ABNORMAL GLUCOSE CHALLENGE TEST AND MILD GESTATIONAL DIABETES
ABNORMALNI TEST OPTEREĆENJA GLUKOZOM I BLAGI GESTACIJSKI DIJABETES

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Summary. Objective. The status of carbohydrate metabolism of pregnant women with positive glucose challenge test (GCT), but normal oral glucose tolerance test (OGTT) and their neonates are not defined clearly. Study Design. Pregnant women with normal GCT (n: 120), with abnormal glucose challenge test (AGCT) but normal OGTT (n: 67) and with gestational diabetes (GDM, n: 67) were included into the study. Insulin sensitivity was evaluated by fasting insulin level, homeostasis model assessment of insulin resistance index (HOME-IR); quantitative insulin check index (QUICKI) and ISOGTT. Serum insulin and glucose values during OGTT were documented. Perinatal outcome and delivery modalities were compared. Results. Both GDM (31.6±5.9 yrs) and AGCT groups (29.0±4.0 yrs) were older than controls (28.1±4.9 yrs). Body mass index (BMI) was the predominant factor affecting both AGCT and GDM groups (OR: 3.78 and 5.97 respectively). Despite there was no significance between insulin indices; serum glucose and insulin values were similarly different; macrosomic infant and caesarean section rates were higher than controls in both GDM and AGCT groups in favor of gestational diabetics (6.6% vs. 18.9%; p=0.0001 and 20% vs. 27.7% p=0.0001 respectively). Conclusion. Pregnant woman with abnormal glucose challenge test have impaired carbohydrate metabolism as in gestational diabetics with a lesser severe degree.

Izvorni članak

Ključne riječi: 50 g test probira glukozom, test opterećenja glukozom, blagi gestacijski dijabetes, gestacijski dijabetes, razina inzulina, trudnoća

Sažetak. Cilj istraživanja. Stanje metabolizma ugljikohidrata u trudnica s pozitivnim testom probira (glucose challenge test test — GCT), s normalnim testom opterećenja glukozom (OGTT) te njihove novorođenčadi, nije jasno definirano. Način istraživanja. U studiju su uključene trudnice s normalnim GCT-om (n: 120), s abnormalnim GCT-om ali normalnim OGTT-om (n: 67). Insulinska osjetljivost je vrednovana jutarnjiom vrijednostima insulina, modelom prosudbe homeostaze indeksom rezistencije na inzulin (HOME-IR), kvantitativnim indeksom provjere insulina (QUICKI) i ISOGTT-om. Vrijednosti serumskih glukoze i inzulina su analizirane. Usprkos je perinatalni ishod i način poroda. Rezultati. Trudnice s GDM (31.6±5.9 godina) i one s AGCT (29.0±4.0 godina) su bile starije od kontrolnih trudnica (28.1±4.9 godina). Indeks tjelesne težine (BMI) je bio presudni čimbenik u skupini s AGCT i GDM (OR: 3.78 odnosno 5.97). Utrudove trudnice su bile starije od kontrolnih. Zaključak. Trudnice s abnormalnim testom probira na glukozu (AGCT) imaju poremećaj metabolisma ugljikohidrata kao i trudnice s gestacijskim dijabetesom (GDM), ali se ne u među manjoj mjeri.

