Maternal and Fetal Glucose Metabolism in Fetal Macrosomia of Diabetic and Non-Diabetic Pregnancies

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Abstract

Macrosomia (birth weight >4,000g) is associated with a variety of maternal risk factors. Abnormality of carbohydrate metabolism during pregnancy, which may not be detectable by glucose tolerance test (GTT) has been suggested as one of the main factors.

Method: We measured blood glucose, glycate hemoglobin (HbA1C), insulin, fructosamine and C-peptide immediately after delivery in 3 groups of mothers. (1) 23 known diabetic and gestational diabetic mothers, (2) 49 non-diabetic mothers. These two groups delivered full-term macrosomic infants. (3) 46 non-diabetic mothers who delivered full-term appropriate for gestational age infants as control.

Results: Mothers of macrosomic infants, compared to mothers of appropriate for gestational age infants, were significantly older, with a higher gravidity and parity. When all the mean values were adjusted for maternal age, parity and gravidity, the HbA1C, fructosamine and glucose were lowest in mothers of appropriate for gestational age infants and highest in diabetic mothers of macrosomic infants. Hypoglycaemia was more common in both groups of macrosomic infants and the cord blood fructosamine and insulin were not different.

Conclusion: Although the trend of maternal blood samples in our study was suggestive of some abnormal carbohydrate metabolism in mothers who delivered macrosomic infants compared to mothers of appropriate for gestational age infants, these findings have not been confirmed in their babies. The possible role of abnormal glucose metabolism as a risk factor for fetal macrosomia in non-diabetic mothers should be further studied.

Key words: Carbohydrate metabolism, fetal macrosomia, infant of diabetic mother

Introduction

Macrosomia is defined as birth weight >4,000g in full term infants and is associated with a wide variety of maternal risk factors, such as advanced maternal age, high parity, obesity, race, prolonged gestation and abnormality of carbohydrate metabolism during pregnancy. Recent studies indicated a rate of macrosomia varying between 8% in the general population to 43% in infants born to mothers with insulin dependent diabetes. Peterson's hypothesis states that fetal macrosomia in infants of diabetic mothers (IDM) is related to chronic fetal hyperinsulinism. Others have suggested that even women with minor abnormalities of carbohydrate metabolism during pregnancy with normal glucose tolerance test (GTT) are at risk for delivering a macrosomic infant. The question that remains is, "do the non-diabetic mothers, who are delivering macrosomic infants, have abnormal carbohydrate metabolism during the last trimester of pregnancy?" To address this question, we measured blood glucose, glycated hemoglobin (HbA1C), insulin, fructosamine, and C-peptide in 3 groups of mothers and insulin, fructosamine and glucose in their babies.

Group 1: Known diabetic and gestational diabetic mothers who delivered full term macrosomic infants.
Group 2: Non-diabetic mothers who delivered full term macrosomic infants.
Group 3: Non-diabetic mothers who delivered full term appropriate for gestational age (AGA) infants.

Patients and Method

All term singleton macrosomic babies born to a known diabetic, gestational diabetic and non-diabetic mothers in Maktar Hospital, Abu Dhabi, United Arab Emirates during 9 months period were enrolled in the study if they were in a healthy stable condition at birth.

For each macrosomic infant, the next singleton AGA infant was enrolled as a control subject. Infants and/or mothers were excluded if the infant had an Apgar score of <5 at 1 minute, needed ventilatory assistance or if they had obvious congenital anomalies. As there was no diabetic screening program, mothers of AGA infants were excluded if they had a fasting blood sugar level of ≥100mg/dl (5.5mmol/L) any time during their pregnancy or if they refused to co-operate.

Informed consent was obtained from all mothers before enrolment. At delivery, 5ml of EDTA, 5 ml of heparinized and 5ml of clotted blood were obtained from the mother and 5 ml of EDTA and 10ml of clotted blood.
from mixed arteriovenous blood was obtained from the double clamped umbilical cord.

During the study period a total of 1678 babies were delivered. 890 (53%) of these were male; 126 (7.5%) were macrosomic, and of these 87 (69%) were males. 54 macrosomic infants were excluded. 50 macrosomic infants of non-diabetic mothers and 4 macrosomic infants of diabetic mothers mainly because their mothers refused to be in the study.

Age gravidity, parity, number of cesarean sections and number of aboritions of all mothers enrolled in the study were compared. The gestational age, weight, and height of all infants were also compared. All macrosomic infants were admitted to the Newborn Intensive Care Unit and serial blood sugar levels were analyzed every 30 minutes for the first 6 hours.

Neonatal hypoglycemia was defined as blood glucose concentration of less than 40 mg/dl (2.27 mmol/L) in the first 24 hours of life, measured by refractolux and confirmed in the laboratory.

