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Evaluation of Blood Glucose Profile and Perinatal Outcomes in Pregnant with Different Levels of Glucose Intolerance

Farklı Düzeylerde Glukoz İntoleransı Bulunan Gebelerin Kan Şekeri Profilleri ve Perinatal Sonuçlarının Değerlendirilmesi

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Abstract

Objectives: The aim of this study is to contribute to the monitoring and treatment in pregnant women with different levels of glucose intolerance by comparing blood glucose profiles and perinatal outcomes.

Materials and Methods: A 50-gram Glucose Tolerance Test (GTT) was performed on pregnant women between 24th and 28th weeks of pregnancy who admitted to the outpatient clinic followed by a 100-gram OGTT on those who tested positive with 50 g GTT. The patients were allocated into three groups according to the test results as Normal, Abnormal Glucose Challenge Test (AGCT) and Gestational Diabetes Mellitus (GDM). All groups were evaluated in terms of demographic data, GTT and OGTT results, prenatal and postnatal blood glucose profiles, maternal complications, and perinatal outcomes.

Results: The prevalence of AGCT was found to be 17.42% while GDM was 14.57%. When compared as to prepregnancy and during 50 g OGTT values, the body mass index (BMI) was found significantly higher in AGTT group than the normal group ($p<0.05$). Twenty-four hour and postpartum first 24-hour blood glucose profiles of the AGCT group were found to be higher than the normal group ($p<0.05$), whereas these values were found to be significantly higher in the GDM group when compared to the AGCT group ($p<0.05$).

Conclusion: We found that glucose intolerance in the AGCT group was slightly higher when compared to GDM group and appears to be significantly increased when compared to the normal group. Therefore, we suggest that the pregnant women with AGCT should be followed up closely and treated if needed, similar to the patients diagnosed with GDM in order to prevent both fetal and maternal complications.

Key words: Abnormal glucose challenge test, gestational diabetes, pregnancy

Öz

Amaç: Bu çalışmanın amacı farklı düzeylerde glukoz intoleransı gösteren gebelerde kan şekeri profilleri ve perinatal sonuçlarını karşılaştırarak gebelerin takip ve tedavilerine katkıda bulunmaktır.

Materyal ve Metot: Gebe Polikliniği'ne müracaat eden 24-28. gebelik haftaları arasında ki gebelere 50 gram Glukoz Tolerans Testi (GTT) yapıldı ve sonucu pozitif olanlara 100 gram Oral Glukoz Tolerans Testi (OGTT) yapıldı. Test sonucuna göre gebeler Normal, Anormal Glukoz Tolerans Testi (AGTT) olanlar ve gestasyonel diyabeti (GDM) olanlar olarak 3 gruba ayrıldı. Her üç grupta demografik veriler, GTT ve OGTT sonuçları, doğum öncesi ve doğum sonrası kan şekeri profilleri, perinatal sonuçlar ve maternal komplikasyonlar yönünden kendi aralarında değerlendirildi.

Bulgular: AGTT görülme sıklığı % 17,42 olarak bulunurken, GDM görülme sıklığı % 14,57 olarak bulundu. Gebelik öncesi ve 50 gram GTT sırasındaki vücut kitle indeksi (VKİ) yönünden karşılaştırıldığında, AGTT grubunda, normal gruba göre yüksek bulundu ($p<0,05$). AGTT grubunun 24 saatlik ve postpartum ilk 24 saatlik kan şekeri profilleri normal grupla karşılaştırıldığında yüksek bulundu ($p<0.05$). Bu değerler GDM grubunda da AGTT grubuna göre yüksek bulundu ($p<0.05$).

Sonuç: AGTT grubunun GDM grubuna göre daha hafif şiddette, ancak normal grup ile karşılaştırıldığında anlamlı kabul edilecek kadar daha şiddetli glukoz intoleransına sahip olduğu görülmüştür. Bu nedenle AGTT saptanan gebelerin de GDM saptanan gebeler gibi yakın takibinin ve gerektiğinde tedavi edilmesinin gerek fetal komplikasyonlar, gerekse maternal komplikasyonların önlenmesi yönünden yararlı olacağı düşünülmektedir.

Anahtar kelimeler: Anormal glukoz tarama testi, gestasyonel diyabet, gebelik

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Introduction

If diabetes is detected before pregnancy it is referred to as pregestastional diabetes mellitus (PGDM) and if it is detected during pregnancy for the first time, it is called gestational diabetes mellitus (GDM).

