Uric Acid Concentrations, Insulin Resistance and Pregnancy Outcome in Obese and Non-Obese Pregnant Women

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Abstract

Objective: The objective of this study is to evaluate possible correlation between serum uric acid and insulin resistance in obese and non-obese pregnant women and its impact on pregnancy outcome.

Methods: A cross section study was carried out on sixty pregnant women. The women were divided into two groups: Obese pregnant women (n=30), and non-obese healthy pregnant women (n=30) came for antenatal care in third trimester. Uric acid, glucose and insulin were measured in maternal serum. Insulin resistance and pre-pregnancy body mass index (BMI) were calculated.

Results: In this study we found serum uric acid level and insulin resistance were higher significantly in overweight and obese pregnant women (BMI $\geq 25$ kg/m$^2$) 5.5±0.8mg/dl, 2.7±0.5 respectively as compared to non-obese healthy pregnant women (BMI >19.9–<25kg/m$^2$) 4.0±0.6mg/dl, 1.6±0.4 respectively. There was significant correlation between serum uric acid concentration and insulin resistance among overweight and obese pregnant women.

There was significant increase in mean birth weight and cesarean section in overweight and obese women and no significant difference in mean gestational age at birth between the two groups.

Conclusion: Increasing uric acid concentrations were associated with insulin resistance in euglycemic, normotensive pregnant women with high body mass index (BMI $\geq 25$kg/m$^2$). Obesity, insulin resistance and serum uric acid increased risk for adverse pregnancy outcomes. Pre-pregnancy health education is important to women with high body mass index.

Key Words: Uric acid – Insulin resistance – Obese.

Introduction

OBESITY is defined as excessive body fat to an extent that is highly likely to impair health and increase morbidity and mortality. Body mass index (BMI) is the most frequently applied indicator of obesity. Thus, individuals with a BMI of 25 to 30kg/m$^2$ are categorized as overweight, and those with a BMI over 30kg/m$^2$ are considered obese. According to the World Health Organization (WHO), the prevalence of obesity in pregnancy ranges from 1.8 to 25.3% [1]. Obesity before and during pregnancy constitutes a major risk factor for both maternal and fetal complications [2,3], while it has been shown that offspring of obese women have a higher likelihood of becoming obese during childhood and of developing metabolic syndrome in adulthood [4].

Obesity is associated with an increase in the frequency of the metabolic syndrome, the prevalence doubles to 13% among women aged 30-39 [5,6]. Both obesity and metabolic syndrome are associated with increased risk for adverse pregnancy outcomes including gestational diabetes, gestational hypertension, preeclampsia, stillbirth, accelerated fetal growth and cesarean section [7-9].

Metabolic syndrome is associated with hyperuricemia as well as insulin resistance [5,10]. Serum uric acid (SUA) is an end product of purine metabolism. Recent studies showed that SUA was a predictor of metabolic syndrome [11,12]. In pregnancy, elevated serum uric acid in hypertensive pregnant patients is associated with poor perinatal outcomes including small for gestational age (SGA) infants and preterm birth (PTB) [13,14].

Insulin resistance, however, is a component of gestational diabetes and increasing risk for excessive fetal growth, as well as gestational hypertension and preeclampsia [15,16]. Thus, although both uric acid and insulin resistance are associated with metabolic syndrome, these conditions could have opposing or perhaps synergistic effects on maternal and fetal health.
In this study, we aimed to assess a possible correlation between serum uric acid and insulin resistance in obese and non-obese pregnant women and its impact on pregnancy outcome.

**Patients and Methods**

This study was carried out among pregnant women attending for antenatal care in primary health care units in Suez governate and Obstetric clinic in Suez Canal University hospital between January, 2009 and July, 2011. An informed written consent was obtained from all women participating in the study.

Sixty pregnant women participated in the study and classified into two groups: The first group was healthy non-obese pregnant women (n=30), the second group was overweight and obese pregnant women in third trimester (n=30). Women with a BMI of >19.9 to <25kg/m² are considered as non-obese; women with a BMI of 25 to 30kg/m² are categorized as overweight, and those with a BMI over 30kg/m² are considered obese.

