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The Association Between Maternal Hypoglycemia on the 75 g Glucose Tolerance Test and Maternal-Neonatal Outcomes: A Matched Case Control Study

Özgün Araştırma
Research Article

Oral Glukoz Tolerans (75 gr) Testi Sırasında Saptanan Maternal Hipoglisemi ile Maternal-Neonatal Sonuçların İlişkisi: Vaka-Kontrol Çalışması

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ÖZ

Amaç: *Çalışmamızın amacı gebelik sürecinde uygulanan 75 gr Oral Glukoz Testi (OGT) sırasında gelişen maternal hipogiseminin obstetrik ve neonatal sonuçlarını değerlendirmektir.*
Yöntem: *Bu vaka-kontrol çalışmasında, Ocak 2015 ve Aralık 2018 tarihleri arasında üçüncü basamak sağlık merkezinde takip edilmiş hastaların verileri analiz edildi. 24- 28 gebelik haftaları sırasında gestasyonel diabet taraması amaçlı 75 gr OGT uygulandı. Bir saat kan glukoz düzeyi 90 mg/dl (Düşük GT) saptanan gebeler yaş, vücut kitle indeksi, gravide, parite ve gestasyonel haftalarına göre normoglisemik hastalar ile eşleştirildi. Obstetrik ve neonatal sonuçlar değerlendirildi.*
Bulgular: *Toplam 1249 gebenin 62'si (%4,9) düşük GT grubunda değerlendirildi. Yenidoğan yoğun bakım internasyonu düşük GT grubunda 3,48 oranında artış gösterdi (güven aralığı: 1,05-11,47, p=0,04). İki grup arasında preeklampsi, erken doğum, doğum ağırlığı, gebelik sürecinde kilo alımı, 5. dakika Apgar skoru, gestasyonel yaşa göre düşük doğum ağırlığı açısından anlamlı bir fark saptanmadı.*
Sonuç: *Düşük 75 gr GTT artmış yenidoğan yoğun bakım internasyonu ile ilişkili olarak değerlendirilmiştir.*

Anahtar kelimeler: *Gestasyonel diyabet, hipoglisemi, perinatal sonuçlar, gebelik sonuçları*

ABSTRACT

Objective: *The aim of this study was to determine whether pregnant women who developed maternal hypoglycemia during the 75 g Oral Glucose Test (OGT) were at an increased risk for adverse obstetric and neonatal outcomes.*
Methods: *This case-control study was conducted from computer-based medical records of women who delivered in a tertiary center between January 2015 and December 2018. OGT had been performed with 75 gr glucose for gestational diabetes screening at 24-28 weeks of gestation. The pregnants with 1st-hour blood glucose levels less than 90 mg/dl (low GT) were matched with normoglycemic patients according to age, body mass index (BMI), gravida and gestational weeks. Obstetric and neonatal outcomes were assessed.*
Results: *Of the 1249 pregnant women included in the study, 62 (4.9%) were in the Low GT group. Admission to the neonatal intensive care unit (NICU) showed a rate of 3.48 increase in the Low GT group (95% confidence interval: 1.05-11.47, p=0.04). There was no difference between the two groups in the other obstetric and neonatal parameters such as: preeclampsia, preterm delivery, birth weight, and weight gained during pregnancy and the 5-minute Apgar scores adjusted for gestational age (SGA) of the fetus.*
Conclusion: *Low 75 g OGT results are significantly associated with increased risk of neonatal intensive care unit (NICU) admissions.*

Keywords: *Gestational diabetes, hypoglycemia, perinatal outcomes, pregnancy outcomes*

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INTRODUCTION

GGestational diabetes mellitus (GDM) is a major complication of pregnancy and associated with several adverse pregnancy outcomes including fetal macrosomia, polyhydramnios, preeclampsia and large for gestational age infants [1-5]. Although many studies have demonstrated the relationship between maternal hyperglycemia and poor maternal and neonatal outcomes, there is no consensus on the potential impact of maternal hypoglycemia. Some researchers have reported that hypoglycemia is a risk factor for small for gestational age (SGA) fetus and growth restriction [6,7], and some have not found an association between hypoglycemia and poor perinatal outcomes [8].