The prevalence of the disease varies according to race and region where it is more common in Central and South America and the Far East compared to the West.[1]

GDM is an important clinical condition that affects both the mother and the fetus. The risks for the mother include complications such as polyhydramnios, birth trauma, increase in the cesarean delivery rates, pregnancy-induced hypertension, preterm labor and pyelonephritis and the risks for the fetus include neonatal complications such as macrosomia and associated shoulder dystocia, birth trauma, hyperinsulinemia-induced hypoglycemia, respiratory distress syndrome, hyperbilurubinemia, polycythemia, and cardiomyopathy. [2]

Before pregnancy occurs, there has already been a deficiency of insulin receptor or weight gain localized to abdomen in 90% of women with gestational diabetes. There also has been insulin deficiency in 10% of the pregnant women and these women are candidates for insulin-dependent diabetes after pregnancy. The risk for developing diabetes 5-10 years after the pregnancy is 10% for normal pregnancies whereas this ratio is 30% in women with GDM.[3]

Which group of pregnant women should be screened is still controversial. American Diabetes Association (ADA) suggests that screening should be done in high risk patients, whereas American College of Obstetricians and Gynecologists (ACOG) suggests screening of all pregnant women.[4,5] The diagnosis of GDM is made by one or two-step tests. One step approach includes a two hour glucose tolerance test with 75 grams of glucose. World Health Organization (WHO) recommends this one step oral glucose tolerance test. Similarly, in the multicenter prospective HAPO (Hyperglycemia and Adverse Pregnancy Outcomes) study which was published in 2008, a significant relationship between maternal hyperglycemia and fetal macrosomia, hyperinsulinemia, neonatal hypoglycemia, and section has been reported.[6] Therefore, screening of all pregnant women for GDM with one step Oral Glucose Tolerance Test (OGTT) with 75g glucose between 24th and 28th weeks was recommended in compliance with the recommendations of International Association of Diabetes and Pregnancy Study Groups (IADPSG). However, ACOG does not recommend the IADPSG criteria, suggesting that there is no concrete data implicating efficacy either for mother or baby and it would precipitate more diagnosis of GDM, which would increase healthcare costs. ADA has been recommending two-step testing until 2010, and begun recommending one-step testing after 2010. However, by 2015 due to the lack of consensus, ADA has begun recommending the use of either approach.[6] Nevertheless, which screening test in pregnancy should be performed is still under debate.

The two-step approach includes using 50 grams of oral glucose for the first step, which is referred as the glucose challenge test (GCT), and using 100 grams at the second step, which is referred as the OGTT.[7,8] American Diabetes Association (ADA) recommends screening only high-risk patients, whereas American College of Obstetricians and Gynecologists (ACOG) recommends screening all pregnant women.[4,5] Currently, the clinical significance of abnormal OGTT (abnormal glucose challenge test, AGCT) in pregnant women with normal GTT is still unknown. Several studies have referred these cases as "borderline glucose intolerance" [9] or "mild gestational diabetes".[10,11]

The purpose of the challenge tests in pregnancy is not to diagnose, rather to identify groups at risk. However, there is no consensus whether diabetes screening is necessary in pregnancy or not, also if all pregnant women or only the ones at risk should be screened. Also, the screening methods to be utilized are still up for debate. Currently, the most accepted approach is a risk assessment at the first prenatal visit and adopting an appropriate screening approach according to the risks identified.[12]

Given the increase in fetal and maternal morbidity in these pregnancies, prenatal screening becomes a salient issue. These patients are at greater risk for certain complications compared to normal pregnant women and the understanding of these complications will be very useful in the treatment these patients.

Our aim in this study is to investigate the antenatal and postnatal blood glucose profiles and perinatal outcomes in pregnant women with a normal GCT, an abnormal OGTT in 50-gram glucose testing and a normal OGTT in 100-gram testing, and the ones with GDM, and to contribute to the follow up of pregnant women with an abnormal GTT in 50-gram glucose testing but a normal OGTT in 100-gram testing.

Materials and Methods

Study Protocol

A total of 700 pregnant women between 24th and 28th weeks of pregnancy who admitted to Inonu University School of Medicine Turgut Ozal Medical Center Pregnant Outpatient Clinic and to whom regular follow-up and delivery were conducted at our hospital, were included in the study. The study was performed using data from 300 pregnant women after the exclusion of women with multiple pregnancies, known diabetes, a history of GDM or macrosomic fetus in the previous pregnancy, intrauterine ex fetus, history of gestational or chronic hypertension. Women who left the follow up or delivered in another center and those who required insulin immediately after the delivery were also excluded.

