Experimental
&
Clinical Article

Prognosis of Pregnancies with Different Degrees of Glucose Intolerance

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OBJECTIVE: The purpose of the present study was to evaluate the effect of different degrees of glucose intolerance on maternal and perinatal outcomes.

STUDY DESIGN: Retrospective data of 500 singleton pregnancies screened for gestational diabetes mellitus were reviewed. Maternal and perinatal outcomes for four different groups were compared. First group consisted of patients with normal 50-g test, second group was formed by patients with abnormal 50-g test but a normal 100-g test. Third group included patients with one abnormal value after 100-g test. Patients in the fourth group were diagnosed to have gestational diabetes mellitus with two or more abnormal values after 100-g test.

RESULTS: Macrosomia, neonatal intensive care unit admission and preterm premature rupture of membranes were the highest in the group with one elevated value after glucose tolerance test. Preterm labor was the highest in the gestational diabetes group. The difference in the rate of preeclampsia, polyhydramnios, neonatal hypoglycemia and hypocalcemia was not statistically significant ($p>0.05$).

CONCLUSION: Although women with one elevated value after glucose tolerance test are not diagnosed with gestational diabetes mellitus, they are still at risk for adverse maternal and perinatal outcomes. They seem to be prone to develop obstetric complications related to glucose intolerance and should be followed up carefully during the antepartum and intrapartum period.

Key Words: Glucose intolerance, Pregnancy, Gestational diabetes, Perinatal outcome

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Introduction

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance that begins or first diagnosed during pregnancy[1] and it complicates 1-5% of all pregnancies.[2] Importantly, the prevalence of GDM is increasing, probably because of increasing rates of overweight and obesity. Although specific risk factors and the degree of their influences on GDM prevalence are difficult to quantify across populations, a number of clinical risk factors have been demonstrated to be associated with an increased likelihood of GDM, including age, ethnicity, obesity, family history of diabetes, and past obstetric history. This condition is associated with variable severity of maternal and perinatal complications such as fetal macrosomia, shoulder dystosia, birth injuries, neonatal hypoglycemia, hyperbilirubinemia, respiratory distress syndrome, perinatal death, and childhood obesity. Maternal risk factors also include preeclampsia, cesarean delivery, and an increased risk of developing type-2 diabetes in later life.[1,3-4] The most widely accepted screening and diagnosing scheme for GDM is the National Diabetes Data Group algorithm, in which a 50-g 1-h glucose challenge test (GCT) is administered universally at 24-28 gestational weeks, followed by a 100-g 3-h oral glucose tolerance test (OGTT) in GCT positive patients.[1,4-5]

We have not enough information about the obstetric outcomes of pregnancies with positive GCT but negative for OGTT. In addition a probably greater debate exists about the significance of one abnormal level in the diagnostic OGTT. Although a solitary elevated value has been found to be related to adverse maternal and perinatal outcomes in some studies,[2-6-8] closer follow-up, dietary management and insulin therapy are not common practices for this group of patients.

The present retrospective study was designed to investigate the prognosis of the patients with different degrees of glucose intolerance on maternal and perinatal outcomes.

Material and Method

The present study was approved by the Ethical Committee and Institutional Review Board of Dr. Zekai Tahir Burak

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Women's Health Research and Education Hospital where the study was conducted. The records of pregnant patients who had been followed at the perinatology department of the study center between 2008 and 2011 were reviewed.

All of the participants were screened for GDM with a 50-g 1 h GCT between 24-28 weeks' gestation. Subjects whose values were greater than 140 mg/dL were referred to 100-g 3 h OGTT. The cut off levels were 95 mg/dL for fasting, 180 mg/dL for the first hour, 155 mg/dL for the second hour, and 140 mg/dL for the third hour for the determinative test for GDM. Exclusion criteria for the present study were maternal diabetes mellitus diagnosed before pregnancy and multiple gestations. Accordingly patients were divided into four groups. First group consisted of patients with a normal 50-g GCT. Second group was formed by patients with an abnormal 50-g GCT but a normal 100-g OGTT. This group of women was defined to have false positive GCT. Third group included patients with one abnormal value after 100-g OGTT. Patients in the fourth group were diagnosed to have GDM after two or more abnormal values wit 100-g OGTT. Participants who were diagnosed to have GDM were consulted to endocrinology department for blood glucose regulation.

