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Does reactive hypoglycemia during the 100 g oral glucose tolerance test adversely affect perinatal outcomes?

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ABSTRACT

Objectives: To determine whether pregnant women who have reactive hypoglycemia during the 100 g oral glucose tolerance test (OGTT) are at an increased risk of poor pregnancy outcomes.

Material and methods: We retrospectively analyzed perinatal data from 413 women who underwent a 3 h OGTT at 24–28 weeks of gestation and gave birth in our clinics between January 2012 and December 2014.

Results: According to OGTT results, the majority of the subjects were normoglycemic (n = 316, 76.5%), while 49 (11.9%) were diagnosed with gestational diabetes, and 33 (8.0%) had single high glucose values. Reactive hypoglycemia was detected in only 15 patients (3.6%). The mean age of the women in the reactive hypoglycemia group was significantly lower than that of the women in the gestational diabetes and single high glucose value groups (26.4 ± 4.4 years, 31.4 ± 5.4 years, and 31.8 ± 4.3 years, respectively; $p < 0.05$). The newborns of the women in the reactive hypoglycemia group had higher rates of APGAR scores < 7, increased admission to the neonatal intensive care unit (NICU), and lower birth weights compared with the other groups ($p < 0.001$, $p < 0.001$, and $p = 0.009$, respectively).

Conclusion: Reactive hypoglycemia during the 3 h 100 g OGTT is significantly associated with low APGAR scores, low birth weights, and prenatal admission to the NICU. Therefore, pregnant women who develop hypoglycemia during the 100 g OGTT performed at 24–28 weeks of gestation should receive attentive follow-up care to decrease the possibility of adverse perinatal outcomes.

Key words: gestational diabetes, oral glucose tolerance test, perinatal outcome, pregnancy, reactive hypoglycemia

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INTRODUCTION

An evaluation for gestational diabetes mellitus (GDM) is widely performed between 24–28 weeks of gestation in women without pre-gestational diabetes. Two methods are commonly used: a one-step approach, the 75 g oral glucose tolerance test (OGTT); and a two-step approach, the 50-g glucose challenge test (GCT) followed by an 100 g OGTT if the threshold is exceeded. An estimated 95% of obstetric patients in the United States undergo sequential model universal screening for GDM using the two-step approach [1, 2].

Some women who have abnormal test results (≥ 140 mg/dL) on the 50 g GCT experience hypoglycemia during the 3 h 100 g OGTT, with symptoms including dizziness, nausea, tachycardia, and perspiration, a condition known as reactive hypoglycemia [3, 4]. Concomitant blood samples may reveal very low blood glucose levels in these women. There is no precise cut-off blood glucose level that can predict hypoglycemic symptoms. Some patients with normal glucose values may experience hypoglycemic symptoms, while others may not have any symptomatic indications of hypoglycemia, even at very low blood glucose concentrations [5, 6]. However, various reports suggest a blood glucose level of 45–50 mg/dL (2.5–2.78 mmol/L) is indicative of reactive hypoglycemia [7–9].

Hypoglycemic symptoms or low blood glucose levels during the test may be sources of anxiety for both patients

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and healthcare providers. Despite the known associations between elevated maternal glucose levels and adverse maternal and neonatal outcomes, the potential relationship between low maternal glucose levels during the 100 g OGTT and adverse perinatal and neonatal outcomes remains unknown.

The aim of the present study was to determine whether pregnant women who have reactive hypoglycemia during the 100 g OGTT are at an increased risk for poor pregnancy outcomes, such as preterm delivery, cesarean delivery, preeclampsia, small-for-gestational age (SGA) fetuses, increased birth weight, or low Apgar scores.

MATERIAL AND METHODS

Study design and population

We conducted a retrospective cohort study by reviewing the perinatal data of all women who underwent a 3 h OGTT and gave birth at the Obstetric and Clinics Department of Gaziosmanpasa University and Tokat State Hospital between January 2012 and December 2014. Women with singleton pregnancies who had abnormal 1 h 50 g GCT results (≥ 140 mg/dL) at 24–28 weeks of gestation and thus underwent the 3 h 100 g oral GTT were included in the study [10]. The exclusion criteria were twin pregnancies, documented type I or II diabetes mellitus, multiple GCTs in the same pregnancy (only one entry per pregnancy was allowed), and incomplete medical records. A total of 421 women met the inclusion criteria. Eight women (1.9%) were excluded due to incomplete medical records; thus, 413 women were included in the study.