The study protocol was approved by the local ethical committee. All patients were explained the procedure by the clinician (B.K.) and the patients' informed consents were obtained.

The gestational age was defined by ultrasonography performed before the 20th week of the pregnancy. Age of the patient, gravida, parity, abortion and the number of living children, history of GDM or macrosomic fetus in previous pregnancies, and history of chronic diseases were recorded. Regarding gravida, first pregnancy was accepted as nulliparous, number of pregnancies between 2 and 4 as multiparous and the number of pregnancies more than four was accepted as grandmultiparous. Body Mass Index

(BMI) for each patient was calculated using the formula below before the pregnancy and during the 50-gram GTT.

In our study, 50-gram GCT was performed as a routine antenatal screening for all pregnant women. 50 grams of powder glucose dissolved in 250 cc of water was given to the patients regardless of the fasting or post-prandial state. Serum glucose levels were measured on the blood withdrawn from antecubital vein, one hour after drinking the solution. The threshold value was set as 140 mg / dl (7.8 mmol / L). The values equal or greater than 140 mg / dL were considered positive. The pregnant women whose GCT results were positive were given a 100-gram OGTT after 8-14 hours of fasting following a three day standard diet containing at least 250 grams of carbohydrates per day. Prior to the test, antecubital venous blood samples were collected from each woman and fasting serum glucose levels were measured. Following the 100 gram glucose intake, blood samples were collected to measure the glucose levels at the first, second, and third hours. The measured values were evaluated according to the criteria utilized by Carpenter and Coustan (95 mg / dL, 180 mg / dL, 155 mg / dL, 140 mg / dL) and the women with two or more abnormally high values were identified as GDM. In addition the women with 50-gram GCT levels above 200 mg/dL were also considered GDM. Plasma glucose levels were measured by using Olympus auto analyser hexokinase method (Olympus Diagnostica GmbH-Irish Branch-Lismeeh). The pregnant women were allocated into three groups according to the GCT and OGTT results. Group 1 (n = 100), which was referred to as normal group and included those with normal GTT results. Group 2 (n = 100) included those with an Abnormal Glucose Challenge Test (AGCT) with a high GCT, but normal OGTT result. Finally, Group 3 (n = 100), which was referred to as GDM group, included those with both GCT and OGTT results higher than normal values.

Group 1 did not receive any treatment. The women in Group 2 and Group 3 were given an appropriate diet according to their ideal weight before pregnancy. The diet consisted of three main meals and three snacks providing 25-35 kcal / kg / day. Fasting and postprandial second hour serum glucose levels in all three groups were measured and recorded eight times a day (at 07:00, 09:00, 13:00, 15:00 19:00, 21:00, 24:00, and 03:00 hours, respectively) before implementing any diet, exercise or (if necessary) insulin therapy.

Pre-treatment blood glucose profiles of all groups were calculated by using the average of these values. The same process was repeated in the first 24 hours after birth in order to calculate postpartum blood glucose profile.

Insulin treatment was initiated on those whose fasting blood glucose levels were above 95 mg/dL (5.3 mmol/L) and above 120 mg/dl (6.7 mmol/L) 2-hour postprandial despite proper diet and exercise. Fast-acting insulin (Insulin Lispro) prior to three main meals and a dose of NPH before bedtime was the choice of insulin regimen.

All three groups were educated for proper diet, exercise, capillary blood glucose measurement and symptoms of hypoglycemia by a team consisting of an obstetrician, endocrinologist, nutritionist, and a specialized nurse. All women were provided with capillary blood glucose measuring device to measure capillary blood glucose at home. The aim of the treatment was to maintain fasting blood glucose level below 95 mg/dL and two hour postprandial blood glucose level below 120 mg/dL. Again, it was

intended to maintain the average blood glucose level above 60 mg/dL (3.3 mmol/L) and an average level of 100 mg/dl (5.5 mmol/L).

Fetal health was evaluated by clinical follow-up including the non-stress test (NST) and detailed ultrasound measurements to estimate fetal weight, and evaluate for polyhydramnios, and other anomalies. All women were followed up between the 24th week (onset of the study) and 40th week for any anomalies using physical examination, ultrasonography and NST. Elective cesarean section (CS) was planned for women when an appropriate indication existed, i.e. history of prior CS or fetal macrosomia. Macrosomia induced CS, perineal laceration, and preeclampsia were identified as maternal complications.