Maternal ages, maternal body mass index (BMI), gestational ages at birth, birth weights, APGAR scores, and maternal and neonatal complications were the main parameters studied. Neonates with a birth weight below 10 percentile were defined as small for gestational age (SGA), with a birth weight above 90 percentile were defined large for gestational age (LGA), and those between 10 and 90 percentile were defined as appropriate for gestational age (AGA). A cut off value 4000 g was considered for the definition of macrosomia. Neonatal hypoglycemia was defined as a blood glucose level below 40 mg/dL and neonatal hypocalcemia was defined as a blood calcium level below 8 mg/dL.

Statistical analysis was done by Statistical Package for Social Sciences (SPSS) 11.5 software (SPSS Inc., Chicago, IL, United States). Distributions of continuous variables were tested by Shapiro Wilkis test. Numerical data were shown as mean ± standard deviation or median (minimum - maximum) where appropriate and qualitative data were presented as percentages. The differences among groups were evaluated by ANOVA or Kruskal Wallis tests, regarding maternal age and gestational ages at birth, or maternal weight gain, body mass index and birth weight, respectively. When p values in one way ANOVA or Kruskal Wallis tests were statistically significant, multiple comparisons by post hoc Tukey method were used to specify which group differs from the others. Categorical changes were evaluated by Pearson's chi-square and Fischer's tests. A p value <0.05 was considered as statistically significant.

Results

The data of 500 patients were suitable for evaluation. Of these, 77 (15.4%) patients formed group 1 with blood glucose level below 140 mg/dL after 50-g GCT. Group 2 consisted of the 111 (22.2%) patients with an abnormal 50-g GCT and a normal 100-g OGTT (false positive GCT). 218 (43.6%) patients with an abnormal 50-g GCT and only one abnormal value detected by 100-g OGTT fell into group 3. Group 4 consisted of 94 (18.8%) patients with two or more abnormal values detected in 100-g OGTT.

Mean maternal age, maternal weight gain, BMI, and gestational ages at birth among the groups were shown in Table 1. Mean maternal age in group 1 was 26.1±4.7 years. Mean maternal age increased to 28.1±5.8 in group 3 and to 30.1±5.4 in group 4. Maternal weight gain was not significantly different between four groups. BMI was the highest in group 4 with 28.7±5.1 kg/m². BMI was 25.2±2.8 kg/m², 28.5±4.3 kg/m², and 26.6±3.2 kg/m² in groups 1,2 and 3, respectively. Group 4 was significantly different from groups 1 and 3 with regard to BMI. However, BMI was not significantly different between groups 2 and 4. Mean gestational ages were 38.8±1.4 in group 1, 39.4±2.8 in group 2, 38.5±1.8 in group 3, and 38.7±1.9 in group 4. The difference between groups with regard to gestational age as detected by ANOVA test was statistically significant (p=0.004). Tukey test revealed difference between groups 2 and 3.

Table 1: Demographic findings of pregnant women among groups

	Group 1 (n=77)	Group 2 (n=111)	Group 3 (n=218)	Group 4 (n=94)	P
Maternal age	26.1±4.7[c,d]	27.8±4.8[a]	28.1±5.8[b,c]	30.1±5.4[a,b,d]	<0.001
Maternal weight gain	12.4±4	15.2±7.4	12.8±3.8	13±6.1	0.179
Body mass index (kg/m²)	25.2±2.8[c,d,e]	28.5±4.3[e,f]	26.6±3.2[b,c,f]	28.7±5.1[b,d]	<0.001
Gestational age at birth (weeks)	38.8±1.4	39.4±2.8[f]	38.5±1.8[f]	38.7±1.9	0.004

[a]difference between group 2 and 4, [b]difference between group 3 and 4, [c]difference between group 1 and 3, [d]difference between group 1 and 4 [e]difference between group 1 and 2, [f]difference between group 2 and 3

Pregnancy complications, maternal and fetal morbidity were also evaluated in the present study (Table 2 and 3). The differences among groups with regard to preeclampsia and polyhydramnios incidence were not statistically significant (p=0.246 and p=0.388 respectively). Preterm premature rupture of membranes (P-PROM) was not observed in groups 1 and 2, but there were 11 (5%) and 1 (1.1%) patients in groups 3 and 4, respectively. Statistical analyses revealed significant difference between groups 2 and 3 (p=0.002). Preterm birth was a more common finding in group 4 with 9 (9.6%) patients. The difference was statistically significant between group 3 and 4 with regard to preterm delivery.