Conventionally, testing for gestational diabetes takes place in the second trimester and two methods are commonly used for this purpose. One of these approaches is the 75 g oral glucose tolerance test (OGTT) and the other is the 50 g glucose challenge test (GCT), which is a two-step approach. If the threshold value is exceeded in GCT, 100 gr OGTT is performed [7, 9,10].

International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommend one-step approach. The diagnosis of GDM is made when any one of the following plasma glucose values are exceeded after a 75-g oral glucose tolerance test: a fasting glucose (FBG) level of 5.1 mmol/L (92 mg/dL), a first-hour glycemic level of 10.0 mmol/L (180 mg/dL), or a second-hour glycemic value of 8.5 mmol/L (153 mg/dL). The IADPSG criteria have been endorsed by WHO, ADA, and the Endocrine Society of USA [11].

In this study, we compared the maternal and fetal outcomes of patients with low blood glucose value (< 90 mg/dl) during the first hour of 75 g OGT with normoglycemic patients. The purpose of this investigation was to determine if pregnancies with hypoglycemia following a 75 gr OGTT were at risk for an adverse maternal and neonatal outcomes such as preterm delivery, cesarean delivery, preeclampsia, small-for-gestational age (SGA) fetuses, low Apgar scores and NICU admissions.

MATERIALS and METHODS

Study Population and Design

This matched case-control study was conducted between January 2015 and December 2018 in Istanbul Bakırköy Sadi Konuk Training and Research Hospital. The study was approved by the Hospital's Ethics Committee (Approval No: 2019/469).

For the diagnosis of GDM in our clinic, we perform a one-step 75 g oral glucose test recommended by IADPSG between 24 and 28 weeks of gestation. If any of the following values is higher than normal reference values it is diagnostic for GDM as follows: fasting blood glucose> 92 mg/dl, 1st-hour post-OGT glucose value> 180 mg/dl, and 2nd-hour post-OGT glucose value> 153 mg/dl. Pregnant women whose blood glucose level was ≤90 mg/dl at the 1st-hour after 75 g oral glucose test were categorized as Low GT group. The reason why we determined 90 mg/dl as the threshold in our study was that this value was accepted for fetal growth restriction and negative perinatal outcomes in previous studies [12,13].

After 75 g oral glucose test, pregnant women with all of the following values, fasting blood glucose <92 mg/dl, 1st hour glycemic value between 90 and 180 mg/dl and 2nd hour glycemic value <153 mg/dl, were matched with hypoglycemic pregnancies according to age, gravida and gestational week.

Women with confirmed gestational diabetes, multifetal gestations, type I or II diabetes before pregnancy, inadequate obstetric records, chronic disease (heart disease, hypertension, asthma, hyperthyroidism or hypothyroidism) with a history of preterm birth or preeclampsia in previous pregnancy were excluded from the study.

There were 1778 cases initially reviewed (Figure 1). Of the 1249 pregnant women eligible for inclusion in