Inclusion criteria were healthy pregnant women aged 20-35 years old, in third trimester, pregestational weight was known and came for antenatal care. Exclusion criteria were any chronic or endocrinical diseases as hypertensive disorders, diabetes mellitus, renal disease, cardiac or thyroid diseases, previous history of cesarean section. Any participant developed hypertension or hyperglycemia during the study was excluded from data analysis.

All the participants were subjected to detailed medical history and complete clinical examination. Body mass index (BMI) was calculated as pregestational weight in kilograms divided by the square of height in meters). Assessment of pregnancy outcomes in our study based on mean birthweight, mean gestational age at birth and mode of delivery.

A fasting blood sample was drawn from the antebrachial vein using sterile syringes. Serum samples were prepared according to standard methods and analyses were performed. Glucose and uric acid were measured using a colorimetric assay from Roche and an ELISA kit for measurement of fasting insulin.

The homeostatic model for insulin resistance (HOMA-IR) was calculated as described by Mathews et al. [17]. Using the formula: Insulin resistance = Glucose (mg/dl) x insulin (U/ml)/405.

**Follow-up:** To assess the pregnancy outcome in each group.

**Statistical analysis:**

Data was processed using SPSS version 15 (SPSS Inc., Chicago, IL, USA). Quantative data was expressed as means ± SD and qualitative data was expressed as numbers and percentages. Student’s t-test was used to test significance of difference for quantitative variables and Chi-square was used to test significance for qualitative variables. A probability value (p-value) <0.05 will be considered statistically significant. Correlation of serum uric acid and insulin resistance was done within each group with reference to uric acid. Significance of correlation was decided based on ‘r’ & ‘p’ values.

**Results**

Sixty pregnant women participated in the study and classified into two groups: The first group was healthy non-obese pregnant women (n=30), the second group was obese pregnant women in third trimester (n=30). The mean age of the groups was 29.3±3.6 and 30.5±4.3 respectively, the difference was statistically insignificant. There was no significant difference in parity between the two groups.

The mean BMI (kg/m²) were 23.9±3.1 for non-obese women and 32.4±4.2 for the second group. The difference was statistically significant (p<0.001). There was no significant difference of the mean gestational age at the first visit or at labor between the two groups. The mean birth weight was 3336±270gm for non-obese women and 3600±322gm for the second group. The difference was statistically significant (p<0.01).

| Table (1): Comparison of clinical parameters between pregnant women with BMI <25kg/m² and BMI ≥25kg/m². |
|--------------------------------------------------|--------------------------------------------------|------------------|
| Age (years)                                      | Mean gestational age at 1st visit                | Weight (kg)      |
| Non obese women BMI <25kg/m²                       | Overweight and obese women BMI ≥25kg/m²           | p value          |
| 29.3±3.6                                         | 30.5±4.3                                         | NS               |
| Mean gestational age at 1st visit                  | 33.6±3.8                                         | NS               |
| 32.8±3.3                                         | Weight (kg)                                      | <0.001*          |
| 65±7.5                                           | 82±9.4                                          | <0.001*          |
| BMI (Kg/m²)                                      | Mean (GA) at labor                               | <0.01*           |
| 23.9±3.1                                         | 39.3±2.2                                         |                 |
| 32.4±4.2                                         | 39.1±1.6                                         |                 |
| Mean birth weight (gm.)                           | 3336±270                                         |                 |
| 3600±322                                         |                                                  |                 |

NS = Not statistically significant.
* = Significant.
Fasting blood glucose showed no significant difference between the two groups while fasting insulin elevated significantly in overweight and obese women than non obese (p<0.001). HOMA-IR was higher in obese pregnant women than non obese group (p<0.001) (Table 2). Serum uric acid in overweight and obese pregnant women was significantly higher than non obese pregnant women. The difference was statistically significant. There was strongly positive correlation between insulin resistance (HOMA-IR) and serum uric acid among euglycemic, normotensive overweight and obese pregnant women, \( r=0.471 \) & \( p=0.009 \) and was not showed among non-obese healthy pregnant women. Regarding the pregnancy outcome there was no significant difference in mean gestational age at labor between the two groups.

There were significant difference in mean birth weight and mode of delivery between the two groups. The cesarean section was higher significantly among overweight and obese women (Table 3).