The study was approved by the institutional ethics committee (Approval number: 14-KAEK-237, Registered date: 23.12.2014) and conducted in accordance with the latest version of the Declaration of Helsinki. The informed consent requirement was waived due to the retrospective design of the study.

Study groups

Based on the OGTT results, patients were classified as follows: patients with reactive hypoglycemia (Group 1: plasma glucose ≤ 45 mg/dL), patients with normoglycemia (Group 2: normal plasma glucose values), patients with only one abnormal glucose value (Group 3), and patients with GDM (Group 4: two or more high plasma glucose values).

In our clinic, we screen non-diabetic pregnancies for GDM at 24–28 weeks of pregnancy using a two-step standard protocol during a routine prenatal visit. This protocol is a 1 h 50 g GCT, followed by a 3 h 100 g diagnostic OGTT if the GCT plasma glucose result is ≥140 mg/dL. GDM is diagnosed when two or more OGTT plasma glucose levels meet the criteria for a positive test as recommended by the National Diabetes Data Group (NDDG), which include plasma glucose thresholds of 95 mg/dL for fasting, 180 mg/dL for 1 h, 155 mg/dL for 2h, and 140 mg/dL for 3 h OGTTs [11]. Reactive hypoglycemia is defined as a plasma glucose level of < 45 mg/dL (2.5 mmol/L) according to the 1986 Consensus Statement of the Third International Symposium on Hypoglycemia [7]. Another reason for choosing this cut-off plasma glucose level (45 mg/dL) for hypoglycemia was that it was detected in less than 10% of our study population during OGTTs.

Study procedures

The following data were recorded from patients' hospital files and compared among the study groups: demographics; results of fetal assessment tests, including fetal biometry; amniotic fluid index; gestational age at delivery; neonatal results, including APGAR scores; fetal birth weight; rates of admission to the neonatal intensive care unit (NICU); administration of phototherapy; and obstetrical results, including the mode of delivery and the presence of dystocia. Large-for-gestational-age (LGA) status was defined as a birth weight above the 90th percentile for age, and SGA was defined as a birth weight below the 10th percentile for age [12]. Macrosomia was defined as an estimated fetal weight of 4,000 g or more, regardless of gestational age [13]. All patients underwent ultrasound examinations before proceeding to the delivery ward. In accordance with the guidelines of the Ministry of Health of Turkey, we recommend elective cesarean delivery to women with GDM and estimated fetal weights of 4,000 g or more and to women without GDM and estimated fetal weights of 4,500 g or more.

Statistical analysis

Statistical analysis was performed using the PASW software package for Windows (Statistical Package for Social Sciences, Version 18.0, SPSS Inc., Chicago, Illinois, USA). The data collected were summarized using descriptive statistics (e.g., mean, standard deviation, range, frequency, and percentage). For a comparison of categorical variables between study groups, a chi-square test was used. For multiple comparisons of continuous variables, analysis of variance (ANOVA) and the Scheffé post-hoc test were used. The statistical level of significance was set at $p < 0.05$.

RESULTS

According to the 100 g OGTT results, the majority of the 413 pregnant women were normoglycemic (n = 316, 76.5%) and 33 (8.0%) had single high glucose values, while 49 (11.9%) were diagnosed with gestational diabetes (Tab. 1). Reactive hypoglycemia was detected in only 15 patients (3.6%).

Maternal and prenatal parameters

Regarding maternal and prenatal characteristics, only age and gestational week at delivery were significantly dif-

Table 1. Distribution of patients according to 100 g oral glucose tolerance test results

	100 g OGTT result	Number of patients (%)
Group 1	Reactive hypoglycemia *(glucose ≤45 mg/dL)*	15 (3.6%)
Group 2	Normoglycemia *(all plasma glucose values are normal)*	316 (76.5%)
Group 3	Single high glucose value *(only one abnormal glucose value)*	33 (8.0%)
Group 4	Gestational diabetes *(two or more high plasma glucose values)*	49 (11.9%)
Total		413 (100.0%)

OGTT — oral glucose tolerance test

ferent among the groups ($p < 0.001$ and $p = 0.029$, respectively; Tab. 2). The mean age of the women in the reactive hypoglycemia group was significantly lower than that of the women in the gestational diabetes and the single high glucose value groups (26.4 ± 4.4 years, 31.4 ± 5.4 years, and 31.8 ± 4.3 years, respectively; $p < 0.05$ for both, Tab. 2). Gestational week at delivery was significantly lower in the reactive hypoglycemia group than in the normoglycemia and gestational diabetes groups (37.2 ± 1.5 weeks, 38.5 ± 1.7 weeks, and 38.7 ± 1.7 weeks, respectively; $p < 0.05$ for both, Table II). However, other maternal parameters (gravida, parity, preterm delivery, preeclampsia, and cesarean section rate) were similar among the groups (Tab. 2).