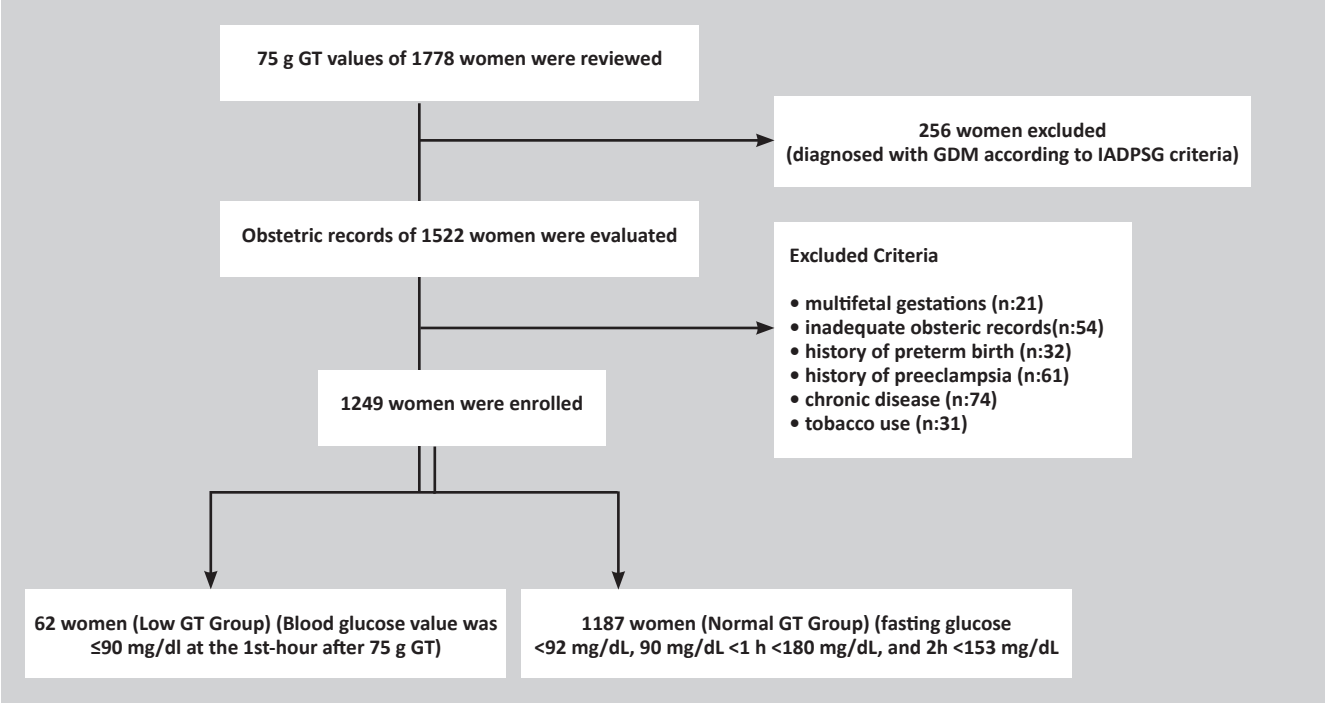

Figure 1. Flow diagram of groups.

the study, 62 (4.9%) had low glycemic valuıe (1st hour blood glucose <90 mg/dl).

The following data were recorded from computer-based patient files and were compared between the Low GT and the Normal GT groups: age, gestational week at delivery, prepregnancy body mass index, maternal weight gain during pregnancy, delivery type (vaginal or caesarean delivery), preterm delivery, preeclampsia, birthweight, 5th-minute APGAR scores, admissions to the neonatal intensive care unit (NICU), small-for-gestational age neonates (SGA) and large-for-gestational age neonates.

Definitions

In a pregnant woman with normal blood pressure, systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg in two measurements taken at least four hours apart after 20 weeks of gestation and ≥300 mg proteinuria in 24-hour urine established the diagnosis of preeclampsia. In addition, preeclampsia was diagnosed in case of new onset of hypertension, thrombocytopenia, hepatic enzyme elevation, renal failure, pulmonary edema, cerebral and vision-related symptoms in the absence of proteinuria [14].

Deliveries before 37 weeks of gestation were considered as preterm births [15]. The weights of the patients before pregnancy and at the last antenatal follow-up visit before birth were recorded. Weight gain and body mass index during pregnancy were calculated according to these values.. Based on Turkish infant weight percentiles, newborns were diagnosed as small for gestational age (SGA) or large for gestational age (LGA) fetuses. SGA defines birth weight below the 10th percentile and LGA defines birth weight above the 90th percentile [16].

Statistical analyses

Statistical analysis was performed using the PASW software package for Windows (Statistical Package for Social Sciences, Version 18.0, SPSS Inc., Chicago, Illinois, USA). For a comparison of categorical variables, Pearson's chi-square test or Fisher's exact test was used. Since parameters did not fit normal

distribution intergroup comparisons were made using Mann-Whitney U Test. Logistic regression analysis was used to demonstrate the relationship between low glucose levels and maternal and fetal outcomes. A p-value of <0.05 was considered statistically significant.

RESULTS

First, 75 g GT results retrieved from 1778 women's computer-based medical records were reviewed for this study. Figure 1 shows the 75 g GT values of the groups, and 256 (13.2%) of these women were diagnosed as GDM according to the criteria recommended by IADPSG. Of the 1249 women eligible for inclusion in the study, 62 (4.9%) had low glucose (1st hour blood glucose <90 mg/dl) and 1187 (95%) had normal 75 g GT results.The main demographic characteristics of the study groups are presented in Table 1. The maternal age, parity, pre-pregnancy BMI, weight gain in pregnancy were comparable between groups (Table 1).