Introduction

It is well documented that the pregnancy is the insulin resistant state which can be tolerated by most of the women with normal glucose metabolism. However, some pregnant women experience carbohydrate intolerance with various degrees during their pregnancies. Although the certain mechanism of this pregnancy dependent carbohydrate intolerance has not been well known yet, excessive insulin resistance, which means reduced insulin response to carbohydrates or low insulin sensitivity and beta cell dysfunction are the common characteristics of the subjects. Diagnostic methods of this heterogeneous group of pregnant women are also under debate. Gestational diabetes mellitus (GDM) affects the 1 to 14 percent of the pregnancies according to the diagnostic test which was preformed by their physician. Today, one-step and two-step approaches are the common tests for the detection of gestational diabetes. The 50-g, 1-hour oral glucose challenge test (GCT), fol-
lowed by 100-g, 3-hour oral glucose tolerance test (OGTT) as the two-step approach, has gained widespread acceptance as a universal screening tool for GDM. At present, the status of carbohydrate metabolism of pregnant women with high glucose levels, which exceeds the critical threshold value of GCT, but normal 100-g, 3-hour OGTT have not been evaluated clearly yet. In few studies the group of pregnant women with positive GCT but normal OGTT has been described as either »borderline glucose intolerance« or »mild gestational hyperglycaemia«. Also some other studies focused on minor degrees of glucose intolerance which is not well defined with either »National Diabetes Data Group« or Carpenter and Coustan's criteria. Despite the increment of perinatal adverse outcomes were pointed out in these studies, a common treatment strategy to this group of pregnant women has not been defined yet. Current approach is to leave them untreated unless their blood glucose levels exceed defined cut-off values. The ideal threshold value for the GCT has also not been identified yet. Sensitivity of the test totally depends on the threshold value for the glucose load. A value of plasma glucose ≥140 mg/dL (7.8 mmol/L) was accepted as the threshold value for the positive glucose challenge test. Pregnant women with a positive challenge test underwent 3-hour 100-g OGTT within 7 days. According to Carpenter and Coustan criteria at least two plasma glucose levels exceeding the cut-off values following OGTT were essential for the diagnosis of GDM. Women with one abnormal value were excluded from the study.

The subjects were classified into 3 groups according to the OGTT and GCT results: group 1 (n: 120) pregnant women with normal GCT served as control group; group 2 (n: 67) women with abnormal glucose challenge test (AGCT), and group 3 (n: 67) gestational diabetics. Blood samples were collected at 8:00 am after 12-hours fast and at 60, 120 and 180 minutes following the 100-g oral glucose load. Plasma glucose levels were measured by hexokinase method using Olympus autoanalyser (Olympus Diagnostica GmbH-Irish Branch-Lismeecan) and plasma insulin levels were measured by chemiluminescent enzyme immunoassay method using Immulite 2000 autoanalyser (Diagnostic Products Corporation, Los Angeles, CA, USA).

The insulin sensitivity index from the OGTT was calculated according to 3 mathematical equations. First equation was HOMA-IR which was derived from the product of fasting plasma glucose (HOMA-IR = (FPG × FPI)/22.5 mmol/L) and fasting plasma insulin (FPI μU/L) divided by a constant. The second equation was QUICKI which was the inverse log sum of fasting insulin (I) and fasting glucose (G) (13). [QUICKI=1/log (I) + log(G)]. The third equation was ISOGTT in which insulin sensitivity is estimated by dividing a constant (10,000) by the square root of the product of fasting plasma glucose (FPG) times fasting plasma insulin (FPI) times the mean glucose (G) times mean insulin (I) [ISOGTT=10,000/√(FPG × FPI) × (G × I)].

Body mass index (BMI) was calculated as the ratio between weight (kg) and height (m²).

Subjects in Group 2 and 3 had diet or diet and insulin therapy as indicated. Daily caloric intake was arranged by a registered dietitian according to the pregestational BMI varying between 25–35 kcal per kg per day of actual weight; as 3 meal and 4 snacks. Insulin therapy with short acting insulin lispro as intensive insulin therapy (3 premeal doses lispro and 1 bedtime NPH insulin)
Glucose value was <35 mg/dl (1.7 mmol/L) in term of hypoglycemia was diagnosed if any of two consecutive blood glucose values were higher in both AGCT and GDM groups compared to controls in favor of GDM group. The baseline metabolic characteristics of the three groups were matched for parity and diabetic family history: the history of gestational diabetes in previous pregnancies was significantly higher in GDM group.

Demographic characteristics of the pregnant women were given on Table 1. The pregnancies in both AGCT and GDM groups were similarly older than control subjects. Both pregestational and in the course of GCT, BMIs were similarly higher than control subjects. There was no significant difference for fasting insulin, HOMA-IR, QUICKI and ISOGTT values between groups; but fasting glucose values were higher in both AGCT and GDM groups compared to controls in favor of GDM group (p = 0.0001).