Perinatal parameters

In terms of perinatal results, the newborns of the women in the reactive hypoglycemia group had significantly lower mean APGAR scores than those born to the women in the other groups (8.3 ± 1.3, $p = 0.006$; Tab. 3). Additionally, the newborns of the women in the reactive hypoglycemia group had higher rates of APGAR scores < 7, admission to NICU, and lower birth weights, compared with the other groups ($p < 0.001$, $p < 0.001$, and $p = 0.009$, respectively; Tab. 3). On the other hand, neonatal gender and SGA and LGA rates were similar among the groups (Tab. 3).

DISCUSSION

The OGTT is a widely accepted and frequently performed test used to diagnose gestational diabetes in pregnant women. In the present study, we evaluated the pregnancy outcomes of women who had reactive hypoglycemia during the 3 h 100 g OGTT. Although it is widely known that a significant number of women experience symptomatic hypoglycemia during OGTT, there are limited reports on the prevalence and perinatal significance of reactive hypoglycemia during the 100 g OGTT. Weissman et al., who defined hypoglycemia as ≤ 50 mg/dL, reported an incidence rate of 6.3% for reactive hypoglycemia during the test among 805 pregnant women over a 3-year period [3]. They found a lower incidence of gestational diabetes in women who experienced reactive hypoglycemia. In the present study, we detected reactive hypoglycemia in only 15 out of 413 women (3.6%) during the 3 h 100 g OGTT. All hypoglycemic events occurred 3 h after glucose ingestion, and there were

Table 2. Maternal and prenatal characteristics of the study groups

Maternal/prenatal parameters	Group 1 (reactive hypoglycemia) (n = 15)	Group 2 (normo-glycemia) (n = 316)	Group 3 (single high glucose value) (n = 33)	Group 4 (gestational diabetes) (n = 49)	p value
Age [years]	26.4 ± 4.4	28.2 ± 5.6	31.4 ± 5.4*	31.8 ± 4.3*	< 0.001
Gravida	2.4 ± 1.1	2.4 ± 1.3	2.7 ± 1.1	2.9 ± 1.5	0.117
Parity	0.6 ± 0.9	0.6 ± 0.9	0.9 ± 0.9	0.8 ± 1.1	0.333
Gestational week at delivery	37.2 ± 1.5	38.5 ± 1.7*	38.5 ± 1.3	38.7 ± 1.7*	0.029
Preterm delivery	3 (20.0%)	19 (6.0%)	3 (9.1%)	5 (10.2%)	0.162
Preeclampsia	0 (0%)	4 (1.4%)	1 (3.3%)	3 (7.0%)	0.113
Cesarean section	42 (28.6%)	90 (28.5%)	11 (33.3%)	17 (34.7%)	0.795

Data are given as mean ± SD or n (%)
*Significantly different from reactive hypoglycemia group (p < 0.05)

Table 3. Perinatal outcomes of the study groups

Perinatal parameters	Group 1 (reactive hypoglycemia) (n = 15)	Group 2 (normo-glycemia) (n = 316)	Group 3 (Single high glucose value) (n = 33)	Group 4 (Gestational diabetes) (n = 49)	p value
Apgar 5 min	8.3 ± 1.3	9.0 ± 0.8*	8.6 ± 1.6	8.8 ± 0.6	0.006
Apgar < 7 (5 min)	3 (20.0%)	6 (1.9%)*	0 (0%)*	1 (2.0%)*	< 0.001
Weight [g]	2852.0 ± 544.6	3282.4 ± 452.8*	3290.6 ± 510.5*	3443.7 ± 468.5*	< 0.001
Male	8 (53.3%)	155 (49.2%)	19 (57.6%)	23 (46.9%)	0.782
NICU admission	4 (26.7%)	29 (9.2%)*	6 (18.2%)	11 (22.4%)	0.009
SGA	3 (20.0%)	17 (5.4%)	3 (9.1%)	2 (4.1%)	0.100
LGA	0 (0%)	9 (2.8%)	1 (3.0%)	2 (4.1%)	0.339

