Influence of Hypoglycemia During The 100-G Oral Glucose Tolerance Test on Obstetrics Outcomes

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OBJECTIVES: We aimed to investigate the impact of hypoglycemia during 100-g oral glucose tolerance test on perinatal outcomes.

STUDY DESIGN: Obstetrics records of 411 pregnant women who delivered singletons at our institution were reviewed. 31/411 (7.5 %) of patients who were diagnosed as Gestational Diabetes Mellitus were excluded from the study. The study group was consisted of pregnant women who experienced hypoglycemia defined as a plasma glucose level of 60 mg/dL or less during the 100-g oral glucose tolerance test. This group were compared with women who had normal glucose levels during 50-g oral glucose loading test (glucose challenge test) and who had normal values and had no hypoglycemia during 100-g OGTT.

RESULTS: We identified 62 hypoglycemic patients (15 %) on 100-g oral glucose tolerance test and 318 non-hypoglycemic patients (77.3 %) as control group. Gestational weight gain was statistically higher in hypoglycemic group. The mean birth weight was 3419±421.9 g in the study group and 3275±491.7 g in the control group (p=0.042). Rates of babies admitted to NICU were similar in both groups.

CONCLUSIONS: Women who experience hypoglycemia during the OGTT have a significantly higher incidence of gestational weight gain and higher neonatal birth weights as well. As a result if a pregnant has hypoglycemia during OGTT we should monitorize her and the fetus as well carefully.

Key Words: 100-g oral glucose tolerance, Hypoglycemia, Obstetrics outcomes

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Introduction

Clinical hypoglycemia rarely occurs in healthy human beings, but it is a fact of life for people with diabetes mellitus. It is feared by many patients not only because of the associated physical discomfort, but mainly because of the risk of cognitive function deterioration that may lead to loss of personal control and adequate conscious behavior, and eventually to coma. Despite recent advances in treatment of Diabetes mellitus, hypoglycemia remains the principal barrier to obtaining true glycemic control, and microvascular and macrovascular complications of diabetes associated with chronic hyperglycemia are to a certain extent the consequence of hypoglycemia.1

It is a wellknown phenomenon that a significant number of women experience hypoglycemia or occasional hypoglycemic reaction including tachycardia, faintness, nausea, and perspi-

Material and Method

In this retrospective study, between January 2002 and April 2006, all pregnant patients attending outpatient clinic of Department of Obstetrics and Gynecology of Fatih University Hospital were screened for gestational diabetes (GDM), with a 50 g oral glucose loading test (glucose challenge test [GCT] between 24 and 28 weeks’ gestation. If the screening plasma glucose value was ≥130 mg/dL, the patient underwent a stan-
dart, 3 hour oral glucose tolerance test (OGTT). The test was performed after 3 days of unrestricted diet with at least 150 g of carbohydrates daily and after an overnight fast of not less than 8 hours. Patients were classified as gestationally diabetic if two or more of the four plasma glucose concentrations equaled or exceeded the following values: fasting blood sugar 95 mg/dL; one-hour level 180 mg / dL; two hour level 155 mg /dL; and three hour level, 140 mg / dL [3]. 31/411 (7.5 %) of patients who were diagnosed as Gestational Diabetes Mellitus were excluded from the study.

The study group was consisted of pregnant women who experienced hypoglycemia defined as a plasma glucose level of 60 mg/dL or less during the 100-g oral glucose tolerance test on 3 hours (n=62). This group were compared with women who had normal glucose levels during 50-g oral glucose loading test (glucose challenge test) and who had normal values and had no hypoglycemia during 100-g OGTT on 3 hours (n=318).

The two groups were compared for the prevalence of family history of diabetes mellitus, pre-pregnancy body mass index (BMI), gestational weight gain, nullipara, obstetric complications such as premature delivery, macrosomia, polyhydramnios, hypertension, mode of delivery. We also compared the two groups for the infants’ birth weight, proportion of babies admitted to neonatal intensive care (NICU).

Data analysis was performed by using SPSS for Windows (version 11.5). Data were presented as mean±std.deviation. Comparison of continuous variables were made by using Student’s-t test or Mann-Whitney-U test, and categorical comparisons were evaluated by Chi-square or Fisher’s exact probability test. A p value of <0.05 was accepted as statistically significant.

### Results

The records of 411 pregnant patients who had been followed and gave birth in the Obstetrics and Gynecology Department of Fatih University Hospital were reviewed. 31 of 411 (7.5 %) patients were diagnosed as GDM and excluded from study. The data of 380 patients were suitable for evaluation. 133 patients were positive for 50-g glucose challenge test (GCT) and negative for OGTT (32,3 %) and 185 patients were negative for GCT (45 %).

We identified 62 hypoglycemic patients (15 %) on 100-g oral glucose tolerance test who had level ≤ 60 mg/dL of blood glucose on 3 hours and 318 non-hypoglycemic patients (77.3 %) as control group who had normal glucose levels during 50-g oral glucose loading test (glucose challenge test) and who had normal values and had no hypoglycemia during 100-g OGTT. Maternal data was showed in table 1.