Intrapartum electronic fetal monitoring was applied to all women during labor. Birth weight, 5th minute Apgar scores, umblical artery blood pH and base deficit, blood glucose levels and indications for neonatal intensive care unit (NICU) hospitalization were evaluated and recorded for each newborn. Newborns with birth weight of 4000 g and above were accepted as macrosomic. Fifth minute Apgar score <7, umbilical artery blood pH ≤ 7.10 and base deficit value ≤ -12 were considered as fetal hypoxia. Blood glucose levels of all neonates were recorded at the 1st, 2nd, and 4th hours as well as cord blood glucose. Neonatal hypoglycemia was defined as two consecutive blood glucose value of ≤ 35 mg/dL.

Statistical Evaluation

The analyses of the data were performed by using SPSS 13.0 (Chicago, IL, USA). Data were expressed as the mean ± standard deviation (SD), percentage (%), median (percentile 25–75), and 95% confidence interval (CI, min to max), where appropriate. The test of normality for continuous variable was tested by Shapiro-Wilk test. Groups were compared with Mann–Whitney U-tests for non-parametric continuous variables or Student's t-tests for parametric continuous variables. Chi-square tests and Fisher's exact tests (if n≤5) were employed for dichotomous variables. A *P*-value <0.05 was considered significant.

Results

There were no significant differences between the groups in terms of age (p=0.226). The study group included a total of 300 pregnant women; each of the groups included 100 pregnant women that meet all the criteria.

In group 1, 32 (32%) pregnant women were nulliparous, 56 (56%) were multiparous and 12 (12%) were grandmultiparous. 29 (29%) pregnant women in group 2 were nulliparous, while 57 (57%) were multiparous and 14 (14%) were grandmultiparous. Finally, group 3 included 24 (24%) pregnant women were nulliparous, 59 (59%) were multiparous and 17 (17%) were grandmultiparous. There were no statistically significant differences between the groups in terms of gravida (p> 0.05). Demographic data of the patients are shown in Table 1.

The BMI values before pregnancy and after 50-gram GCT were compared between all three groups. Regarding average pre-pregnancy BMI values, we found significant differences between groups 1 and 2 and groups 1 and 3 (p<0.001 and p<0.001, respectively), while no statistically significant difference was observed between group 2 and group 3 (p=0.303). Regarding average BMI values during 50-gram GCT, the

differences between groups 1 and 2 and groups 1 and 3 were statistically significant (p<0.001 and p<0.001 respectively), however there was no significant difference between groups 2 and 3 (p=0.948). The distribution of average BMI values of in all groups before pregnancy and during 50-gram GCT are shown in table 2 (mean ± standard deviation, minimum-maximum).

Table 1. Demographical characteristics parameters of the groups

Demographical parameters	**Group 1 (Normal)**	**Group 2 (AGCT)**	**Group 3 (GDM)**
Age* (mean±SD)	28.02±5.29	29.41±4.90	29.41±5.14
Gravida (n)			
Nulliparous (85)	32	29	24
Multiparous (172)	56	57	59
Grandmultiparous (43)	12	14	17
Parity (median (min-max))	3 (0-7)	3 (0-6)	3 (0-5)
Abortion(median (min-max))	0 (0-2)	0 (0-2)	1 (0-3)
Live birth(median (min-max))	3 (0-6)	3 (0-6)	2 (0-5)

*Group 1-2: p> 0.05, Group 1-3: p>0.05, Group 2-3: p>0.05, AGCT: Abnormal Glucose Challenge Test, GDM: Gestational Diabetes Mellitus, SD: standard deviation.

The average insulin values at first hour after GCT were statistically significant between groups 1 and 3 (p<0.001), whereas we found difference between groups 1 and 2 (p=0.018), and groups 2 and 3 (p=0.151).

Table 2. Distribution of mean BMI values before pregnancy and at the time of 50 g GTT

BMI	**Group 1 (Normal)**	**Group 2 (AGCT)**	**Group 3 (GDM)**
Before pregnancy*	22.82±2.05 (19-27)	24.58±3.02 (20-32)	**24.98±3.18 (21-33)**
During GTT**	**24.58±2.38 (21-29)**	**28.83±3.56 (23-37)**	**28.87±3.70 (23-39)**

*Group 1-2: p< 0.05, Group 1-3: p< 0.05, Group 2-3: p> 0.05, **Group 1-2: p< 0.05, Group 1-3: p<0.05, Group 2-3: p> 0.05, BMI: Body Mass Index, GTT: Glucose Tolerance Test, AGCT: Abnormal Glucose Challenge Test, GDM: Gestational Diabetes Mellitus

In the comparison of groups1 and 2 for average blood glucose values after 100-gram OGTT, statistically significant differences were observed at all hours of measurements (for fasting p<0.001, for the first hour p<0.001, for the second hour p<0.001, and for the third hour p<0.002). However, the differences between the two groups in terms of insulin levels [for fasting (p=0.121), for the first hour (p=0.997), for the second hour (p=0.207), and for the third hour (p=0.205)] were not statistically significant (Table 3).