DM — diabetes mellitus; NICU — neonatal intensive care unit; SGA —small-for-gestational age; LGA — large-for-gestational age
Data are given as mean ± SD or n (%)
*Significantly different from reactive hypoglycemia group ($p < 0.05$)

no cases of fasting hypoglycemia (after fasting for at least 8 h). In our population, the rate of gestational diabetes after a positive screening test was 11.9%, which is similar to the prevalence rate of 10.6–23.2% seen in the literature [14, 15].

The adverse effects of gestational diabetes on maternal and neonatal health are well-documented [16]. Women with even one abnormal 3 h 100 g OGTT value reportedly have an increased risk of poor neonatal outcomes [17]. Therefore, the presence of gestational diabetes is screened in the clinical practice of obstetrics, and confirmed most commonly via OGTT, when indicated [18]. However, some patients experience reactive hypoglycemia during OGTT. Pregnant women are more prone to developing hypoglycemia due to pregnancy-related changes in their glycemic profiles, such as increased basal insulin and decreased glucagon secretion [19, 20]. In addition to these physiological changes, other mechanisms may play a role in the development of reactive hypoglycemia. Eik et al. suggested that reactive hypoglycemia was associated with increased levels of anti-inflammatory and proinflammatory cytokines in the blood [21]. In another study, Berlin et al. reported that patients with suspected postprandial hypoglycemia had increased beta-adrenergic sensitivity, and emotional distress [22].

A few studies have evaluated the effects of reactive hypoglycemia on perinatal and neonatal outcomes, with conflicting results [3, 4, 23–25]. Pugh et al. compared 436 pregnant women who developed hypoglycemia during GCT with 434 normoglycemic pregnancies, and found that the hypoglycemic patients were significantly younger, had lower pre-pregnancy body mass indices, and were more likely to develop preeclampsia than normoglycemic women [4]. Langer et al. reported an association between maternal hypoglycemia and SGA [23]. Feinberg et al. found increased NICU admissions among pregnant women who experienced hypoglycemia during GCT [24]. On the other hand, Calfee et al. found no relationships between hypoglycemia on GCT and fetal growth restriction or other adverse perinatal consequences [25]. Weissman et al. even reported that reactive hypoglycemia was associated with favorable pregnancy outcomes, such as a lower rate of gestational diabetes, low birth weights, and cesarean delivery for macrosomia [3]. In the present study, we found that younger pregnant women were more likely to develop reactive hypoglycemia during the 3 h 100 g OGTT, which is significantly associated with adverse pregnancy outcomes, such as low APGAR scores, low birth weights, and prenatal admission to the NICU. As these associations with hypoglycemia were seen at the 3 h level, we recommend that the 3 h measurement be retained until the clinical significance of hypoglycemia in pregnancy is fully elucidated.

The main limitation of the present study was its retrospective design, which is associated with disadvantages such as selection bias, potential recording errors, and difficulty in controlling exposures and outcomes. This limitation precluded us from reaching any definitive conclusion regarding the perinatal significance of reactive hypoglycemia during the 100 g OGTT. Furthermore, in our study population, the sample size of pregnant women with reactive hypoglycemia was relatively low (n = 15), which also limited the power of the study. Nevertheless, this study is one of only a handful in the literature providing evidence of the perinatal effect of reactive hypoglycemia. On this basis, further large-scale prospective studies are needed to clarify the maternal and perinatal effects of reactive hypoglycemia during the 100 g OGTT.

CONCLUSIONS

Although the prevalence of reactive hypoglycemia during the 3 h 100 g OGTT is relatively low, it is significantly associated with low APGAR scores, low birth weights, and prenatal admission to the NICU. Therefore, pregnant women

who develop reactive hypoglycemia during the 100 g OGTT performed at 24–28 weeks of gestation should be followed up closely, and care should be taken to prevent adverse perinatal outcomes. Further studies are needed to explore the mechanisms underlying the relationship between reactive hypoglycemia and adverse perinatal outcomes, and its implications for clinical practice.

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Disclosure

Authors have no interest to disclose.

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