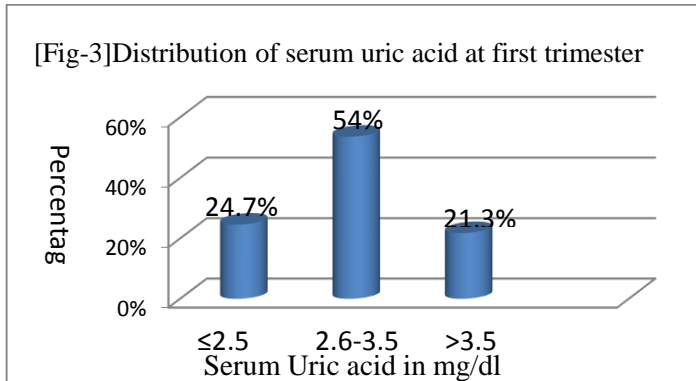
The levels of serum uric acid at < 15 week of gestation were divided into three parts according to the concentrations ( $\leq 2.5$  mg/dl, 2.6 - 3.5 mg/dl, > 3.5 mg/dl). Majority of the subjects were in the middle part (54 %) [Figure 3].



**Figure (1):** Distribution of age of studied pregnant women

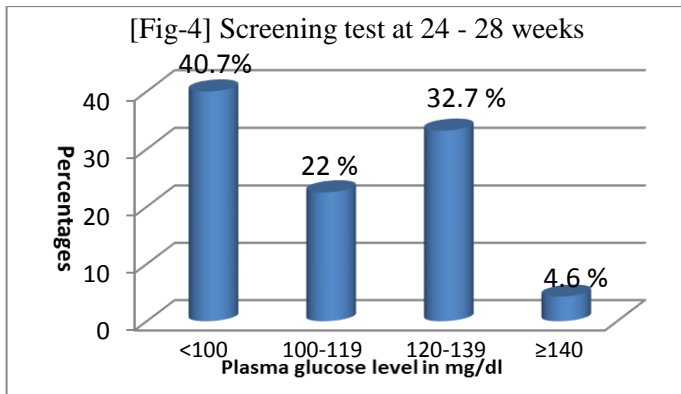


**Figure (2):** Distribution of parity of studied pregnant women



**Figure (3):** Distribution of serum uric acid at first trimester

The levels of plasma glucose at 24 to 28 weeks of gestation ranged between 70 to 150 mg/dl with a mean value of 110.83 mg/dl, out of which only 14 women had value more than 140 mg/dl [Figure 4 and Table 1].



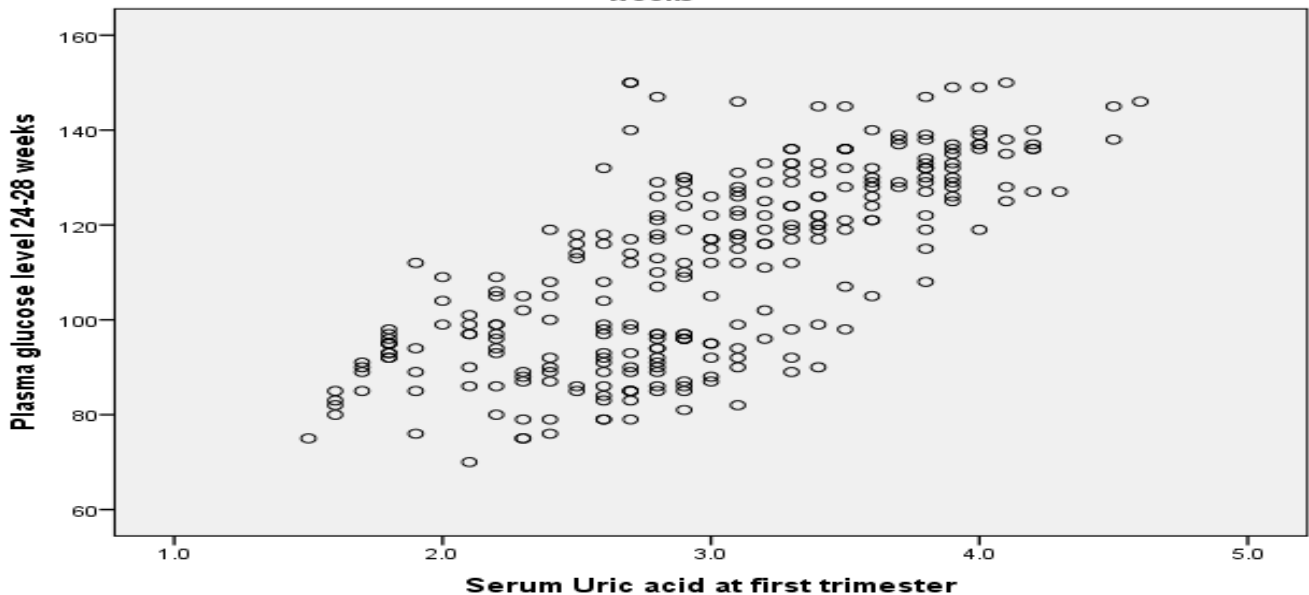
**Figure (4):** Screening test at 24-28 weeks