Table 3. Distribution of the average value of serum glucose and insulin obtained in 100 g OGTT

100 g OGTT	**Group 2 (AGCT)**	**Group 3 (GDM)**
pre-prandial serum glucose (mg/dl)*	82.49±6.74 (69-94)	92.44±10.85 (70-126)
1st h serum glucose (mg/dl)*	166.45±23.53 (103-179)	205.25±21.02 (165-245)
2nd h serum glucose (mg/dl)*	133.63±19.16 (82-154)	172.66±29.25 (111-239)
3rd h serum glucose (mg/dl)*	107.03±25.95 (50-139)	125.66±29.70 (69-186)
Fasting insulin**	8.21±22.80 (2-101)	10.10±5,.87 (2-27,70)
1st insulin**	69.42±42.46 (18,50-216)	71.45±25.36 (33.10-120.40)
2nd insulin**	66.32±43.59 (14,2-300)	77.47±36.09 (29.20-173)
3rd insulin**	41.61±38.50 (5.62-225)	51.39±30.71 (13.60-170)

*Group 2-3: p< 0.05, **Group 2-3: p> 0.05 OGTT: Oral Glucose Tolerance Test, AGCT: Abnormal Glucose Challenge Test, GDM: Gestational Diabetes Mellitus

When we compared all three groups for average value of 24-hour blood glucose profiles, we found statistically significant differences between groups 1 and 2 and groups 1 and 3 at all intervals of measurement. The p values for the comparisons between groups 1 and 2 were 0.001 at 07:00 hours, 0.001 at 09:00 hours, 0.001 at 13:00 hours, 0.002 at 15:00 hours, 0.001 at 19:00 hours, 0.001 at 21:00 hours, 0.001 at 24:00 hours, and 0.002 at 03:00 hours, respectively. The p values for the comparisons between groups 1 and 3 were 0.001 at 07:00 hours, 0.001 at 09:00 hours, 0.001 at 13:00 hours, 0.002 at 15:00 hours, 0.001 at 19:00 hours, 0.001 at 21:00 hours, 0.001 at 24:00 hours, and 0.002 at 03:00 hours, respectively. The p values for the comparisons between groups 2 and 3 were 0.01 at 07:00 hours, 0.03 at 09:00 hours, 0.01 at 13:00 hours, 0.02 at 15:00 hours, 0.01 at 19:00 hours, 0.01 at 21:00 hours, 0.04 at24:00 hoursand 0.02 at 03:00 hours respectively.

Our results showed that; when we compared all three groups for average postpartum blood glucose profiles at all measurement points during the first 24-hour period, the differences were statistically significant. The p values for the comparisons between groups 1 and 2 were 0.002 at 07:00 hours, 0.001 at 09:00 hours, 0.002 at 13:00 hours, 0.001 at 15:00 hours, 0.001 at 19:00 hours, 0.001 at 21:00 hours, 0.002 at 24:00 hours, and 0.003 at 03:00 hours respectively. The p values for the comparisons between groups 1 and 3 were 0.001 at 07:00 hours, 0.002 at 09:00 hours, 0.001 at 13:00 hours, 0.001 at 15:00 hours, 0.002 at 19:00 hours, 0.001 at 21:00 hours, 0.003 at 24:00 hours, and 0.002 at 03:00 hours respectively. The p values for the comparisons between groups 2 and 3 were 0.01 at 07:00 hours, 0.03 at 09:00 hours, 0.02 at 13:00 hours, 0.01 at 15:00 hours, 0.02 at 19:00 hours, 0.01 at 21:00 hours, 0.03 at 24:00 hours, and 0.01 at 03:00 hours, respectively.

Fetal hypoxia was evaluated on each neonate and none had fetal hypoxia who were born to Groups 1 and 2. However, a 5-minute APGAR score was calculated five in one neonate (1%) who was born to a mother in group 3 and was considered to have fetal hypoxia.

The average blood glucose values measured on the cord blood for each newborn showed statistically significant differences when compared among three groups (p=0.006 between groups 1 and 2, p=0.004 between groups 1 and 3, and p=0.003 between groups 2 and 3, respectively). Our results also revealed statistically significant differences between the groups for the blood glucose levels of the neonates at the first hour (p=0.005 between groups 1 and 2, p=0.003 between groups 1 and 3, and p= 0.02 between groups 2 and 3, respectively), the second hour (p=0.004 between groups 1 and 2, p=0.002 between groups 1 and 3, and p=0.02 between groups 2 and 3, respectively), and the fourth hour (p=0.007 between groups 1 and 2, p= 0.004 between groups 1 and 3, and p= 0.01 between groups 2 and 3, respectively) (Table 4).