**Laboratory Data**

1. **Plasma glucose**

   Plasma glucose was measured using the Beckman ASTRA8 automated analyzer (Beckman, CA, USA). The method is based on the enzymatic oxidation determination of glucose in plasma samples. (Reference range for glucose in this laboratory is 70-110 mg/dl (3.8-6.1 mmol/L))

   **Precision study:**
   - Within-batch: N: 22 Mean: 121 CV: 1.11
   - Between-batch: N: 22 Mean: 126 CV: 0.91

2. **Haemoglobin A1c (HbA1c)**

   Glycated haemoglobin (HbA1c) was measured on the Hitachi 704 automated analyzer (Boehringer Mannheim, Germany). This method employs monoclonal antibody to detect total HbA1c on red blood cell haemolysates. The concentration of antigen-antibody complex is then measured by a peroxidase reaction. (Reference range for HbA1c is 3.4-6.4%).

   **Precision study:**
   - Within-batch: N: 21 Mean: 4.89 CV: 1.98
   - Between-batch: N: 46 Mean: 9.80 CV: 4.45

3. **Plasma Fructosamine (glucated protein)**

   This was performed on Hitachi 704 automated analyzer (Boehringer Mannheim, Germany). This method is based on the kinetic reduction of glycated protein with the dye (nitroblue tetrazolium) on plasma samples. (Reference range for fructosamine is 205-285 mmol/L.)

   **Precision study:**
   - Within-batch: N: 21 Mean: 434 CV: 0.40
   - Between-batch: N: 18 Mean: 460 CV: 2.03

4. **Serum Insulin**

   The Serum Insulin was measured by a competitive radioimmunoassay method (Diagnostic Products Corporation, DPC USA), using a double antibody manual procedure. The final results were read on Gamma counter by Radioimmunoassay on patients sera. (Reference range for insulin is 3-20 mIU/ml).

   **Precision study:**
   - Within-batch: N: 22 Mean: 16.2 CV: 7.8
   - Between-batch: N: 21 Mean: 49 CV: 7.33

5. **Serum C-peptide**

   This was performed by a competitive radioimmunoassay method (DPC USA), using a double antibody manual procedure. Final results were read on Gamma counter by Radioimmunoassay (reference range for C-peptide is 0.1-3 ng/ml).

**Data Analysis**

The Stata program package (Stata Corp. Stata Statistical Software Reference Manual: Release 5.0 College Station, Texas: Stata Corporation, 1997) was used for the statistical analysis of the data. For descriptive purposes we calculated unadjusted means, medians, and percentages. Using multiple linear regression models, we also calculated means adjusted for maternal age, parity, and gravidity. We logarithmically transformed all non-normally distributed continuous variables before computing descriptive statistics and applying statistical significance tests. For two-groups comparison we used the two-sample t-test for unadjusted means, multiple linear regression analysis for adjusted means, the Mann-Whitney test for medians, and the chi-square test for percentages. Whenever applicable, the P values calculated were two-sided. A P value was considered significant if it was <0.05.

**Results**

The maternal and fetal characteristics in the study population are shown in Table 1. There was significant difference in age, parity and gravidity in the 3 groups. The mother of macrosomic babies were older and had a higher gravidity and parity than mothers of AGA infants. There were five cesarean sections in both groups of mothers who delivered macrosomic infants and none in the mothers with normal size babies. The indications for cesarean section were failure to progress, abnormal presentation, previous cesarean and cephalopelvic disproportion. More than 70% of total macrosomic infants delivered were male and this proportion remained in the study population. The lengths were significantly shorter in AGA infants compared to macrosomic infants and the gestational age was significantly longer for macrosomic infants of non-diabetic mothers compared to AGA infants. 7 out of 23 (30%) macrosomic infants of
diabetic mothers and 2 of 49 (4%) macroscopic infants of non-diabetic mothers developed hypoglycemia. We did not monitor the blood sugar levels of AGA infants. When all mean values were adjusted for maternal age, parity and gravidity, (Table 2) HbA1C, fructosamine and glucose were highest in diabetic mothers of macroscopic infants and lowest in mothers of AGA infants but these differences were only significant between mothers of AGA infants and diabetic mothers. Due to the presence of high fetal hemoglobin concentration in cord blood, HbA1C could not be measured with confidence in the newborn. Hence, the results were not included. Fructosamine and insulin were not elevated in macroscopic infants of non-diabetic mothers compared to AGA infants.

Table 1: Maternal and fetal characteristics

<table>
<thead>
<tr>
<th></th>
<th>AGA non-diabetic (group 1)</th>
<th>Macroscopic non-diabetic (group 2)</th>
<th>Macroscopic diabetic (group 3)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mother</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>28.4 (26.5-30.2)</td>
<td>30.9 (29.4-32.4)</td>
<td>34.7 (32.5-36.9)</td>
<td>0.0367</td>
</tr>
<tr>
<td>Parity (No. median)</td>
<td>4 (3-6)</td>
<td>6 (5.5)</td>
<td>6 (5.7)</td>
<td>0.0096</td>
</tr>
<tr>
<td>C-section (No. section)</td>
<td>0</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>0.4529</td>
</tr>
<tr>
<td><strong>Newborn</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (g)</td>
<td>3328 (3294-3429)</td>
<td>4273 (4188-4316)</td>
<td>4492 (4273-4675)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>50.8 (30.3-51.3)</td>
<td>53.3 (52.8-53.9)</td>
<td>53.1 (52.1-54.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gestational age (week)</td>
<td>40.0 (39.6-40.4)</td>
<td>40.9 (40.4-41.3)</td>
<td>39.6 (38.9-40.0)</td>
<td>0.0188</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>74</td>
<td>70</td>
<td>70</td>
<td>0.0188</td>
</tr>
<tr>
<td>Hypoglycemia (No.)</td>
<td>0</td>
<td>2</td>
<td>7</td>
<td>-</td>
</tr>
</tbody>
</table>

* For some variables medians (95% confidence intervals), percentages, or actual numbers are shown as indicated.

