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Effect of borderline glucose intolerance on fetal maternal outcome

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Summary

Purpose of investigation: The aim of this study was to compare the maternal and neonatal adverse outcomes in pregnant women whose glucose challenge test (GCT) results were below 130 mg/dl and between 130-139 mg/dl. *Materials and Methods:* Three hundred and six women with 50-gram GCT results of 130-139 mg/dl and 305 women with 50-gram GCT results of < 130 mg/dl were recruited. *Results:* Higher pre-postpartum hemoglobin difference ($p = 0.001$), longer postpartum hospitalisation time ($p = 0.001$), and increased cesarean section rates ($p = 0.01$) were reported in the study group. There were no differences between two groups in rates of preeclampsia, polyhydramnios, ablatio placenta, and chorioamnionitis. *Conclusions:* The authors suggest that a GCT result between 130-139 mg/dl is not associated with higher maternal and neonatal morbidity. Results do not support a conclusion of high maternal and neonatal morbidity in the study group and give an impression that the 140 mg/dl threshold value is adequate for screening.

Key words: Gestational diabetes mellitus; Glucose challenge test; Screening; Neonatal morbidity; Healthcare.

Introduction

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy [1]. The real incidence is still debated, but it is considered that the prevalence ranges from 3% to 15%, since the data is variable due to different societies and diagnostic criteria used in different studies. Several studies have suggested that gestational hyperglycemia is associated with perinatal morbidity-mortality and maternal long-term morbidity [2, 3]. Therefore, the correct diagnosis GDM is extremely important.

Currently, there is no international consensus regarding criteria for either screening and definitive testing for GDM. Most of the clinicians use the method of American Diabetic Association (ADA) which recommends glucose challenge test (GCT) with a 50-gram oral glucose load, with measurement of venous plasma glucose one hour later as the initial step at 24- 28 weeks of gestation if there is no risk factor. This is followed by either 100-gram three-hour glucose tolerance test (GTT) as recommended by American College of Obstetrics and Gynecologists (ACOG) or the 75-gram oral GTT according to ADA criteria for confirmation, if screening is positive. There are controversial assessments about the issue which threshold should be used for screening with 50-gram GCT; 140 mg/dl or 130 mg/dl, but no definitive screening threshold for a positive GCT, necessitating further diagnostic testing, was adopted by the ACOG which stated that either threshold is acceptable [4-6].

Diminishing the threshold value would enable to diagnose more GDM patients; on the other hand, this would increase false positive results. In this case, performing further tests to the patients with false positive results would eventually lead to increased costs and need for healthcare. In contrast, a higher threshold gives better specificity but a number of women who may have GDM will remain undiagnosed and untreated. In the present study, the medical records of the cases who were administered to the clinic for routine controls were reviewed retrospectively and the cases who had a 50-gram GCT value of 130-139 mg/dl were compared with the ones who had a value below 130 mg/dl, in order to ascertain this controversial issue. This study focused primarily on the association between different levels of GCT and maternal-neonatal outcomes.

Materials and Methods

This retrospective cohort study was designed to assess the pregnancy outcomes in a study group of 306 pregnant women with a venous blood glucose of 130 - 139 mg/dl at the first hour following a 50-gram GCT at 24 - 28 weeks' gestation compared with those in a control group of 305 women with glucose values below 130 mg/dl. Patients were recruited among women screened for GDM who delivered at Zeynep Kamil Research Hospital between January 2009 and December 2010. The study protocol was conducted according to the revised Declaration of Helsinki and approved by the Local Research and Ethics Committee. Patients were offered screening for GDM during the routine prenatal follow-up at 24 - 28 weeks'

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Table 1. — *Maternal demographics.*

