



**RESEARCH ARTICLE**

**URIC ACID LEVELS IN EARLY PREGNANCY AS A PREDICTOR OF PREECLAMPSIA AND GESTATIONAL DIABETES MELLITUS**

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**ABSTRACT**

A Prospective study was conducted in a tertiary hospital to examine whether uric acid levels in early pregnancy were associated with development of GDM (Gestational Diabetes Mellitus) and Hypertensive disorders during the second half of pregnancy in 178 women. Women who came before 20 weeks of pregnancy for antenatal check-ups underwent uric acid level estimation, followed by GCT (Glucose challenge test) and OGTT (Oral glucose tolerance test) if required between 24-28 weeks periods of gestation (for GDM). These women were followed up until delivery for development of Hypertensive disorders complicating pregnancy. Results showed the prevalence of Preeclampsia and GDM was 0.57% and 2.28% respectively. In the present study, Uric acid as a predictor for both Preeclampsia and GDM was found to be statistically insignificant. Our findings did not support the hypothesis that assessing uric acid concentration in pregnant women in the first trimester predicts the development of GDM and Preeclampsia.

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**INTRODUCTION**

Gestational Diabetes Mellitus (GDM) and Hypertensive disorders complicating pregnancy are considered as predictors for the subsequent development of cardiovascular disease and metabolic syndrome in future non pregnant life.<sup>1</sup> Recently, because of the obesity epidemic and the rise in maternal age, the coexistence of both GDM and Hypertensive disorders complicating pregnancy is increasing.<sup>2</sup> Uric acid is associated with insulin resistance in non-pregnant women.<sup>3</sup> Outside of pregnancy, hyperuricemia is also associated with the markers of metabolic syndrome, including obesity and dyslipidaemia.<sup>4-7</sup> Uric acid is an independent risk factor for developing Type 2 Diabetes Mellitus within 10 years in non-pregnant adults, an association that was stronger in women compared to men.<sup>8</sup>

In pregnancy, uric acid is correlated with insulin resistance in women with hypertensive disorders complicating pregnancy.<sup>9</sup> Serum uric acid is higher at 24-28 weeks gestation in women diagnosed with Gestational Diabetes compared to women without Gestational Diabetes.<sup>10</sup> Uric acid is also higher in non-pregnant women with a history of Gestational diabetes, independent of body mass index.<sup>11</sup> It was hypothesized that higher uric acid in the first trimester would be associated with the development of Gestational Diabetes and Preeclampsia. It is possible that the association of uric acid with insulin

resistance is causal. Two mechanisms have been hypothesized by which uric acid can cause insulin resistance.<sup>12</sup> Nakagawa *et al* proposed that uric acid causes endothelial dysfunction and decreases nitric oxide production by the endothelial cells.<sup>4</sup> In animals, insulin's action on glucose uptake into cells in the skeletal muscle and adipose tissue is dependent on nitric oxide.<sup>13-14</sup> Thus, decrease in nitric oxide lead to decreased glucose uptake and the development of insulin resistance. Another 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.<sup>15-16</sup> As GDM and Preeclampsia are linked to metabolic syndrome and serum uric acid (UA) is known as a marker for metabolic syndrome in non-pregnant subjects, the current study was aimed to examine whether there is a relationship between UA level in the first 20 weeks of pregnancy and the development of these complications in the later course of pregnancy.

**MATERIALS AND METHODOLOGY**

**Location and duration of study**

Study was carried out in Government Lady Goschen Hospital, Mangalore & KMC Hospital Attavar from January 2011 to September 2012

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**Experimental design**

A Prospective hospital-based study was conducted to examine whether uric acid levels in early pregnancy were associated with development of GDM and Hypertensive disorders during the second half of pregnancy in 178 women. Institutional ethical clearance was given for the study.

**Inclusion criteria**

1. Patients who come before 20 weeks of Pregnancy for antenatal check-ups (for uric acid level estimation)
2. Patients who underwent uric acid level estimation before, following up for GCT and OGTT (if required) between 24-28 weeks periods of gestation (for GDM)
3. Patients fulfilling above mentioned both criteria were followed up until delivery for development of Preeclampsia.