Table (2): Comparison of biochemical parameters between pregnant women with BMI <25kg/m² and BMI ≥25kg/m².

<table>
<thead>
<tr>
<th></th>
<th>Pregnant women with BMI &lt;25kg/m²</th>
<th>Pregnant women with BMI ≥25kg/m²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>79.8±11.5</td>
<td>81.3±10.8</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting insulin (IU/ml)</td>
<td>9.3±6.3</td>
<td>13.3±5.8</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Homeostatic model (HOMA)</td>
<td>1.6±0.4</td>
<td>2.7±0.5</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Serum uric acid (mg/dl)</td>
<td>4.0±0.6</td>
<td>5.5±0.8</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

NS = Not statistically significant. * = Significant.

Fig. (1): Shows correlation between HOMA-IR and serum uric acid among the overweight and obese pregnant women (BMI ≥25kg/m²) with a high statistical significance \( p<0.01 \).

Table (3): Comparison of the mode of delivery between the non-obese and obese pregnant women.

<table>
<thead>
<tr>
<th></th>
<th>Non-obese pregnant women</th>
<th>Overweight-obese pregnant women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal delivery</td>
<td>25</td>
<td>21</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>83.3%</td>
<td>70%</td>
<td>76.7%</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>5</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>16.7%</td>
<td>30%</td>
<td>23.3%</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

NS = Not statistically significant. * = Significant.

Discussion

The alarming increase in the prevalence of obesity worldwide, currently the commonest metabolic disease, has led the World Health Organization (WHO) to consider obesity as one of the most serious global health problems of the 21st century [1]. Obesity before pregnancy constitutes a major risk factor for both maternal and fetal complications [2], we studied the association between uric acid and insulin resistance in obese and non obese pregnant women and the possible impact on pregnancy outcome.

The mean serum uric acid in healthy non-obese pregnant women was 4.0±0.6mg/dl at third trimester in our study while it was 5.5±0.8mg/dl in overweight and obese women. This result is consistent with the average uric acid level during pregnancy, in healthy pregnancies, uric acid decreases from an average of 4.2mg/dl pre-pregnancy to 3.1 ± 1.1mg/dl in the first trimester, and slowly increases during gestation to an average of 5.1 ± 1.2mg/dl from 35 weeks gestation to term [18].

There was significant increase in the mean serum uric acid and insulin resistance in overweight and obese pregnant women. Recent studies have documented the association among serum uric acid, obesity, and metabolic syndrome in adults [19-23]. Several investigators have shown that insulin resistance plays a central role in the link between metabolic syndrome and high serum uric acid [19,23,24]. Insulin resistance is thought to cause decreased excretion of uric acid [25,26,27].

We found an association between uric acid and insulin resistance in third trimester pregnancy among the overweight and obese pregnant women and this association was not showed among healthy non obese pregnant women. This finding is consistent with the result of recent study which showed that For all women at 20 weeks gestation, the...
HOMA concentration increased by 1.40 units \((p<0.001)\) for every 1mg/dl increase in uric acid. When stratified by BMI, the relationship between HOMA and uric acid was apparent among normal weight \((\text{BMI} <25\text{kg/m}^2)\) women \((p=0.02)\), and there was an even stronger association among overweight \((\text{BMI} >25\text{kg/m}^2)\) women \((p=0.001)\).

In women who remained normotensive, the HOMA increased per 1mg/dl rise in uric acid concentration in normotensive women \((p=0.003)\), however remained significant only in overweight women \((\text{BMI} <25\text{kg/m}^2, p=0.17 \& \text{BMI} >25\text{kg/m}^2, p=0.03)\) \cite{28}.

Our findings agreed with the well-established association between uric acid and insulin resistance in non-pregnant adults. In a study of 83 women with insulin resistance, serum insulin was linearly associated with serum uric acid concentrations after controlling for other causes of hyperuricemia and hyperinsulinemia \cite{29}. Another large study confirmed that Body mass index (BMI), fasting insulin, were significantly higher, in subjects with hyperuricemia \((p<0.001)\). BMI showed the strongest positive correlation with uric acid among the insulin resistance syndrome (IRS) components \cite{30}.