Table 4. The distribution of the average blood glucose value of newborns

Serum Glucose*	**Group 1 (Normal)**	**Group 2 (AGCT)**	**Group 3 (GDM)**
Cord.	68.00±6.76 (58-81)	63.85±9.48 (41-91)	60.88±9.78 (43-87)
1. hour	66.00±7.13 (54-78)	60.75±10.50 (49-74)	57.34±11.45 (39-83)
2. hour	71.25±5.62 (60-87)	65.35±8.15 (52-93)	62.50±8.35 (48-90)
4. hour	72.50±5.04 (63-97)	66.50±7.45 (55-95)	61.79±8.78 (44-91)

*Grup 1-2: p< 0,05, Grup 1-3: p< 0,05, Grup 2-3: p< 0,05. AGCT: Abnormal Glucose Challenge Test, GDM: Gestational Diabetes Mellitus

Twelve (12%) neonates born to the women in group 1, ten (10%) neonates in group 2, and fifteen (15%) neonates in group 3 were admitted to NICU due to hyperbilirubinemia. Three neonates (3%) of the group 3 mothers were diagnosed with transient tachypnea of the newborn (TTN) and admitted NICU, whereas no TTN was observed in any other groups. The single neonate (1%) with Respiratory Distress Syndrome (RDS) was born to a mother in group 3 and was also admitted to the NICU.

No statistically significant differences found between the groups in terms of average birth weights of the neonates (p=0.850 between groups 1 and 2, p=0.770 between groups 1 and3, and p=0.729 for groups 2 and 3, respectively). Macrosomia was detected in three (3%) neonates in group 3, which lead to a CS, whereas no macrosomia was observed in the other groups. Preeclampsia developed in one (1%) woman in group 3.

Discussion

Whether diabetes screening should be required in pregnancy, whether it should be applied to all pregnant women or only to those in the risk group and screening methods are still under debate. However, the most accepted and most applied method in our state is the two-step approach. The first step of this approach includes GCT with 50-gram of glucose which is applied to all pregnant women between the 24^{th} and 28^{th} weeks, and OGTT with 100-gram of glucose which is applied to those with positive results after the first step. Considering the positive 50-gram GCT but a normal 100-gram OGTT in pregnant women is accepted as normal glucose tolerance, and exclusion from the follow up for gestational diabetes is generally accepted worldwide. Only a few studies refer to this condition as “borderline glucose intolerance," or "mild gestational

diabetes".[9,10,11] There are no sufficient data addressing how to follow up this group and perinatal outcomes.

In our study, the average age was 25 and there were no significant differences between the three groups in terms of age. Both ADA [13] and ACOG [14] recommend 25 years as the age limit for selective screening. Studies conducted under this age are reported low sensitivity to detect GDM. Danilenko et al. [15] studied 18.834 pregnant women 3.683 of whom were applied OGTT and the results showed that GDM rate in women under 25 years old was 12.7%. Similarly, a study by Solomon at al. [16] included 14.613 pregnant women and all were above 25 years of age. Weijers et al. [17] showed that advanced age disrupted the carbohydrate metabolism. However, in our study we have not found any difference between the pregnant women in the normal group and those in GDM and AGTT in terms of age. Therefore, we concluded that age is not a factor which increases the glucose intolerance alone.

In the current study, we evaluated BMI before pregnancy and during 50-gram GCT. The average BMI of the AGTT and GDM groups were significantly higher both before pregnancy and during 50-gram GCT when compared to the normal group, whereas we observed no difference between the GDM group and AGTT group. It is well known that insulin resistance is more pronounced and an increased BMI affects this process adversely during the normal pregnancy process. One of the main factors is the increase in adipose tissue. In the current study, we found that severity of glucose intolerance correlates with increased BMI. Therefore we concluded that an increased BMI is an important factor for the severity of glucose intolerance. Several studies performed by Buchanan et al.[18], Metzger et al.[13] and Morissette AS et al.[19] demonstrated that a high BMI is a risk factor for GDM. However, Riskin-Mashiah et al.[20] conducted a multivariate analysis in their study and found a significant relationship only between pre-pregnancy BMI and maternal hypererglisemia. They also reported that the prevalence of GDM in normal pregnant women was 2.3% and it was 10.7% in obese women. Alanbayat al.[21] compared healthy pregnants with patients with GDM in terms of BMI in their study, but they did not find a difference between these two groups and concluded that BMI was not a risk factor for GDM.