**Exclusion criteria**

1. Multiple gestations
2. Chronic hypertension
3. Pre-gestational Diabetes Mellitus

**Uric Acid Measurements**

- Serum Uric acid was measured by means of automated calorimetric assay with detection limit of 0.2 - 25mg/dl at Central Laboratory, KMC Hospital, Ambedkar Circle, Mangalore.

The UA levels in the first half of pregnancy were sorted into the following groups:

- UA = 1.41mg/dl;
- UA = 1.42–2.35 mg/dl;
- UA = 2.36–3.24 mg/dl; and
- UA > 3.24mg/dl.

For each group of UA the rate of Hypertensive disorders and GDM were recorded.

**Diagnosis of GDM**

- GDM was screened by GCT with 50gms of glucose and diagnosed by oral GTT with 100 grams of glucose if required.
- GCT values >200 mg/dl were considered to have GDM and value >140 mg/dl were considered significant, and were subjected to OGTT with 100 grams glucose.
- OGTT values were evaluated according to

**Carpenter-Coustan Criteria**

- Fasting sample- >95 mg/dl
- 1<sup>st</sup> Hour sample- >180 mg/dl
- 2<sup>nd</sup> Hour sample- >155 mg/dl
- 3<sup>rd</sup> Hour sample- >140 mg/dl

- With at least 2 OGTT values met or exceeded were diagnosed to have GDM

**Statistical Analysis**

Statistical significance was calculated using the Chi-square test, and one-way ANOVA for differences in continuous variables. Multivariate analyses were performed to demonstrate whether UA level was an independent factor for the prevalence of Preeclampsia and GDM. A *p*-value <0.05 was considered statistically significant.

**RESULTS**

- Total number of women who followed up till delivery : 175
- Total number of women who had Abortion : 3

**Table 1** Mean gestational age of women at which uric acid level estimation was done

Uric acid quartiles	Mean gestational age
1.41mg/dl	11wks + 1day
1.42-2.35 mg/dl	11wks + 3days
2.36-3.24mg/dl	13wks + 5days
> 3.24 mg/dl	13wks
	12wks + 3days

The mean gestational age of women at which uric acid level was estimated was 12 weeks 3 days.

**Table 2** Mean uric acid levels of women in different quartiles

Uric acid quartiles	Mean uric acid(in mg/dl)
1.41mg/dl	1.3
1.42-2.35 mg/dl	2.0
2.36-3.24mg/dl	2.75
> 3.24 mg/dl	3.54
	2.83

Mean uric acid level of women was 2.83 mg/dl

**Table 3** Distribution of women in different quartiles

Uric acid quartiles	Number of patients
1.41mg/dl	1 (0.5%)
1.42-2.35 mg/dl	45(25.2%)
2.36-3.24mg/dl	81 (45.5%)
> 3.24 mg/dl	51 (28.6%)
Total	178

Majority of patients were found in 3<sup>rd</sup> quartile group and the least in 1<sup>st</sup> quartile group.

**Table 5** Prevalence of Hypertensive disorders of pregnancy in different quartiles

Uric Acid Quartiles	Normotensives	Gestational Hypertension	Preeclampsia
1.41mg/dl	1	-	-
1.42-2.35 mg/dl	45	-	-
2.36-3.24mg/dl	79	1 (1.23%)	1 (1.23%)
> 3.24 mg/dl	50	1 (1.96%)	-
Total	175	2 (1.14%)	1(0.57%)
<b>p value</b>		<b>0.384</b>	<b>0.656</b>

Number of women who developed mild Preeclampsia was 1, who belonged to 3<sup>rd</sup> quartile. Number of women who developed Gestational Hypertension was 2, one each in 3<sup>rd</sup>

quartile and 4<sup>th</sup> quartile.

