Association between Unexplained Recurrent Miscarriage and Insulin Resistance -  

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ABSTRACT

Methods: The current case-control study was conducted at Ain Shams University Maternity Hospital. The study included two groups of women: group A, including pregnant women with a history of unexplained recurrent miscarriage; and group B, including control pregnant women with no prior miscarriage. Women included in either group were at their first trimester of pregnancy (6-13 weeks of gestation). For all included women, 3-hour oral glucose test was performed. Serum insulin levels were measured at the same times. Markers of insulin resistance, including HOMA-IR, HOMA-B, AUCG and AUCI were calculated.

Results: There were no significant differences between women of both groups regarding HOMA-IR and HOMA-B. The mean values of AUCG and AUCI were, however, significantly higher in women of group A when compared to group B.

Keywords: Recurrent Pregnancy Loss; Insulin Resistance

INTRODUCTION

Recurrent early miscarriage was traditionally described as three or more clinically diagnosed consecutive pregnancy losses prior to the 20th gestational week [1]. Since similar etiologic factors have been identified between two or three pregnancy losses has been detected in recent years, investigation of the couple for the etiology is currently sought for, after two consecutive pregnancy losses [2]. The incidence of two or three subsequent miscarriages is 2% and 0.3-1%, respectively [3]. The list of etiologies for recurrent miscarriage includes a number of chromosomal, anatomical, endocrine, infectious, immunologic factors. Nevertheless, the underlying cause is not infrequently identifiable in most of cases [4]. Glycemic control and insulin sensitivity are of the most important factors in reproductive pathophysiology. Impaired glucose tolerance, diabetes mellitus and Insulin Resistance (IR) have been long known to be lined to adverse reproductive outcomes, including infertility, miscarriages, and adverse pregnancy outcomes [5]. Several studies have shown a biochemical and clinical association between miscarriage and both poor glycemic control and IR [6]. The aim of the current study is to evaluate association between recurrent early miscarriages and IR in early pregnant women.

Methods

The current case-control study was conducted at Ain Shams University Maternity Hospital during the period between December 2013 and June 2014. The study protocol was in agreement to the Helsinki declaration of Ethical Medical Research [last updated in South Korea, 2013] and had been approved by the Ethical Research Committee of Obstetrics and Gynecology Department at Ain Shams University. All participating women had to sign informed written consent after thorough explanation of the purpose and procedure of the study. Any participating woman had the right to withdraw from the study without being adversely affected regarding the medical service she should have received.

The study included two groups of women: group A, including pregnant women with a history of unexplained recurrent miscarriage; and group B, including control pregnant women with no prior miscarriage. Women included in either group were at their first trimester of pregnancy (6-13 weeks of gestation). Women with history of gestational or pregestational diabetes mellitus, women on medications that might affect glucose metabolism (e.g. metformin), those who were obese (Body Mass Index (BMI) ≥ 30 kg/m²) or had Polycystic Ovarian Syndrome (PCOS) were not included in the study. Unexplained recurrent miscarriage was defined as two or more failed clinical pregnancies (as documented by ultrasonography or histopathological examination) with no detectable underlying (endocrine, anatomical, chromosomal or immune) cause [7].

All included women were asked to go on a normal diet for 3 days prior to Oral Glucose Tolerance Testing (OGTT). A fast for 8–10 h was required prior to sampling. A venous blood sample was drawn on the following morning from each woman to determine the concentrations of Fasting Glucose (FG) and Fasting Insulin (FI). Women were then asked to drink a mixture of 75 g of pure glucose in 250 ml of water; venous blood samples were drawn after 1, 2, and 3 hours to determine the concentrations of glucose and insulin [8]. Glucose concentration was determined using the hexokinase endpoint method; while insulin concentration was determined using the immunoluminescence method. The Immulite2000 Immunoassay Analyzer* [Siemens Healthineers®, Erlangen, Germany] was used along with the necessary reagents. The homeostasis model assessment of insulin resistance index (HOMA-IR) for each subject was calculated as follows: [(FI (U/ml) × FG mmol/l)]/22.5. The larger the HOMA-IR, the more severe the degree of Insulin Resistance (IR). HOMA-B, which represents the endocrine function of insulin, is calculated as 20× FI / (FG-3.5). The Area under the Curve of Glucose (AUCG) is equal to half of the FG plus 1-hour glucose, 2-hour glucose, and half of the 3-hour glucose. The Area under the Curve of Insulin (AUCI) is also computed in this manner for insulin. The ratio AUCI/AUCG represents the rate of AUCI to AUCG; and the higher the rate, the more severe the degree of IR [9].