### Table 1: Maternal Data

<table>
<thead>
<tr>
<th></th>
<th>Hypoglycemia group (n=62)</th>
<th>Non hypoglycemia group (n=318)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.4 ± 4.6</td>
<td>29.1 ± 6.4</td>
<td>0.313</td>
</tr>
<tr>
<td>Gravidity</td>
<td>2.14 ± 1.18</td>
<td>2.16 ± 1.37</td>
<td>0.620</td>
</tr>
<tr>
<td>Parity</td>
<td>0.98 ± 0.96</td>
<td>0.90 ± 1.1</td>
<td>0.262</td>
</tr>
<tr>
<td>Pre-pregnancy BMI (kg/m²)</td>
<td>25.4 ± 9.5</td>
<td>23.1 ± 3.4</td>
<td>0.586</td>
</tr>
<tr>
<td>Post-pregnancy BMI (kg/m²)</td>
<td>32.9 ± 9.9</td>
<td>28.5 ± 3.8</td>
<td>0.030*</td>
</tr>
<tr>
<td>Gestational weight gain</td>
<td>15.8 ± 3.8</td>
<td>14.6 ± 4.3</td>
<td>0.019*</td>
</tr>
<tr>
<td>Family history of DM (%)</td>
<td>15 (24.2 %)</td>
<td>76 (23.9 %)</td>
<td>0.960</td>
</tr>
<tr>
<td>Nullipara (%)</td>
<td>20 (%32.3)</td>
<td>127 (%40.1)</td>
<td>0.249</td>
</tr>
</tbody>
</table>

Data are presented as mean ± Standard deviation
* p < 0.05

In hypoglycemic group the mean values of fasting, 1 hour, 2 hours and 3 hours on OGTT were 76,5 ± 6,6; 141,7 ± 34,0 ; 106,3 ± 23,4; 53,5 ± 6,7 respectively. Gestational weight gain, post-pregnancy BMI were significantly higher in hypoglycemic group. The mean birth weight was 3419±421,9 g in the study group and 3275±491,7 g in the control group (p=0.042). Rates of babies admitted to NICU were similar in both groups. Pregnancy and neonatal outcomes were showed in table 2.

### Table 2: Pregnancy and Neonatal Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Hypoglycemia group (n=62)</th>
<th>Non hypoglycemia group (n=318)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite adverse perinatal outcome</td>
<td>15 (24.2%)</td>
<td>84 (%26.4)</td>
<td>0.715</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>0 (0%)</td>
<td>7 (2.2%)</td>
<td>0.605</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (12.9%)</td>
<td>24 (7.5%)</td>
<td>0.165</td>
</tr>
<tr>
<td>Polyhydramnios</td>
<td>9 (14.5%)</td>
<td>25 (7.9%)</td>
<td>0.093</td>
</tr>
<tr>
<td>Macroismos (&gt;4000 g)</td>
<td>7 (11.3 %)</td>
<td>28 (8.8 %)</td>
<td>0.287</td>
</tr>
<tr>
<td>Delivery &lt; 37 weeks</td>
<td>8 (12.9%)</td>
<td>31 (9.7%)</td>
<td>0.454</td>
</tr>
<tr>
<td>Birth trauma</td>
<td>2 (3.2%)</td>
<td>8 (2.5%)</td>
<td>0.670</td>
</tr>
<tr>
<td>Frequency of admission to NICU</td>
<td>2 (3.2%)</td>
<td>15 (4.7%)</td>
<td>0.455</td>
</tr>
<tr>
<td>Induction of labor</td>
<td>37 (59.7%)</td>
<td>166 (52.2%)</td>
<td>0.280</td>
</tr>
<tr>
<td>Cesareae delivery</td>
<td>38.4±1.24</td>
<td>38.3±1.83</td>
<td>0.689</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>3419 ± 421.91</td>
<td>3275 ± 491.77</td>
<td>0.042*</td>
</tr>
</tbody>
</table>

* p <0.05

### Discussion

Hypoglycemia is a clinical and biological entity defined as an abnormal decrease in plasma glucose concentrations and the clinical consequences thereof. Hypoglycemia-related symptoms are multiple, non specific and with many guises,
and thus cannot be used to define hypoglycemia. Their only common feature is that they can be reverted by glucose administration. However, it is also difficult to set a plasma glucose level to define hypoglycemia.\(^5\,^6\)

In various reports 50 mg/dL was considered to be a suitable glucose concentration for the diagnosis of hypoglycemia.\(^6\,^7\) Because clinical symptoms of hypoglycemia such as tachycardia, sweating, tremor, dizziness, headache and faintness usually manifest at a plasma glucose level 50 mg/dL. On the other hand it is well known that there is no clear cutoff blood glucose level for experiencing hypoglycemic symptoms; some patients may exhibit a hypoglycemic reaction at a ‘normal’ glucose range whereas others may be unaware of hypoglycemia even at very low blood glucose concentrations.\(^2\,^8\) In the present study Cutoff level was chose as 60 mg/dL because biochemical reactions to hypoglycemia manifest at this glucose level. The first event to be elicited by a progressive decrement in plasma glucose levels is an inhibition of insulin secretion, for a mean arterial venous glucose of 4.5 mmol/l (0.80 g/l). This inhibition has a major role in the defence against hypoglycemia, as recovery is negatively correlated with peripheral and portal insulin levels.\(^9\) The second event is counterregulatory hormone release, which occurs at a glucose threshold of 3.3 to 3.6 mmol/l (0.60 to 0.65 g/l). Glucagon is the first line of defence, mainly for correcting brief hypoglycaemia.\(^10\)