**Table 6**Prevalence of Gestational Diabetes Mellitus in different quartiles

Uric Acid Quartiles	Abnormal GCT	Impaired GTT	Gestational Diabetes
1.41mg/dl	0	-	-
1.42-2.35 mg/dl	3	-	-
2.36-3.24mg/dl	16	2(2.4%)	4(4.93%)
> 3.24 mg/dl	5	-	-
Total	24(13.71%)	2(1.14%)	4(2.28%)
<b>p value</b>	<b>0.103</b>	<b>0.347</b>	<b>0.563</b>

Number of women who were diagnosed to have Gestational Diabetes Mellitus was 4; all of them belonged to 3<sup>rd</sup> quartile. Number of women who were diagnosed to have Impaired GTT was 2; both belonged to 3<sup>rd</sup> quartile. Number of women who had abnormal GCT was 24, 16 of them belonged to 3<sup>rd</sup> quartile, 5 of them belonged to 4<sup>th</sup> quartile and 3 of them belonged to 2<sup>nd</sup> quartile.

## DISCUSSION

Uric acid in the first trimester likely approximates pre-conception uric acid, and elevated uric acid may identify women who are predisposed to metabolic syndrome with an increased risk of developing GDM and Preeclampsia, independent of obesity. Alternatively, uric acid decreases early in pregnancy, so perhaps women with elevated uric acid have a poor adaptation to pregnancy (i.e. abnormal placentation), putting them at risk for adverse pregnancy outcomes such as GDM and Preeclampsia. Present study was aimed to assess the significance of uric acid levels as a predictor of both GDM and Preeclampsia.

The mean uric acid level of the women in the study done by S K Laughon *et al*<sup>8</sup> was 3.08 ± 0.85 mg/dl and in present study it was 2.83 mg/dl which was comparable.

The mean gestational age of the women at which uric acid level was estimated by S K Laughon *et al*<sup>8</sup> was 8.9 ± 2.5 weeks and in present study it was 12 wks 3 days which was comparable.

The mean age of women in studies conducted by S K Laughon *et al*<sup>8</sup> was 25.1yrs, in Talya Wolak *et al*<sup>9</sup> was 29.5yrs and in present study it was 25.7yrs.

Prevalence of mild Preeclampsia in study conducted by Talya Wolak *et al*<sup>9</sup> showed overall incidence to be 3.4% when compared to 0.57% in present study. In the study conducted by Talya Wolak *et al* there was a significant linear association between uric acid levels in first 20 weeks of pregnancy and the prevalence of mild preeclampsia in second half of pregnancy (p value < 0.001), and highest prevalence was noticed in the 3<sup>rd</sup> quartile group.<sup>19</sup> The same trend was found in severe preeclampsia however the difference did not reach statistical significance. In present study none of the women were diagnosed to have severe preeclampsia.

Uric acid level was found to be an independent risk factor for pregnancy induced hypertensive disorders using multiple logistic regression models controlling for maternal age. Women who developed mild preeclampsia and hypertensive disorders in general had a significantly higher uric acid level in first 20

weeks of pregnancy compared to women who didn't develop them (p value < 0.001).<sup>19</sup>

In study conducted by S K Laughon *et al*<sup>8</sup> it was reported that the mean first trimester uric acid concentration for women who remained normotensive was 3.1 ± 0.8 mg/dl, which was similar to concentrations in women who developed gestational hypertension (mean 3.1 ± 0.8 mg/dl, p value = 0.9) but significantly less than the mean first trimester uric acid concentration of women who developed preeclampsia (mean 3.4 ± 1.0 mg/dl, p value= 0.01). First trimester uric acid in the highest quartile compared to the lowest three quartiles was not associated with developing gestational hypertension (p value = 0.5) compared to remaining normotensive, but was associated with an increased risk of developing preeclampsia (p value = 0.03). There was a significantly increasing risk for women to develop either of the hyperuricemic forms of hypertensive disease with increasing first trimester uric acid quartile (p value < 0.001). This was not the case for women who developed the non-hyperuricemic forms of hypertensive disease or for women who remained normotensive [p value = 0.1 for both]. The risk of developing HU or HPU compared to women who remained normotensive was more than 3-fold higher if women had first trimester uric acid in the highest quartile (> 3.56 mg/dl) compared to the lower three quartiles.<sup>17</sup>