**Statistical Analysis**

Statistical analyses were performed by SPSS® for Windows version 13.0 (Chicago, IL, USA). Data are expressed as means ± SD (standard deviation). Normality for continued variables in groups was determined by the Shapiro Wilk test. The ANOVA was used to compare parametric data and Least significant difference (LSD) test was used for comparison of variables. Pearson chi-squared test was used for the evaluation of categorical data; i.e. age, history, pregestational BMIs. Fisher’s exact test was used for comparison of fasting glucose values of the groups. A p value of less than 0.05 was considered significant. To quantify the prediction of developing both AGCT and GDM based on patients characteristics, logistic regressions were performed to select the significant factors when the characteristics were considered jointly.

**Results**

Intrapartum electronic fetal monitoring was done for all pregnant women during labor. Birth weight, 5-min-ute Apgar score, umbilical artery pH values and base deficit ≤ 12. Neonatal hypoglycemia was diagnosed if any of two consecutive blood glucose value was < 35 mg/dl (1.7 mmol/L) in term off-springs.

<table>
<thead>
<tr>
<th>Maternal characteristics</th>
<th>Control</th>
<th>AGCT</th>
<th>GDM</th>
<th>p value</th>
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<tr>
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<td>Family history of diabetes (%)</td>
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<td>34</td>
<td>23</td>
<td>NS</td>
</tr>
<tr>
<td>Gestational diabetes (%)</td>
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<td>12†</td>
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<tr>
<td>Prepregnancy BMI (kg/m²)</td>
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<td>Neonatal characteristics</td>
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<td>Gestational age at birth</td>
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<td>38 weeks 2 days</td>
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<td>Birth weight</td>
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<td>3330.0±524.5</td>
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**Table 1.** Maternal and neonatal characteristics of control, AGCT and GDM groups

**Table 1. Majínske i novorođene karakteristike kontrolne, AGCT i GDM skupine**

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GCT BMI: Body mass index during glucose challenge test
* AGCT vs. control p = 0.02; † GDM vs. control p = 0.001; ‡ GDM vs. AGCT and control p = 0.002; § AGCT vs. control p = 0.04; ¶ GDM vs. control p = 0.04; ¶¶ GDM vs. AGCT p = 0.001; §§ AGCT vs. control p = 0.001
After adjustment for maternal age (≥25 years), pre-pregnancy BMI, family history for diabetes and fasting glucose values, pre-pregnancy BMI was the common and most predictive factor for the development of both AGCT and GDM (p=0.0001 for both). The odds ratios (OR) and confidence intervals (CI) of the parameters are documented on Table 3.

Blood glucose and insulin values of OGTT were shown in Figure 1 and Figure 2. Glucose levels in whole OGTT intervals were significantly higher in both AGCT and control groups but only the 60 minute value was significantly higher in AGCT group compared to the controls. The insulin levels were similarly high in both GDM and AGCT groups compared to controls in all time intervals. Additionally, except for 60-minute value, insulin levels were significantly higher in GDM group compared to AGCT group.

The rate of macrosomia was significantly higher in both AGCT and GDM groups compared to controls in favor of GDM group (6.6% vs. 18.9%; p=0.0001). In addition, the rate of caesarean section due to macrosomia was significantly higher in both AGCT and GDM groups compared to controls; in favor of GDM group (20% vs. 27.7%; p=0.0001 respectively). One of the patients in GDM group experienced severe preeclampsia. The complications of neonatal hypoglycemia, low Apgar score (5 min <7), low umbilical artery pH (≤7.10) and base excess (≥12) and NICU stay were all seen in the unique neonate of these mothers. The neonates were comparable for gestational age at birth; and mean birth weight for all the three groups (Table 1). As reflecting the increment of insulin resistance with advanced age and increased body fat mass, maternal age was significantly and positively correlated with fasting glucose levels.
glucose, HOMA-IR, glucose and insulin values during the course of GCT. Pregestational BMI was also positively correlated with fasting glucose-insulin; and glucose-insulin concentrations during the course of GCT; and negatively correlated with QUICKI. The correlation coefficients and p values are documented on Table 4.

Discussion

To our knowledge, this is one of the first prospective clinical trials evaluating the characteristics of the carbohydrate metabolism in pregnant women with abnormal glucose challenge test, but normal 100-g 3-hour OGTT in Turkish population.