The prevalence of GDM varies between 1% and 14% in various communities. In our country the prevalence of GDM is reported to be between 1.23% and 6.6%.[22,23] In our study the prevalence of GDM was found to be 14.57% which we attribute this discordance to the fact that our institution is a reference hospital. We found the prevalence of AGCT to be 17.42%. We have not been able to make comparisons due to the lack of sufficient data published in the literature.

The threshold value for one hour GCT has been accepted as 140 mg / dL. Although there are several studies suggesting to scan all pregnant women with 50-gram GCT and accepting a one hour threshold of higher than 140 mg / dL in order not to reduce sensitivity;[24,25] the general consensus reached by many studies is that; with a lower threshold point the sensitivity of the screening test increases, but the specificity decreases.

In the comparison of the average one-hour serum glucose and insulin levels after 50-gram GCT among normal, AGCT and GDM groups, serum glucose and insulin levels of AGCT and GDM groups were found to be higher than the normal group. On the other

hand, in the comparison of GDM group with AGCT group, we found significant differences between the serum glucose levels, whereas we found no significant difference in terms of insulin levels. In the comparison of fasting, first, second, and third hours' serum glucose and insulin levels between AGCT and GDM groups after 100-gram OGTT, we found significant differences in terms of serum glucose levels at all measurement points, whereas there were no significant differences between insulin levels.

In the light of these findings, we concluded that the AGCT group have less severe glucose intolerance than the GDM group, but significantly more severe than the normal group. Considering that there were no differences between the AGCT and GDM groups in terms of insulin levels, we concluded that insulin resistance of the AGCT group is almost as severe as the GDM group. In the literature, there are several studies indicating that the pregnant women with GDM tend to have chronic insulin resistance.[7,26,27] Again, it has been suggested in some studies that insulin resistance plays a role in the pathogenesis of GDM rather than beta-cell dysfunction or decreased levels.[28,29] Our findings also support this hypothesis.

Diet and exercise were planned for pregnant women in the AGCT and GDM groups as a first line therapy. In accordance with the predetermined follow up criteria, the pregnant women requiring insulin therapy have been treated with insulin. Regarding 24-hour blood glucose profiles, we found significant differences between the average values of the pregnant women when the three groups were compared. Similarly, we found significant differences between the groups, in terms of postpartum first 24 hour's average blood glucose levels.

Regarding these statistical results, given that pregnant women with GDM demonstrate significant glucose intolerance, the difference between the GDM group and normal group is an expected result, and again the difference between the AGTT group and GDM group is also not surprising. The real striking result is the difference between the AGCT group and the GDM group. Given that it is widely accepted pregnant women with AGCT are considered to hava a normal glucose tolerance, it is expected that there would be no difference between the normal group and the AGCT group. However, in our study, we observed that the AGCT group, which was generally accepted as normal worldwide, has not been included in any of the classifications and no there are no treatment recommendations. In the light of these findings, we concluded that the AGCT group had relatively less severe glucose intolerance than the GDM group; but had significantly more prominent glucose intolerance than the normal group. In order to evaluate the severity of glucose intolerance, evaluating postpartum blood glucose profile would be more appropriate, as the 24-hour blood glucose profile may reflect the pretreatment values. In order to demonstrate the glucose intolerance of the AGCT group, it is important to show that the pregnant women in the AGCT group, who haven't been given any treatment or follow-up regimen, had higher blood glucose profiles than the normal group and levels were closer to upper limits, despite we have given them diet and exercise during our follow-up period. It can be suggested that if they were not given diet and exercise, the pregnant women in the AGCT group would have similar or higher glucose intolerance when compared to the GDM group. The results showing differences of post partum blood glucose levels among the three

groups suggest that glucose intolerance does not improve immediately in the first 24 hours and maintains the prenatal value.

Our results showed that none of the neonates in the AGCT group had an APGAR score below seven. Where only one (1%) neonate had an APGAR score below seven in the GDM group and one in the GDM group of newborns below seven was found. This low rate of fetal hypoxia may be attributed to regular monitoring during pregnancy and choosing the correct method of delivery. The low score of the neonate in the GDM group was a result of the premature delivery due to developing preeclampsia which was an additional complication.