As birth weights were evaluated in each group, birth weights were similar in all four groups and no significant difference was observed (p=0.418). Macrosomia was most common in group 3 with a percentage of 19.3%. Group 3 was significantly different from groups 2 and 4 with regard to the incidence of macrosomia. AGA, SGA and LGA incidences were similar between groups.

As first minute APGAR scores were evaluated, there were no neonates with an APGAR score <7 in group 2. Group 2 was significantly different from groups 1,3 and 4. Neonatal intensive care unit (NICU) admission was also evaluated in the present study. Similarly with APGAR scores, group 2 was different from group 3 and 4, with at the very least percentage of 1.8%. (p=0.015 and p=0.006 respectively). The difference in the rate of neonatal hypoglycemia and hypocalcemia was not statistically significant (p>0.05). Cesarean rates were 27.3%, 49.5%, 39% and 51.1%, in groups 1,2,3 and 4, respectively (p=0.004). The rate of cesarean delivery was significantly higher in group 4 as compared to groups 1 and 3 (p=0.002 and p=0.048). (Table 4)

Table 2: Pregnancy complications

	Group 1 (n=77)	Group 2 (n=111)	Group 3 (n=218)	Group 4 (n=94)	P
Preeclampsia	3 (3.9%)	2 (1.8%)	14 (6.4%)	4 (4.3%)	0.246
P-PROM	0 (0%)	0 (0%)[a]	11 (5%)[a]	1 (1.1%)	0.002
Polyhydramnios	2 (2.6%)	3 ((2.7%)	13 (6%)	3 (3.2%)	0.388
Preterm birth	2 (2.6%)	5 (4.5%)	4 (1.8%)[b]	9 (9.6%)b	0.025

[a]difference between group 2 and 3, [b]difference between group 3 and 4

Table 3: Distribution of neonates with regard to birth weights and macrosomia incidence

	Group 1 (n=77)	Group 2 (n=111)	Group 3 (n=218)	Group 4 (n=94)	P
AGA	68 (88.3%)	100 (90.1%)	177 (81.2%)	83 (88.3%)	0.108
SGA	2 (2.6%)	2 (1.8%)	7 (3.2%)	4 (4.2%)	0.261
LGA	7 (9.1%)	9 (8.1%)	34 (15.6%)	7 (7.4%)	0.280
Mean birth weight (g)	3273±429	3361±474	3302±600	3341±467	0.418
Macrosomia	9 (11.7%)	9 (8.1%)[a]	42 (19.3%)[a,b]	7 (7.4%)[b]	0.007

[a] difference between group 2 and 3, [b] difference between group 3 and 4

Table 4: Neonatal complications

	Group 1 (n=77)	Group 2 (n=111)	Group 3 (n=218)	Group 4 (n=94)	P
APGAR (1. min)					
<7					
≥7	8 (10.4)[b]	0 (0)[a,b,c]	13 (6)[a]	6 (6.4)[c]	
	69 (89.6)[b]	111 (100)[a,b,c]	205 (94)[a]	88 (93.6)[c]	0.015
NICU admission	6 (7.8%)	2 (1.8)[a,c]	30 (13.8)[a]	9 (9.6)[c]	0.006

[a] difference between group 2 and 3, [b]difference between group 1 and 2, [c] difference between group 2 and 4

Discussion

The present study was designed to investigate the prognosis of the patients with different degrees of glucose intolerance on maternal and perinatal outcomes. Although not meeting the criteria for the diagnosis of GDM, if women with false positive GCT and with one elevated value in OGTT were at risk for maternal and perinatal outcomes, was investigated. The subject is a great debate and some of the current literature declares an increased incidence of adverse outcomes, whereas other publications fail to support this relationship.