	Study group (n = 306)	Control group (n = 305)	*p* value
Mean age (years)	28.59 ± 5.9	27.86 ± 5.1	0.12
Gravidity	2.24 ± 1.4	1.95 ± 1.1	0.15
Parity	0.89 ± 1.035	0.75 ± 0.9	0.34
BMI (kg/m^2)	28.02 ± 3.9	27.97 ± 3.65	0.16
Vaginal delivery (%)	60.7	76.2	0.01
Cesarean section (%)	39.3	23.8	0.01
Gestation week of delivery	38.6 ± 2.1	38.4 ± 2.1	0.37
Birth weight	3320 ± 603	3254 ± 495	0.16

BMI: Body Mass Index.

gestation with 50-gram glucose, regardless of the time and fasting. The test was conducted by oral administration of 50-gram glucose with 200 ml water in five minutes. Venous blood glucose level was measured after one hour, in any time of the day in accordance with the ACOG's practice recommendations [6]. Exclusion criteria for this study were as follows: history of diabetes, chronic hypertension, other endocrine diseases, drug use which can cause impairment in glucose metabolism, non-cephalic presentation, multiple gestations, presence of fetal anomaly, and presence of prior deliveries with cesarean section (CS). Demographic data [maternal age, gravida, parity and body mass index (BMI)] were recorded for each patient. BMI values were classified as underweight (< 19.8 kg/m^2), normal weight (19.8 - 26 kg/m^2), overweight (26 - 29 kg/m^2), and obese (> 30 kg/m^2). Maternal conditions such as prior history of GDM, macrosomic baby, and preterm delivery (< 37 weeks' gestation) were recorded as well. Presence with preeclampsia, polyhydramnios, chorioamnionitis, ablatio placenta, postpartum hospitalisation time, and maternal hemoglobin levels before and after delivery of the current pregnancies were recorded in each patient. Medical reports regarding the deliveries of the patients were investigated retrospectively.

Neonatal data including prematurity, hyperbilirubinemia, hypoglycemia, polycythemia, admission to the neonatal intensive care unit (NICU), and neonatal hospitalisation time were recorded as well. Blood glucose levels of neonates were evaluated at the first and fourth hour following birth and venous hematocrit levels were evaluated at the fourth hour after birth. Hypoglycemia was defined as a blood glucose level below 40 mg/dl and polycythemia was defined as a venous hematocrit level above 65%. Hyperbilirubinemia was defined as > five mg/dl increase of bilirubin levels daily or total bilirubin level higher than 12 mg/dl for term newborns and 15 mg/dl for preterm newborns.

All statistical analyses were performed using Number Cruncher Statistical System (NCSS) 2007 and Power Analysis and Sample Size (PASS) 2008 Statistical Software. Outcome variables between the two groups were calculated and compared using Mann Whitney U and Chi-Square test. $P < 0.05$ was regarded as statistically significant. As a result of Power analysis, approximately 10,000 cases of pregnant women admitted to the present outpatient clinics in one year, it was assumed that 50-gram OGTT test was required. Power analysis, in anticipation of 50-gram GCT that would be abnormal in 15% of cases, the study required to recruit at least 192 cases.

Table 2. — *Maternal history, pregnancy complications, and maternal morbidity outcome.*

	Patients with GCT results between 130-139 mg / dl (n = 306)	Patients with GCT results < 130mg / dl (n = 305)	*p* value
Family history of diabetes (%)	21 (n = 66)	48 (n = 17)	0.39
History of gestational diabetes (%)	7.2 (n = 22)	4 (n = 12)	0.36
History of macrosomic delivery (%)	6.9 (n = 21)	4 (n = 12)	0.41
History of preterm delivery (%)	6.9 (n = 21)	5 (n = 15)	0.65
Chorioamnionitis	0 (n = 0)	0 (n = 0)	
Preeclampsia (%)	12 (n = 37)	6.9 (n = 21)	0.21
Polyhydramnios (%)	9.2 (n = 28)	5 (n = 15)	0.29
Ablatio placenta (%)	2.6 (n = 8)	2 (n = 6)	1.00
Postpartum hospitalisation time (day)	3.02 ± 1.9	2.56 ± 2.4	0.001
Prepartum-postpartum hemoglobin difference(gr/dl)	1.5 ± 1.05	1.1 ± 0.8	0.001