Table 2: HbA1C, fructosamine and glucose level in diabetic mothers of macroscopic infants and mothers of appropriate for gestational age infants

<table>
<thead>
<tr>
<th></th>
<th>AGA (Group 1)</th>
<th>Macroscopic non-diabetic group 2</th>
<th>Macroscopic diabetic group 3</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mother</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>42</td>
<td>4.1 (3.8-4.3)</td>
<td>45</td>
<td>4.4 (4.2-4.7)</td>
</tr>
<tr>
<td>Fructosamine (umol/L)</td>
<td>42</td>
<td>165 (158-174)</td>
<td>44</td>
<td>169 (160-177)</td>
</tr>
<tr>
<td>C-peptide (mg/mL)</td>
<td>32</td>
<td>0.64 (0.43-0.96)</td>
<td>29</td>
<td>0.61 (0.41-0.91)</td>
</tr>
<tr>
<td>Insulin (mIU/mL)</td>
<td>40</td>
<td>29.9 (28.3-30.23)</td>
<td>41</td>
<td>27.1 (21.98-33.45)</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>45</td>
<td>107 (99-118)</td>
<td>49</td>
<td>122 (110-133)</td>
</tr>
<tr>
<td>Insulin-glucose ratio</td>
<td>40</td>
<td>0.28 (0.23-0.34)</td>
<td>41</td>
<td>0.23 (0.19-0.27)</td>
</tr>
<tr>
<td><strong>Newborn</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fructosamine</td>
<td>43</td>
<td>159 (150-169)</td>
<td>45</td>
<td>153 (145-161)</td>
</tr>
<tr>
<td>Insulin</td>
<td>40</td>
<td>117 (100-13.6)</td>
<td>39</td>
<td>112 (97.7-13.6)</td>
</tr>
<tr>
<td>Glucose</td>
<td>45</td>
<td>79 (72-87)</td>
<td>49</td>
<td>89 (73.88)</td>
</tr>
<tr>
<td>Insulin-glucose ratio</td>
<td>40</td>
<td>0.13 (0.12-0.17)</td>
<td>39</td>
<td>0.13 (0.13-0.18)</td>
</tr>
</tbody>
</table>

* All means are adjusted for maternal age, parity and gravidity.
** Derived through multivariate logistic regression analysis with adjustment for maternal age, parity, and gravidity.

Discussion

Pregnancies in mothers with diabetes mellitus are at increased risk for fetal macrosomia. As some macroscopic infants of non-diabetic mothers act as IDMs with neonatal hypoglycemia, the question remains, as to whether these mothers have minor abnormalities in glucose metabolism late in gestation, that is hard to detect. Although strict glycemic control in diabetic mothers does not always prevent fetal macrosomia, most studies have demonstrated a causal relationship between fetal hyperinsulinemia and macrosomia in infants of diabetic mothers (IDM's). At the time of birth, the umbilical cord insulin levels or C-peptide concentrations were elevated in macroscopic IDMs.
compared with infants of normal birth with both in diabetic and non-diabetic pregnancies. The elevated C-peptide levels in the cord blood of these infants in one study suggested that hyperinsulinemia may be one of the causes of macrosomia and neonatal hypoglycemia. Our study also indicates that in fact both diabetic and non-diabetic mothers of macrosomic infants have elevated HbA1C, fructosamine and glucose levels at the time of delivery, compared to non-diabetic mothers who have normal size babies. These values were highest in diabetic mothers and lowest in mothers of AGA infants, but the difference were only significant between mothers of AGA infants and diabetic mothers. These could be due to small sample size. Our findings may indicate some minor abnormality in glucose metabolism late in gestation in non-diabetic mothers who delivered macrosomic infants. Two of the macrosomic infants of non-diabetic, and 7 macrosomic infants of diabetic developed hypoglycemia. We were unable to measure the cord C-peptide levels in these infants and when the mean cord blood insulin and fructosamine levels were adjusted for maternal age, parity and gravidity, they were only Elevated in macrosomic infants of diabetic pregnancies (Table 2).

Although the trend of carbohydrate metabolism in non-diabetic mothers of macrosomic infants was in favor of minor abnormality these findings were not consistent in their babies mainly because:

1. The C-peptide and insulin were not measured in all infants, it is possible that and C-peptide level were elevated on those infants whom we were not able to measure.
2. The number of infants in our study were too few to draw any firm conclusions.
3. It was not possible to measure HbA1C in cord blood. A further study with larger numbers of patients is needed to answer these questions.

References


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