Gumus et al.[5] compared 141 patients with false positive GCT and 189 patients with normal GCT with a cut-off value of 130 and reported that patients with false positive GCT should be followed up carefully during the antepartum and intrapartum period. They found gestational weight gain and polyhydramnios to be significantly higher in the study group, whereas prevalence of preterm labor, hypertension, cesarean delivery, mean birth weight, NICU admission was similar. In a retrospective study Gezer et al.[9] designed to investigate the prognosis of patients with abnormal diabetes screening test and a negative 100-g OGTT, and concluded that although these patients seem to prone to develop adverse pregnancy outcomes related to glucose intolerance, there is not a proper means to detect these patients in clinical practice. In addition, Dudhbhai et al.[10] reported similar pregnancy outcomes in patients with an abnormal GCT and a subsequent normal OGTT compared to patients in whom both test results are normal. Similarly, Grotegut et al.[11] conducted a study to determine if pregnancies complicated by a false positive GCT have higher rates of adverse maternal and neonatal outcomes. They found no significant differences in study and control groups with regard to mode of delivery, gestational age at delivery, birth weights, macrosomia rates, shoulder dystocia, rates of preeclampsia, NICU admission, and neonatal hypoglycemia. In contrast to aforementioned studies, Gruendhammer et al.[8] evaluated the feto-maternal outcome of pregnancy in 152 women with abnormal glucose values during the 100-g OGTT and in 304 women with normal GCT values. Their results suggested that the number of abnormal glucose values is associated with the feto-maternal outcome of pregnancy. The percentage of premature birth was significantly increased in women with abnormal OGTT values compared to non-diabetic control group. Only in women with three abnormal OGTT values mean birth weight, the percentage of LGA and macrosomic infants were significantly increased. They also concluded that women with only one abnormal OGTT value revealed an increased risk indicating a need for further control and therapy because of higher incidence of hypertension and higher rate of cesarean section.

Reviewing the aforementioned data, the present study was conducted to determine whether patients with different degrees of glucose intolerance should be considered to be at high risk. The data of the present study showed that mean maternal age increased progressively from patients with normal GCT to GDM group. BMI was found to be the highest in the GDM group and lowest in the control group, however patients with one abnormal value in the OGTT had lower BMI compared to false positive GCT group. Maternal weight gain in pregnancy was similar among groups. This may be attributed to more careful dietary management of patients with glucose intolerance. We found no significant difference in terms of preeclampsia among the four groups similar to Grotegut et al.[11] whereas McLaughlin et al.[6] Kim et al.[7] and Nordin et al.[12] reported higher incidence of preeclampsia in patients with one abnormal OGTT value as compared to patients with normal screening. Although Gumus et al.[5] reported incidence of polyhydramnios to be higher in patients with positive GCT but negative for OGTT than those of patients with negative GCT, we found similar rates with regard to polyhydramnios in four groups, similar to the study designed by Gruendhammer et al.[8] The percentage of preterm birth was significantly increased in women with GDM in the present study similar to the data reported by Greundhammer et al.[8] however some publications reported similar rates.[5-11] Interestingly, the data of the present study showed P-PROM ratio was the highest in patients with one elevated OGTT value.

Macrosomia incidence was the highest in patients with one elevated value in OGTT in the present study similar to the findings of McLaughlin et al.[6] Dudhbhai et al.[10] and Corrado et al.[13] however, Grotegut et al.[11] reported similar rates. Our data reported similar birth weight among four groups. Gruendhammer et al.[8] also reported that only in women with three abnormal OGTT values mean birth weight, the percentage of LGA and macrosomic infants were significantly increased. Interestingly, the percentage of macrosomia was significantly higher in women with one abnormal value as compared to GDM group in the present study, probably due to more careful perinatal management of these patients.