**Table 8**Comparison of prevalence of mild Preeclampsia

Uric acid quartiles	Talya Wolak <i>et al</i>	Present study
1.41mg/dl	2.1%	-
1.42-2.35 mg/dl	3.3%	-
2.36-3.24mg/dl	5.3%	1.23%
> 3.24 mg/dl	4.5%	-
Mean	3.4%	0.57%
<b>p value</b>	<b>&lt;0.001</b>	<b>0.656</b>

The mean prevalence of Gestational Diabetes Mellitus in studies done by Talya Wolak *et al*<sup>9</sup> was 7.6%, S K Laughon *et al*<sup>8</sup> was 4.6% and in the present study it was 2.28%. There was a rising trend which was noticed in 4<sup>th</sup> quartile in the previous 2 studies, but not in the present study.

In the study conducted by Talya Wolak *et al* significant linear association was seen between UA level in the first half of pregnancy and the prevalence of GDM in the second half of pregnancy. Highest prevalence was seen in the 4<sup>th</sup> quartile. Uric acid level was found to be an independent risk factor for mild GDM using multiple logistic regression models controlling for maternal age. Women who developed GDM had a significantly higher uric acid level compared to women who didn't develop them (p value < 0.001).<sup>19</sup>

In the study conducted by S K Laughon *et al*<sup>8</sup> almost half (46.6%) of the women with GDM had first trimester uric acid concentrations in the highest quartile (>3.57-8.30 mg/dl). Women with uric acid in the highest quartile had a 3.25-fold increased risk of developing GDM after adjustment for BMI and age. This effect was concentration dependent as risk increased with increasing uric acid quartiles. Using a cut point of 3.6 mg/dl yielded a positive predictive value (PPV) of 9.0% and negative predictive value (NPV) of 96.7% for development of GDM. When restricted to non-obese women (BMI < 30 kg/m<sup>2</sup>) a first trimester uric acid concentration 3.6mg/dl was not associated with an increased risk of Gestational Diabetes.

They concluded that their findings did not support assessing uric acid concentration in pregnant women in the first trimester to predict the development of GDM as area under the ROC curve was 0.7 for first trimester uric acid levels.<sup>18</sup> S K Laughon *et al* also proposed that it is possible that of the women who developed GDM, those with elevated first trimester uric acid concentrations are the women who are at risk to develop type 2 Diabetes Mellitus in the future and this warrants future investigation.<sup>18</sup>

**Table 8** Comparison of prevalence of Gestational Diabetes Mellitus

Uric acid quartiles	Talya Wolak <i>et al</i>	Present study
1.41mg/dl	6.3%	-
1.42-2.35 mg/dl	7.4%	-
2.36-3.24mg/dl	9.5%	4.93%
> 3.24 mg/dl	10.5%	-
MEAN	7.6%	2.28%
<b>p value</b>	<b>0.005</b>	<b>0.563</b>

In the study conducted by S K Laughon *et al*, it was seen that there was no linear association between first trimester uric acid and birth weight or birth weight percentile in the entire cohort. (p value = 0.4). First trimester uric acid in fourth quartile (>3.56 mg/dl) compared to the lowest three quartiles was not associated with an increased risk of having an SGA in the entire cohort nor in women who developed gestational hypertension or preeclampsia.<sup>20</sup> In the present study also there was no significance seen between uric acid levels and birth weight (p value - 0.841).

## CONCLUSION

In the present study, Uric acid as a predictor for both Preeclampsia and Gestational Diabetes Mellitus statistically is insignificant contrary to the association of uric acid levels in highest quartile with Preeclampsia and Gestational Diabetes in previous studies. Our findings do not support the hypothesis that assessing uric acid concentration in pregnant women in the first trimester predicts the development of GDM and Preeclampsia.

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