Sample size justification

Sample size was calculated, setting the type-1 error (α) at 0.05 and the power (1-β) at 0.80. Data from a previous study [10], showed that mean values of HOMA-IR were 4.2 ± 6.3 and 1.6 ± 1.6 in the recurrent miscarriage and control groups, respectively. Calculation according to these values to find such a difference produced a minimal sample size of 37 cases in each group. Assuming a drop-out ratio of 10%, the sample size will be 40 women in each group.

Statistical methods

Statistical analysis was performed using SPSS for Windows version 20.0. Difference between two groups was analyzed using independent student’s t-test as well as the mean difference and its 95% confidence interval (95% CI). Receiver Operator Characteristics (ROC) curves were constructed for estimating the association between unexplained recurrent miscarriage and measured markers of IR. Significance of association was presented in terms of Area under the Curve (AUC) and its 95% CI. Validity of the association was presented in terms of sensitivity and specificity and their 95% CIs. Significance level was set at 0.05.

RESULTS

Forty women were included as group A [RPL group], along with 40
women as group B [control group]. The mean age of included women was 30.4 ± 4.3 years (range: 22-39 years). The mean gestational age at recruitment was 7.3 ± 0.6 weeks (range: 6-10 weeks). There were no significant differences between women of both groups regarding the age, BMI and gestational age (table 1).

The mean levels of fasting blood glucose and fasting serum insulin were comparable in both groups. The mean values of 1-hour, 2-hour and 3-hour postprandial levels of blood glucose and serum insulin were, however, significantly higher in women of group A when compared to group B (table 2).

There were no significant differences between women of both groups regarding HOMA-IR and HOMA-B. The mean values of AUCG and AUCI were, however, significantly higher in women of group A. The AUCI/AUCG ratio was slightly higher in women of group A; this latter difference was not statistically significant.

ROC curves for estimating the association between unexplained recurrent miscarriage and measured markers of IR showed that AUCG and AUCI were the only markers significantly associated with unexplained recurrent miscarriage (table 3, figure 1). The difference between area under the curves for both AUCI and AUCG, and other markers of IR was statistically significant. The difference between the two markers (AUCI and AUCG) themselves was, however, not significant (table 4).

**DISCUSSION**

The current study showed significantly higher postprandial blood levels of glucose and insulin, as well as, significantly higher AUCG and AUCI among women with recurrent miscarriage when compared to their age- and BMI-matched controls. The fasting levels of blood glucose and insulin, along with HOMA-IR and HOMA-B were, however, comparable in both groups of women. This can be explained

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**Table 1: Difference between Groups regarding Demographic Data.**

<table>
<thead>
<tr>
<th></th>
<th>Group A [RPL Group] (n = 40)</th>
<th>Group B [Control Group] (n = 40)</th>
<th>MD (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.5 ± 4.3</td>
<td>30.2 ± 4.3</td>
<td>0.3 (-1.61 to 2.21)</td>
<td>0.756</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.9 ± 4.2</td>
<td>25.7 ± 4.3</td>
<td>-0.8 (-2.69 to 1.09)</td>
<td>0.403</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td>7.2 ± 0.8</td>
<td>7.5 ± 0.6</td>
<td>-0.3 (-0.62 to 0.02)</td>
<td>0.615</td>
</tr>
</tbody>
</table>

BMI body mass index
Data presented as mean ± SD
1 Analysis using independent student’s t-test