The maternal outcomes are summarized in Table 2. There was no statistically significant difference between the groups in terms of adverse maternal outcomes such as preeclampsia, preterm birth and cesarean delivery.Although a 1.38-fold increase in the risk of preeclampsia in hypoglycemic pregnant women was seen without reaching statistical significance. (95% Cl 0.45 - 4.24, p=0.57).

The neonatal outcomes are presented in Table 3. NICU admissions in the low GT group were significantly higher than the control group (p=0.04). Although not significant, there was an increase in in the rates of SGA infants in the hypoglycemic group (0.25). Additionally, birth rates of LGA infants, distribution of neonatal gender, birth weights and 5 -minute Apgar scores were comparable among the groups.

Table 1. Maternal characteristics of groups according to glucose test results.

	Low GT Group (n=62)	Normal GT Group (n=62)	p value
Age(years)	29,7±5,1	30,1±4,7	0,677
Gestational week at delivery	38,2±1,4	38,4±1,3	0,653
Gravida	2,1±0,9	2,5±1,5	0,386
Primiparity, % (n)	%29 (18)	%33(21)	0,256
Pre-pregnancy BMI (kg/m^2)	23,4±3,2	23,3±3	0,854
Weight gain in pregnacy, kg, (mean ± SD)	12,9±2,5	12,7±2,8	0,444

Data expressed as number (%) or mean ± SD. GTT, glucose tolerance test; BMI, body mass index. Mann-Whitney U Test was used for statistical evaluation because the parameters did not match the normal distribution.

Table 2. Maternal outcomes according to glucose test results.

	Low GT Group (n=62)	Normal GT Group (n=62)	p value
Delivery Type, % (n)			
C-section	30,6 (19)	32,3 (20)	
Vaginal delivery	69,4 (43)	67,7 (42)	0,84
Preterm birth (<37 weeks), % (n)	14,5 (9)	19,3 (12)	0,73
Preeclampsia,% (n)	12(8)	9,6 (6)	0,64
Term birth, % (n)	85,4 (53)	82,2 (51)	0,8

Data expressed as number (%) or mean ± SD. GTT C-section, cesarean section.

Table 3. Neonatal outcomes according to glucose test results.

	Low GT Group (n=62)	Normal GT Group (n=62)	p value
Birthweight (gr), [mean ± SD]	3187±360	3133±344	0,473
Apgar < 7 (5 min) % (n)	11,2(7)	14,5(9)	0,71
SGA % (n)	14,5(9)	8(5)	0,25
LGA % (n)	6,4(4)	4,8(3)	0,83
NICU admission % (n)	19,3(12)	6,4(4)	0,04
Male sex % (n)	48,3(30)	53,2(33)	0,59

Data expressed as number (%) or mean ± SD. SGA, small for gestational age; LGA, large for gestational age; NICU, neonatal intensive care unit.

Table 4. Association of low GT values with adverse maternal-neonatal outcomes.

	OR	95% CI	p value
Preterm Delivery	0.70	0.2745 - 1.8235	0.47
Preeclampsia	1.38	0.4500 - 4.2488	0.57
Cesarean section	0.92	0.4347- 1.9808	0.84
Apgar <7 (5 min)	0.74	0.2604- 2.1576	0.59
SGA	1.93	0.6096 - 6.1471	0.26
LGA	1.35	0.2907 -6.328	0.69
NICU admissions	3.48	1.0554 - 11.4751	0.04

OR, odds ratio; CI, confidence interval; ,SGA, small for gestational age; LGA, large for gestational age; NICU, neonatal intensive care unit

Logistic regression analysis was used to determine the relationship between maternal and fetal outcomes of pregnant women with 1 hour blood glucose <90 mg/dl in one-step 75 g OGGT (Table 4). The risk of admission to the neonatal intensive care unit (NICU) in the newborns of the hypoglycemic group was 3.48 times higher than that of normoglycemic pregnant women (95% CI 1.05 - 11.47, p=0.04).