As first minute APGAR scores were evaluated, there were no neonates with an APGAR score <7 in group 2. Group 2 was significantly different from groups 1, 3 and 4. As a challenging finding, the percentage of neonates with an APGAR score <7, was the highest in the normal screening group. This may be attributed to other factors except for glucose intolerance. Dudhbhai et al.[10] and Corrado et al.[13] reported similar first minute APGAR scores in their control and study groups. Neonatal intensive care unit (NICU) admission was also evaluated in the present study. Similarly with APGAR scores, group 2 was different from group 3 and 4, with at the very least percentage of 1.8%. On the contrary, McLaughlin et al.[6] reported higher ratio of NICU admission in patients with one

elevated OGTT value as compared to control group, however Grotegut et al.[11] reported similar rates in women with normal screening and with a false positive GCT. The rate of cesarean delivery was significantly higher in group 4 as compared to groups 1 and 3 in the present study,however this may not be attributed to glucose intolerance because cesarean indications varied in a large spectrum, such as previous cesarean delivery, cephalo-pelvic disproportion, malpresentations, placental abruption, placenta previa, cord prolapsus, meconium and fetal distress.

Di Cianni et al.[14] conducted a study to define the metabolic phenotype of pregnant women with one abnormal value during OGTT and to test whether one abnormal value could be considered metabolically comparable to GDM or a specific entity between GDM and normal pregnancy. They concluded that one abnormal value and GDM are clinically indistinguishable, and both groups are different from women with normal GCT. Their results reported that women with GDM and one abnormal value showed impaired insulin secretion and insulin sensitivity, although these defects are more pronounced in women with GDM. However, Fassett et al.[15] stated that women with one elevated OGTT value did not benefit from a structured program of medical nutritional therapy and self blood glucose monitoring.

According to the data of the present study, the explanation to the highest rate of macrosomia incidence in the group with one elevated OGTT value lies beneath the lack of treatment in this group of patients. Patients with the diagnosis of GDM after two or more abnormal values on the OGTT receive treatment and close glycemic control leading to significantly less macrosomic newborns compared to patients with one abnormal value for whom appropriate treatment is usually neglected.

Although women with one elevated glucose tolerance test are not diagnosed with gestational diabetes mellitus, they are still at risk for adverse maternal and perinatal outcomes. They seem to be prone to develop obstetric complications related to glucose intolerance and should be followed up carefully during the antepartum and intrapartum period. They warrant close glucose monitoring and treatment even in the absence of a diagnostic OGTT.

Farklı Düzeylerde Glukoz Entoleransının Gebelik Prognozuna Etkileri

AMAÇ: Bu çalışmada gebelerde farklı düzeylerdeki glukoz intoleransının maternal ve perinatal sonuçlara olan etkisinin araştırılması amaçlanmıştır.

GEREÇ VE YÖNTEM: Gestasyonel diyabet için tarama programına alınan 500 tekil gebeliğin retrospektif verileri değerlendirilmiştir. Test sonuçlarına göre hastalar 4 gruba ayrılmış ve maternal ve perinatal sonuçlar karşılaştırılmıştır. Birinci grupta normal 50 g tarama testi olan gebeler, ikinci grupta 50 g tarama testi yüksek olup, 100 g glukoz yükleme testi normal olan gebeler, üçüncü grupta 50 g tarama testi yüksek olup, 100 g glukoz yükleme testinde tek değer yüksekliği olan gebeler, dördüncü grupta gestasyonel diyabet tanısı almış gebeler mevcuttu.

BULGULAR: Makrozomi, neonatal yoğun bakım ünitesi gereksinimi ve preterm erken membran rüptürü 100 g testinde tek değer yüksekliği olan gebelerde diğer gruplara göre yüksek oranda tespit edildi. Preterm eylem gestasyonel diyabet grubunda en yüksek oranda bulundu. Preeklampsi, polihidramnioz, neonatal hipoglisemi oranları arasında gruplar arasında fark yoktu (p>0,05).

SONUÇ: 100 g glukoz tolerans testi sonuçlarına göre tek değer yüksekliği olan hastalar gestasyonel diyabet tanısı almamalarına rağmen kötü maternal sonuçlar için risk grubundadırlar. Bu grup hastalar glukoz intoleransına bağlı olduğu düşünülen obstetrik komplikasyonlara meyilli gibi görünmektedir. Dolayısıyla antenatal ve intrapartum dönemde çok dikkatli izlenmeleri gereklidir.

Anahtar Kelimeler: Glukoz entoleransı, Gebelik, Gestasyonel diyabet, Perinatal sonuçlar

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