Table 3. — *Postpartum hospitalisation time according to the mode of delivery.*

	Hospitalisation time(day) Cases	Control	*p* value
Vaginal delivery mean ± SD (median)	2.35 ± 1.22	2.12 ± 1.50	0.008
Cesarean delivery mean ± SD (median)	3.80 ± 2.19	4.00 ± 3.87	0.05

Results

No significant difference was found in terms of age, BMI, gravidity, and parity between the groups (Table 1). There was no statistically significant difference in terms of prior history of GDM, family history of GDM, history of a macrosomic delivery, and a preterm delivery between both groups. Postpartum hospitalisation time, prepartum, and postpartum hemoglobin differences were statistically higher in the group with higher GCT results (Table 2). Postpartum hospitalisation time above three days was higher in the cases that had CS (88% *vs.* 26%). Postpartum hospitalization time was higher in the study group who had vaginal delivery ($p <$ 0.01). In the cases who had CS, postpartum hospitalization time was similar between study and control group (Table 3). No statistically significant difference in terms of birth weight and mean week of gestation between the groups was found. CS rates were significantly higher in the in the group with higher GCT results (39.3 % *vs.* 23.8 %) ($p = 0.01$) (Table 1).

Rates of maternal complications such as preeclampsia, polyhydramnios, ablatio placenta, and chorioamnionitis were similar in both groups (Table 2). One- and five-minute Apgar scores of neonates were evaluated and no significant difference was observed between both groups. Shoulder dystocia was reported in three cases in the group with higher GCT results, whereas only two cases were reported in the group with

Table 4. — *Neonatal outcomes.*

	Patients with GCT results between 130 - 139 mg / dl (n = 306)	Patients with GCT results < 130mg / dl (n = 305)	*p* value
1-minute Apgar score	7.7 ± 1.4	7.9 ± 0.9	0.75
5-minute Apgar score	8.9 ± 0.6	8.9 ± 0.6	0.14
Shoulder dystocia	3	2	0.38
AGA	81 (n = 248)	86.1 (n = 262)	0.41
SGA	8.8 (n = 27)	7.9 (n = 24)	0.40
LGA	10.1 (n = 31)	5.9 (n = 19)	0.42
Neonatal hospitalisation time (day)	2.1 ± 3.7	1.3 ± 0.8	< 0.001
Prematurity (%)	8.9 (n = 27)	5.9 (n = 18)	0.47
NICU admission (%)	8.5 (n = 26)	8.9 (n = 27)	1.00
Hyperbilirubinemia (%)	16 (n = 49)	11.9 (n = 36)	0.39
Hypoglycemia (%)	4.9 (n = 15)	0 (n = 0)	0.05
Polycythemia (%)	3.6 (n = 11)	2 (n = 6)	0.64

SGA: small for gestational age; AGA: appropriate for gestational age; LGA: large for gestational age; NICU: neonatal intensive care unit.

GCT results lower than 130 mg / dl ($p > 0.05$) (Table 4).

The rates of neonatal morbidity were similar in both groups. Although not statistically different, hypoglycemia was more common among neonates in the group with higher GCT results with a rate of 4.9 % ($p = 0.05$) (Table 4).

Discussion

Although the diagnostic criteria for GDM were published more than 40 years ago, by O'Sullivan and Mahan, there is still a lack of international consistency with regards to the screening and diagnosis of GDM [6-8]. The results of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study support the 1952 Pederson hypothesis linking maternal hyperglycemia to fetal hyperglycemia and hyperinsulinemia; maternal hyperglycemia being the messenger leading to fetal overgrowth and, more importantly, fetal morbidity and mortality. However the results show that there is no apparent glycemic cut-off value for development of complications [9]. Although the HAPO study is being used to redefine diagnostic criteria for GDM in relation to adverse outcomes, most of the clinicians in the present country still use the method of ACOG for GDM screening.