Table (1): Comparison between plasma glucose levels at 24 to 28 weeks according to Sr. Uric Acid at < 15 weeks

Serum Uric acid at first trimester	Plasma glucose level in mg/dl				Mean ±SD
	<100	100-119	120-139	≥140	
≤2.5 mg / dl	57 (77.03%)	17 (22.97%)	0	0	93.46 ± 11.01
2.6-3.5 mg / dl	65 (40.12%)	44 (27.16%)	47 (29.01%)	6 (3.71%)	110.2 ± 18.17
>3.5 mg / dl	0	5 (7.8%)	51 (79.7%)	8 (12.5%)	132.4 ± 8.97
<b>Total</b>	122 (40.7%)	66 (22%)	98 (32.7%)	14 (4.6%)	110.8 ± 19.98

Figure (5) showed the significant increase of plasma glucose levels at 24-28 weeks with increased values of serum uric acid at < 15 weeks of gestation with a P-value of < 0.001.

**ScatterPlot Relation between serum uric acid during first trimester and plasma glucose level 24-28 weeks**



**Figure (5):** Scatterplot relation between serum uric acid during first trimester and plasma glucose level 24-28 weeks

The Pearson's test showed that serum uric acid at < 15 weeks of gestation was highly significant correlated to plasma glucose levels at 24-28 weeks (P < 0.001) [Table 2].

**Table (2):** The Pearson's correlation between serum uric acid at < 15 weeks of gestation.

		Uric	Screening
Uric	Pearson Correlation	1	.723**
	Sig. (2-tailed)		.000
	N	300	300
Screening	Pearson Correlation	.723**	1
	Sig. (2-tailed)	.000	
	N	300	300

\*\* . Correlation is significant at the 0.01 level (2-tailed).

Age was a highly-significantly correlated to plasma glucose level at 24 to 28 weeks [Table 3].

**Table (3):** Comparison of age with plasma glucose level at 24-28 weeks

Age	Plasma glucose level in mg/dl				Total	P-value
	<100	100-119	120-139	≥140		
≤20	22(18%)	11(16.7%)	6(6.1%)	0(0%)	39	.000
21-25	64(52.5%)	24(36.4%)	44(44.9%)	5(35.7%)	137	
26-30	27(22.1%)	19(28.8%)	37(37.8%)	6(42.9%)	89	
>30	9(7.4%)	12(18.1%)	11(11.2%)	3(21.4%)	35	
Total	122	66	98	14	300	

There was a moderately significant correlation between parity and plasma glucose concentration between 24 and 28 weeks (P = 0.006) [Table 4].

**Table (4):** Comparison of parity with plasma glucose level at 24-28 weeks

Women in our study were categorized according to age into 4 categories: (≤ 20 years, 21-25 years, 26-30 years and > 30 years old). The mean age was 25.13 ± 4.34 years old. Out of three hundred women studied, 51.3% were primi-gravida and 48.7% were multigravida.