DISCUSSION

Even though the adverse effects of maternal hyperglycemia on obstetrics and neonatal outcomes are well-known, the importance of maternal hypoglycemia has still been unknown. However pregnant women are prone to develop hypoglycemia due to the pregnancy- related changes in glycemic profile like; increase of basal insulin level and decrease of glucagon secretion [17]. While some studies have not reported any negative effects of maternal hypoglycemia on maternal and fetal outcomes, others have shown the presence of an association. Inconsistencies between the studies are derived from the different amounts of glucose that have been used, differences in the methods of glucose administration and disregarding confounding variables while creating the groups. In our study, we did not find any association between low GT values and maternal outcomes such as preterm labor, preeclampsia, cesarean section, and weight gain during pregnancy. However, the risk of admission to the neonatal intensive care unit (NICU) in newborns of hypoglycemic pregnants was 3.4 times higher than in normoglycemic pregnants.

There are a limited number of studies in the literature showing an association between maternal hypoglycemia and NICU admission. Feinberg et al. reported that there was an increase in NICU admissions in newborns of women with a blood glucose level less than 88 at postprandial 1st hour after a 50 g glucose test [18]. On the other hand, Kwan et al. [19] claimed that there was no association between low GT values and NICU admissions. In our study, we found an increase in neonatal NICU admissions in pregnant women with blood sugar <90 mg/dl in the first hour after 75 gr GT. Although, there is an increased rate of NICU admissions at the hypoglycemia group; the Apgar scores were not strikingly different between the two groups studied. Since blood glucose levels were not routinely examined in each newborn, it was not possible to clearly identify the relationship between neonatal hypoglycemia and NICU admissions. Even though it was shown by Ma et al. [20] that there is a relation between low GCT values and neonatal hypoglycemia; any relationship between neonatal hypoglycemia and NICU admissions could not be demonstrated.

Glucose uses a facilitated diffusion route to cross the placental barrier. Therefore, fetal glucose levels are directly affected by maternal glucose levels. Insulin is the main hormon for fetal development and fetus produces its own insulin according to blood glucose level. Thereby ; maternal hypoglycemia may cause growth retardation at the fetus [21]. Rogne et al. [21] have shown that , inadequate increase of maternal blood glucose levels after glucose challenge test is related to fetal growth retardation. Similarly; Shinora et al. [22] reported that there was a significant relationship between low GCT results and the prevalence of SGA infants when they considered a cut-off value of 90 mg/dl at 50 g OGCT. In support of these studies, Topçu et al. [23] showed that the neonates of hypoglycemic women had a lower birth weight than normoglycemic ones.

As we consider all of these studies, our hypothesis before starting our study was that there should be an increased prevalence of low birth weight and SGA among newborns of hypoglycemic pregnants. In our study even though we detected a tendency to SGA newborns at pregnants with low GT values, when compared with pregnants who have a normal GT values; the intergroup difference was not statistically significant (p=0.2) In addition to this, there were no difference between both groups in terms of the birth weights of newborns.

There are limited studies showing the effects of hypoglycemia on maternal outcomes, and these studies have reported conflicting results. Pugh et al reported that pregnant women who developed hypoglycemia during the GCT test were younger, had a lower body mass index, a higher risk of preeclampsia when compared with normoglycemic pregnant women [24]. In the present study , we did not find any difference between hypoglycemic and normoglycemic pregnant women in terms of adverse maternal outcomes such as preeclampsia, preterm delivery and cesarean delivery.

This study has some limitations. We could not evaluate laboratory parameters such as insulin and C-peptide showing pathophysiology of hypoglycemia due to retrospective design of the study. In addition, we could not demonstrate the relationship between maternal hypoglycemia and neonatal hypoglycemia, since not all neonates were evaluated for hypoglycemia. Despite these limitations , the present study has several strengths. First of all , we determined hypoglycemic patients according to results of one-step 75 gr OGTT. Therefore we both created a more specific hypoglycemia definition than the studies which use 50 gr GCT , and at the same time excluded the pregnants with gestational diabetes. Secondly, by matching hypoglycemic pregnants with normoglycemic ones according to their age, gestational week and BMI values; we increased the value of our study. Also, our study population was composed of patients with alike socioeconomic status.

In conclusion, low 75 gr GT results are associated with increased NICU admissions. Therefore, pregnant women who develop hypoglycemia during the 75 g GTT performed at 24-28 weeks of gestation should be followed up closely, and care should be taken to prevent adverse neonatal outcomes.

Ethics Committee Approval: Istanbul Bakırköy Sadi Konuk Training and Research Hospital. The study was approved by the Hospital's Ethics Committee (Approval No: 2019/469).

Conflicts of Interest: All authors have declared that they have no conflicts of interests in connection with this article.

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