In the literature, incidence of neonatal hypoglycemia in neonates given birth by pregnant women with GDM, has been reported to be 9%.[30] In our study, we did not detect neonatal hypoglycemia in any of the neonates. We found differences between the groups in terms of the four blood glucose levels measured at three different times. Based on these findings, we suggest that the glucose intolerance developing in the mother affects the infant, and the infant tends to have hypoglycemia depending on the severity of maternal glucose intolerance. We concluded that effective control of blood glucose during pregnancy and delivery is a very important factor for preventing neonatal hypoglycemia.

When the neonates in all three groups were evaluated according to the indications for hospitalization in the NICU, 12 (12%) neonates in the normal group of pregnant women, ten (10%) in the AGCT group, and 15 (15%) in the GDM group were hospitalized in the NICU due to hyperbilirubinemia. In the literature, the incidence of hyperbilirubinemia in neonates who were delivered by mothers with GDM is reported to be 29%.[30] In our study, this rate was found to be 15%.

None of the neonates in the Normal and AGCT groups were diagnosed with TTN whereas the three (3%) neonates in the GDM group were admitted to NICU due to TTN. The rate of TTN in the babies who were born to mothers with GDM was found to be 3% in our study, near to 2% reported in the literature.[30]

None of the neonates in the normal and AGCT groups were diagnosed with RDS, except one (1%), who was delivered prematurely at the 30th week due to preeclampsia. However, RDS development in this neonate was thought to be due to prematurity rather than GDM. In the literature,[30] the rate of RDS in neonates born to pregnant women with GDM has been reported to be 3%. In our study, this rate was 1%.

No macrosomia was observed in any of the neonates in the normal and AGCT groups, however macrosomia was found in three neonates born to pregnant women in the GDM group (3%). No differences were observed between these three neonates in terms of birth weight. Based on these findings, we suggest that ensuring effective blood glucose control during pregnancy is one of the most important factors in preventing macrosomia. The risk for the babies of the mothers with GDM is always higher due to additional factors, even though effective blood glucose control is ensured.

Buchanan et al.[31] showed that the rate of macrosomia decreased from 18% to 7%, when insulin is added to the treatment where desired blood glucose levels could not be maintained, despite strict diet and exercise. In GDM patients who received no treatment, the incidence of macrosomia has been reported to be 25%. In our study, we

found that six neonates in the AGCT group were near the border of macrosomia (> 3800 gr), which is a significant result suggesting that the treatment with diet and exercise can prevent macrosomia in this group. Many studies reported GDM as a high risk for macrosomia,[32,33] whereas some authors suggested increased maternal BMI, namely, the gained weight during pregnancy, rather than maternal hyperglycemia as the cause macrosomia. [33,34] On the other hand, Alanbay et al.[21] compared healthy pregnant women and those with GDM and found no relation between the pre-pregnancy BMI or weight gaining during pregnancy and macrosomia. These results indicate that the relationship between macrosomia and maternal hyperglycemia is still unclear.

The increase risk of cesarean section and perineal lacerations due to macrosomia and development of preeclampsia have been reported to be significant birth complications in pregnant women with GDM.[35,36] In our study, we also found significant differences between the GDM group and the normal and AGCT groups in terms of the rate of cesarean section due to macrosomia.

Increased risk of preeclampsia as a result of insulin resistance is another complication in pregnant women with GDM. In our study, preeclampsia developed in one (1%) pregnant woman in the GDM group. We suggest that this low rate of preeclampsia is a result of effective treatment that prevented hyperglycemia and associated insulin resistance, which are the most predisposing factors for preeclampsia.

Perineal lacerations, which occur due to macrosomia during delivery, were not observed in our study since there were no macrosomic babies in normal and AGCT groups. The babies with weight reaching up to the limit of macrosomia were delivered by cesarean section because either the mother had a prior CS or it had already been planned due to macrosomia in the GDM group.

The results of this study indicate that the pregnant women in the AGCT group, who are widely accepted to be normal, therefore not included in any classification or given any treatment regimen as they have less severe glucose intolerance when compared to the GDM group, had more severe glucose intolerance than the normal group.

We suggest that the pregnant women with AGCT should be followed up closely and treated when necessary, similar to GDM, in order to prevent fetal and maternal complications. The incidence of DM has been increasing gradually and the babies of these mothers with gestational glucose intolerance are known to have a greater risk of developing DM in the long term. In conclusion, screening larger numbers of pregnant women for varying degrees of glucose intolerance during pregnancy increases the chance of providing proper management and thus preventing fearsome complications. Larger scale studies including long-term follow-ups of pregnant women during and after pregnancy as well as their babies are warranted to develop effective management of the pregnant women with AGCT.

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