According to serum uric acid levels at 9-13 weeks of gestation women were categorized into 3 categories (≤ 2.5, 2.6-3.5, > 3.5 mg/dl); majority of the subjects were in the second part (54 %). Also they were categorized according to plasma glucose levels at 24-28 into 4 categories (<100, 100-119, 120-139, ≥140 mg/dl).

The subjects with uric acid ≤ 2.5 had a normal plasma glucose levels at 24-28 (<120mg/dl). At serum uric acid 2.5-3.5, we found that 29.2% had plasma glucose levels of 120 to 140 mg/dl and 3.7% had plasma glucose levels of ≥ 140 mg/dl. At serum uric acid > 3.5, 79.7% had plasma glucose levels of 120 to 140 mg/dl and 12.5% had plasma glucose levels of ≥140mg/dl.

This distribution demonstrated that increased level of serum uric acid in the first trimester was strongly correlated with higher levels of plasma glucose level at 24-28 weeks of gestation though only 4 % could be diagnosed to have gestational diabetes.

## DISCUSSION

A study by Langhon *et al.* (8), which was in agreement with our results declared that in 1570 pregnant women, uric acid was estimated at mean gestational age of 8.9 ± 2.5 weeks. They found that first trimester uric acid concentration > 3.6 mg/dl was associated with a trend towards increased risk of developing gestational diabetes compared to women with concentrations below this concentration.

Wolaak el al. (9) also found that uric acid concentrations at high normal levels during the first 20 weeks of pregnancy are accompanied by increased risk for the development of mild preeclampsia and GDM. Zhou *et al.* (10) in their study estimated lipids and uric acid

Parity	Plasma glucose level in mg/dl				Total	P-value
	<100	100-119	120-139	≥140		
Primi	78(63.9%)	24(36.4%)	46(46.9%)	6(42.8%)	154	.006
Multi	44(36.1%)	42(63.6%)	52(53.1%)	8(57.2%)		
Total	122	66	98	14	300	

concentrations in one thousand healthy nulliparous women during the first 20 weeks of gestation. They showed that women with elevated serum uric acid concentrations experienced a 2.34-fold risk for GDM and 1.99-fold risk for preeclampsia.

Our findings were consistent with Yoo *et al.* (11) who found in a large cross-sectional study of 53,477 non-pregnant adults, that serum uric acid had a positive correlation with insulin resistance and fasting serum glucose, as well as characters of the metabolic syndrome, including waist circumference, hyper-triglyceridemia, hypertension and low HDL cholesterol. However our study did not assess the other criteria of the metabolic syndrome.

Also Choi *et al.* (12) found that uric acid in the first trimester likely approaches pre-conception uric acid, and

raised uric acid might determine women who are predisposed to metabolic syndrome with high risk to have gestational diabetes.

In contrast, Gungor *et al.* <sup>(13)</sup> compared the relationship between serum uric acid, albumin and creatinine levels in women during pregnancy with GDM. Of total 112 patients, 56 women had gestational diabetes. All of the patients underwent estimation of serum uric acid, albumin, creatinine and liver enzymes on booking between 24-28 weeks gestation. They found that levels of serum uric acid were higher in the diabetic patients, but this increase was not statistically significant and also albumin concentrations did not show significant difference between a normal pregnant group and a GDM group <sup>(13)</sup>, which is contrary to the findings of our study. This might be due to the differences in the number of cases and gestational age of serum uric acid evaluation.

In our study, a highly significant correlation was found between age and plasma glucose levels at 24 to 28 weeks ( $P < 0.001$ ). There was increase in the mean of plasma glucose levels with increase of age group.

There was a moderately significant correlation between parity and plasma glucose levels at 24 to 28 weeks ( $P = 0.006$ ). Similar finding was found in Al-Rowaily *et al.* <sup>(14)</sup> study, which concluded that multiparous women showed 8.29 times higher risk to have GDM than nulliparous women. In contrast, a study by Nagalakshmi C.S *et al.* <sup>(15)</sup> showed an increased risk of developing GDM among primi-gravida.

## CONCLUSION

Based on the results found, we have concluded that there is higher risk of development of GDM with increased levels of serum uric acid estimated in the first trimester. There is association of maternal age and parity with GDM.

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