Glucagon stimulates a cascade of phosphorylation, inducing an increase in hepatic glucose production by stimulation of glycogenolysis and neoglucogenesis. Epinephrine becomes of primary importance when glucagon secretion is deficient, and is important in correcting prolonged hypoglycemia, by direct and indirect mechanisms. Epinephrine increases hepatic glucose output by stimulation of glycogenolysis and neoglucogenesis, directly and through actions on insulin and glucagon secretion. Epinephrine increases substrates forneoglucogenesiss (lactates, alanine).\(^11\)

In the normal nonpregnant individual declining blood glucose levels trigger an organized sequence of responses first and foremost insulin secretion is suppressed when blood glucose levels fall within the physiological range. The resultant reduction in peripheral glucose uptake and increase in hepatic glucose production usually terminates the decline in blood glucose and prevents true hypoglycemia. In addition, the fall in intra-islet insulin appears to have a signaling role for the glucagon response to hypoglycemia by alleviating its suppressive effect on pancreatic \(\beta\)-cells, thus permitting glucagon release. It promotes hepatic glucose production by stimulation of glycogenolysis and gluconeogenesis.\(^3\)

Hypoglycemic episodes are more common during pregnancy because of the physiological changes that take place: basal insulin levels are increased, while glucagon release is suppressed by estrogen, progesterone, human placental lactogen, and probably other mediators.\(^12\) The result is that pregnant women may experience postprandial hypoglycemia more often. Some pregnant women may be more prone to this condition and may react with an exaggerated response.

The occurrence of hypoglycemia and occasional hypoglycemic reaction during the 3-hour oral GTT is a well-known phenomenon. However, its incidence and possible effect on perinatal outcome have not been directly addressed. Searching the literature we find only one literature about this question.\(^2\) In that study, the incidence of hypoglycemia during the 100-g oral GTT was found 15%. No cases of fasting hypoglycemia were observed (after fasting of at least 8 hours). All hypoglycemic events were reported to occur 3 hours after the glucose ingestion. In the present study we have found an somewhat higher incidence of 15% of hypoglycemia during the 100-g oral GTT however if we look at the curves presented in the original report by O'Sullivan and Mahan\(^13\) it can be seen that approximately 25% of the patients showed a glucose values below 50 mg/dL in the third hour during 100-g oral GTT.

What is the clinical implication of maternal reactive hypoglycemic events during OGTT for fetal well-being? There is a scarcity of data concerning this question. In some studies there had been suggested that relative maternal hypoglycemia was associated with growth restriction.\(^14\) Nevertheless in these studies the definition of maternal hypoglycemia was drawn from the OGTT rather than from the glycemic profile in pregnancy. In our study there was no baby below 2500 gr in hypoglycemia group. In the control group there were 13 (4.08 %) pregnant who delivered < 2500 gr babies.

Weissman et al\(^12\) showed the newborns' birth weights in women with hypoglycemia were significantly lower than in the control group although the gestational ages at deliveries were similar. They speculated that difference was not due to a higher rate of SGA, but to a lower rate of LGA infants. They have also reported a lower rate of cesarean delivery with indication of macrosomia in patient who showed reactive hypoglycemia In the present study, contrary to former study birth weight in women with hypoglycemia were found higher than control group but rate of cesarean delivery with indication of macrosomia was found similar. This can be explained by the fact that study was retrospective and did not consider some variables that could potentially affect fetal growth such as obesity, weight gain during pregnancy. In the present study gestational weight gain, post-pregnancy BMI were found significantly higher in hypoglycemic group so higher birthweight in women with reactive hypoglycemia can be associated with excess weight gain in pregnancy on the other hand perhaps it can be speculated that reactive hypoglycemia may be carbohydrate intolerance of different type with onset or first recog-
There is limited information about the impact of low blood glucose levels or hypoglycemia during the OGTT on obstetric outcomes. Although Weissman et al. claimed that hypoglycemia during OGTT is not unusual, is transitory, and carries a favorable prognosis in terms of obstetric outcome including lower incidence of GDM, lower birth weights, and a lower rate of cesarean deliveries for macrosomia, we do not think the event so simply. If such a phenomenon may occur more frequently in women who experience during the OGTT and sometimes these hypoglycemic attack become deep and more than fetal brain sparing mechanism it is easily cause fetal mortality or morbidity.

In a conclusion, pregnant who experienced hypoglycemia during OGTT should be monitored during and after pregnancy. The impact of maternal hypoglycemia during OGTT on perinatal outcomes requires prospective and larger further studies.

References

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