This study was designed to evaluate adverse maternal and neonatal outcomes in the cases whose 50-gram GCT value was between 130-139 mg/dl. The only significant differences were the hospital stays for the mother and newborn and higher difference in hemoglobin values in the study group than in the control group. Probably these differences may be due to 60-70% higher CS rate in the study group. Naturally, cesarean deliveries cause more bleeding and longer postpartum follow up periods when compared to vaginal deliveries. However cases who had CS, postpartum hospitalization time was similar between groups. Although the mean pre- and postpartum differences in hemoglobin are statistically higher in study group, the difference is remarkably small. As GTT was not performed in both study and control groups, and the present authors do not know if the difference between the GTT values might have effected the outcomes or not. In pregnancies complicated with diabetes, most of the specialists do not wait for spontaneous labor, and terminate the pregnancy with labor induction or CS due to the fact that macrosomia and unexplained intrauterine death incidence increases in the latter weeks of these pregnancies [10]. Also, due to the fear of presumptive shoulder dystocia, CS implications are more common in diabetic pregnants. This rate is reported as 50-80% in different departments [11]. In the present study, the authors reported CS rates as 39.3% *vs.* 23.8% in the study and control groups, respectively. They also reported that neonatal hospital stay was statistically higher in the study group. This is probably due to longer maternal hospitalization time. The rates of prematurity, hyperbilirubinemia, polycythemia, and NICU admission were similar between groups.

Prior studies which examined the threshold for 50-gram GCT have focused on the sensitivity and specificity of different thresholds by demonstrating adverse pregnancy and neonatal outcomes. Unlike the present study, Cheng *et al.* reported increased perinatal complication rates in the cases with GCT values of 130-139 mg/dl [12]. In the study, cases were classified into four groups according to 50-gram GCT values (< 120 mg/dl, 120-129 mg/dl, 130-139 mg/dl, and > 140 mg/dl), and the group who had GCT values of 130-139 mg/dl demonstrated to have more maternal and neonatal morbidity when compared with other groups. They even demonstrated that women with a GCT value between 130-139 mg/dl experienced high maternal complication rates than women with a GCT value > 140 mg/dl. They reported that women with a GCT value of 130-139 mg/dl and > 140 mg/dl were more likely to have preeclampsia, operative vaginal deliveries, and CS than women with a GCT value < 130 mg/dl. The rate of CS was 14.5%, 13.8%, and 11.3% in women with GCT of 130-139 mg/dl, 120-129 mg/dl, and < 120 mg/dl, respectively. Unlike the present study, neonatal morbidity was also higher in women with a GCT values between 130-139 mg/dl when compared with GCT values between 120-129 mg/dl and below 120 mg/dl (19.0% *vs.* 15.0% *vs.* 16.7%) [12]. However, Gabbe *et al.* reported that lowering the cut-off value from 140 mg/dl to 130 mg/dl would increase the sensitivity to nearly 100%, but would require GTTs in nearly 25% of all patients [2]. Although perinatal benefits of GDM treatment have been demonstrated, the cost-benefit of diagnosing GDM in this group remains complicated and controversial. In the present study, no cost benefit analysis was done, so it is unclear if the benefit of decreasing the threshold for a higher rate of CS will outweigh the costs of GDM management.

Differences in the physician practice styles, absence of GTT results, and small number of cases are the limitations of this study. Despite these limitations, the results do not support a conclusion of high maternal and neonatal morbidity in the study group and give an impression that the 140 mg/dl threshold value is adequate for screening. Since the recent trials show that there is no clear glycemic cut-off value for the development of complications, but rather a continuum, the exact values will be determined. The problems from lowering the threshold will lead to a higher incidence of GDM and increased cost of treatment and healthcare, with no clear benefit in terms of either short or long term fetal-maternal outcomes.

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