Recent study agreed with our findings, they studied Insulin resistance and serum uric acid in normotensive and hypertensive pregnant women, the correlation held true for women who remained normotensive \((r^2=0.17, p=0.003)\) and women who developed the less severe form of preeclampsia \((\text{HP}, r^2=0.86, p=0.02)\) \cite{28}.

Our study showed significant increase in mean birthweight in overweight and obese women, Roberts et al. \cite{31} confirmed that there was no relation between the uric acid concentration and the odds of small for gestational age among women without hypertension and without proteinuria \((n=615)\). Our result disagree with the previous study of Laughan \cite{32} who found significant association between increased serum uric acid, high insulin resistance and low birth weight infants. They showed that SGA occurred in 30.8% of pregnancies in normotensive women with uric acid in the highest quartile \((\text{uric acid }>4.1\text{mg/dl})\) compared to only 3.4% of normotensive women with uric acid in the lowest quartile \((\text{uric acid} <2.9\text{mg/dl}, p<0.001)\) \cite{28}.

Our result agreed with many studies which showed the association between maternal obesity and fetal macrosomia \cite{32}. Maternal weight and insulin resistance before pregnancy affect fetal growth, as is reflected in the birth weight \cite{33}. Obese women even with normal glucose tolerance have a two-fold higher risk of giving birth to macrosomic babies. Obesity and insulin resistance alter placental function which, during the last weeks of pregnancy, increases the availability of glucose, free fatty acids and amino acids to the fetus \cite{34}.

Regarding the mean gestational age at delivery, there was no significant difference between the obese and non obese pregnant women in our study. This agreed with that of Roberts et al. \cite{31}. They confirmed that there was no relation between the uric acid concentration and the odds of preterm birth among women without hypertension and without proteinuria \((n=615)\).

The risk of preterm birth in overweight and obese women shows conflicting data. Several retrospective cohort studies have described an increased risk of delivery at less than 32 weeks' gestation in obese women \cite{35-38}, but others have found no difference \cite{39-42} or even a decreased risk \cite{43,44}.

A population-based cohort study in the United States found that, compared with lean women, women with a BMI of greater than 30kg/m² had 1.6 times the risk of delivering prematurely; this risk remained significant after adjusting for antenatal complications \cite{45}. Contrasting results were found in a population based cohort analysis in the United Kingdom, which showed that women with an increased BMI were less likely than women of normal weight to deliver at less than 32 weeks' gestation \cite{44}.

There was significant increase in cesarean section (CS) in obese women in our study which is consistent with previous studies in obese pregnant women. Delivery by CS has been shown to occur more frequently in obese women \cite{37,46-53}. The association between excessive BMI and the need for CS is independent of other factors such as maternal height and age, primiparity, macrosomia, and maternal diabetes \cite{54,55}.

Obese women are at increased risk of complications at the time of labor and delivery. The rate of successful vaginal delivery decreases progressively as maternal BMI increases. A meta-analysis of 33 studies showed that the ORs of cesarean delivery were 1.46 \((95\% \text{ CI}, 1.34-1.60)\), 2.05 \((95\% \text{ CI}, 1.86-2.27)\), and 2.89 \((95\% \text{ CI}, 2.28-3.79)\) among overweight, obese, and severely obese women, respectively, compared with normal weight pregnant women \cite{56}. According to Ehrenberg and coworkers, the cesarean delivery rate for women weighing less than 200 lb was 18%, versus 39.6%
in women who were classified as extremely obese [57]. This 2- to 3-fold increase in cesarean delivery rate is true for both primigravid and multigravid women. Whether this is secondary to increased fetal size or another maternal characteristic is not known [58].

Our results revealed increased cesarean section in obese women, this could be explained as obese women may have suboptimal uterine contractility, increased fat deposition in pelvic soft tissues [44], failure to progress in labor [55,59] in addition to increased fetal size [58].

Conclusion: Increasing uric acid concentrations were associated with insulin resistance in euglycemic and normotensive pregnant women with high body mass index (BMI ≥25kg/m²). Obesity, insulin resistance and serum uric acid increased risk for adverse pregnancy outcomes. Pre-pregnancy health education is important to women with high body mass index.

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