**Table 2: Difference between Groups regarding Blood Glucose, Serum Insulin and Markers of Insulin Resistance.**

<table>
<thead>
<tr>
<th></th>
<th>Group A [RPL Group] (n = 40)</th>
<th>Group B [Control Group] (n = 40)</th>
<th>MD (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Glucose (mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>4.7 ± 0.3</td>
<td>4.7 ± 0.2</td>
<td>0.0 (-0.11 to 0.11)</td>
<td>0.999</td>
</tr>
<tr>
<td>1-hour postprandial</td>
<td>9.0 ± 1.3</td>
<td>7.6 ± 1.0</td>
<td>1.4 (0.88 to 1.92)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2-hour postprandial</td>
<td>7.5 ± 1.3</td>
<td>6.0 ± 0.8</td>
<td>1.5 (1.02 to 1.98)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3-hour postprandial</td>
<td>5.8 ± 1.1</td>
<td>4.3 ± 0.8</td>
<td>1.5 (1.07 to 1.93)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fasting</td>
<td>6.9 ± 1.8</td>
<td>6.4 ± 2.4</td>
<td>0.5 (-0.44 to 1.44)</td>
<td>0.295</td>
</tr>
<tr>
<td>1-hour postprandial</td>
<td>89.4 ± 15.9</td>
<td>79.5 ± 14.9</td>
<td>9.9 (3.04 to 16.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2-hour postprandial</td>
<td>77.3 ± 14</td>
<td>58.3 ± 13.5</td>
<td>19 (12.9 to 25.12)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3-hour postprandial</td>
<td>56.9 ± 14.2</td>
<td>31.8 ± 12</td>
<td>25.1 (19.2 to 30.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.41 ± 0.41</td>
<td>1.33 ± 0.50</td>
<td>0.08 (-0.1 to 0.28)</td>
<td>0.436</td>
</tr>
<tr>
<td>HOMA-B</td>
<td>117.46 ± 43.18</td>
<td>108.65 ± 48.22</td>
<td>8.81 (-11.6 to 29.2)</td>
<td>0.392</td>
</tr>
<tr>
<td>AUCG (mmol<em>L⁻¹</em>h)</td>
<td>22.4 ± 3.1</td>
<td>18.3 ± 1.8</td>
<td>4.1 (2.97 to 5.22)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AUCI (mIU/L*h)</td>
<td>206.5 ± 48.6</td>
<td>153.5 ± 32.5</td>
<td>53 (34.6 to 71.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AUCI/AUCG</td>
<td>9.37 ± 2.52</td>
<td>8.43 ± 1.94</td>
<td>0.94 (-0.06 to 1.94)</td>
<td>0.065</td>
</tr>
</tbody>
</table>

AUCG area under the glucose-time curve
AUCI area under the insulin-time curve
HOMA-B
HOMA-IR homeostasis model assessment of insulin resistance index
Data presented as mean ± SD
1 Analysis using independent student’s t-test

**Table 3: ROC Curves for Association between Markers of Insulin Resistance and Recurrent Miscarriage.**

<table>
<thead>
<tr>
<th></th>
<th>AUC (95% CI)</th>
<th>P</th>
<th>Best Cutoff Value</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMA-IR</td>
<td>0.574</td>
<td>0.258</td>
<td>≥ 1.17</td>
<td>77.5% (61.5% to 89.2)</td>
<td>47.5% (31.5 to 63.9)</td>
</tr>
<tr>
<td>HOMA-B</td>
<td>0.563</td>
<td>0.335</td>
<td>≥ 0.22</td>
<td>77.5% (61.5% to 89.2)</td>
<td>40% (24.9 to 56.7)</td>
</tr>
<tr>
<td>AUCG</td>
<td>0.876</td>
<td>&lt; 0.001</td>
<td>≥ 21.48</td>
<td>65% (48.3 to 79.4)</td>
<td>97.5% (86.8 to 99.9)</td>
</tr>
<tr>
<td>AUCI</td>
<td>0.824</td>
<td>&lt; 0.001</td>
<td>≥ 201.25</td>
<td>62.5% (45.8 to 77.3)</td>
<td>97.5% (86.8 to 99.9)</td>
</tr>
<tr>
<td>AUCI/AUCG</td>
<td>0.605</td>
<td>0.100</td>
<td>≥ 0.36</td>
<td>50% (33.8 to 66.2)</td>
<td>72.5% (56.1 to 85.4)</td>
</tr>
</tbody>
</table>

AUCG area under the glucose-time curve
AUCI area under the insulin-time curve
HOMA-B
HOMA-IR homeostasis model assessment of insulin resistance index
AUC (95% CI) area under the ROC curve and its 95% confidence interval
by the observation that IR of both the liver and the peripheral tissues (e.g. muscle and fat) tend to exhibit a ‘separation’ phenomenon. In the liver, the IR phenomenon is mainly manifested as elevated fasting blood glucose, while in peripheral tissues IR manifests as elevated post-prandial blood glucose after glucose loading. HOMA-IR estimates an individual’s overall insulin sensitivity via the insulin fasting blood glucose, while in peripheral tissues IR manifests as increased risk for miscarriage [20]. Hyperinsulinemia may increase the level of plasminogen activator inhibitor-1 and induce villous thrombosis, thereby reducing the blood supply to the placenta and leading to trophoblastic hypoplasia, resulting in miscarriage [21].

REFERENCES