The close relationship between impaired carbohydrate metabolism and increased age and BMI are reported by several authors. In our study fasting glucose, glucose-insulin levels of GCT, and HOMA-IR values were found to be strongly and positively correlated with age. Additionally in both of our GDM and AGCT groups the patients were older than control subjects, as supporting the hypothesis that advanced age detoriaties the carbohydrate metabolism. Also, age over 25 years was one of the affecting factors for development of AGCT (odds ratio 3.12).

Although our study groups were consisted of women with BMI<30 kg/m² – to exclude the effect of obesity-the severity of carbohydrate intolerance was found to be increased correlated with BMI. Furthermore BMI was the common and significant predictive factor for development of both AGCT and GDM (odds ratios were 3.78 and 5.97 respectively). Normal pregnancy is accompanied by an ascending insulin resistance that increases as gestation proceeds. It can be concluded that, on the basis of this physiology, the increased BMI has an additive and worsening effect on the process, but not enough to predict the subsequent AGCT or GDM during the current pregnancy.

As supporting the previous data, parity was found to be insignificant as an predictive factor for both subsequent AGCT and GDM in our study groups.

Chronic insulin resistance in GDM has been documented by various studies. Also, a compensatory pancreatic insulin production leading to a state of hyperinsulinemia which is an essential event preceding the development of GDM during pregnancy has been well documented. In the present study fasting glucose values were significantly higher in both AGCT and GDM groups compared to controls, while the fasting insulin levels were similar in all 3 groups. Additionally GCT insulin and glucose values were similarly high in both AGCT and GDM groups compared to control group. Significant increments have been detected in insulin levels at the second hour of glucose load during OGTT both in AGCT and GDM groups. Putting together, our data supports the hypothesis of increased tissue resistance to insulin secretion together with reduced early insulin response in the pathogenesis of glucose intolerance in AGCT group similar but in lesser degree to GDM.

We have measured three indices to evaluate insulin resistance and insulin sensitivity in our study subjects. HOMA-IR model was the first index that we used to evaluate insulin resistance based on liver and pancreatic β-cell interactions related to plasma glucose and insulin levels. Although HOMA-IR has some limitations to reflect the peripheral insulin sensitivity, it was proven to be a good predictor of the total insulin sensitivity. We used QUICKI as the second index to measure insulin sensitivity, which is preferred in clinical trials, since single blood sample is enough for the mathematical calculation. We also calculated ISOGTT to assess and compare the peripheral insulin sensitivity. ISOGTT is considered a more informative index for prediction of peripheral insulin sensitivity, since it reflects the insulin-mediated glucose uptake after glucose load. However none of these indexes were statistically different between our study groups. As reflecting the increased insulin resistance, insulin levels were found to accelerate during OGTT but not in fasting state; this could be the possible result of insignificant indexes; HOMA-IR and QUICKI which root from fasting values. Despite showing no statistical significance ISOGTT values were found to decrease parallel to severity of carbohydrate intolerance.

According to our follow up protocol we treated our patients no matter with AGCT or GDM, until achieving the goals for defined glucose values: either with diet or if needed with insulin. However the macrosomic infant rates were significantly higher in both of the groups compared to controls with a higher rate in GDM group. The caesarian section rates due to macrosomia were similarly high in both AGCT and GDM groups. But the subjects could be preserved from other well known
complications. There was no difference for gestational age at birth and mean birth weight of the newborns. Tight diet and insulin therapy prevented the maternal and neonatal adverse outcomes except macrosomia in AGCT and GDM groups.

The limitation of this study is the lack of an untreated AGCT group i.e. of comparing their outcomes with normal pregnant women. But for avoiding both maternal and fetal complications, we could not consist such an untreated group ethically.

In conclusion, data obtained from this Turkish pregnant women based study, demonstrate that pregnant women with abnormal glucose challenge test have impaired carbohydrate metabolism as in gestational diabetics. Decreased insulin sensitivity and increased insulin resistance in AGCT group is similar with the gestational diabetics, with a less severity. So, it would be appreciable to these pregnancies to be followed up and treated as gestational diabetics. Comparable results with new studies will allow us to define and treat the pregnant women with abnormal glucose challenge test thoroughly.

References


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