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ABNORMAL GLUCOSE CHALLENGE TEST AND MILD GESTATIONAL DIABETES

ABNORMALNI TEST OPTEREĆENJA GLUKOZOM I BLAGI GESTACIJSKI DIJABETES

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Original paper

Key words: 50 g glucose challenge test, glucose tolerance test, mild gestational diabetes, gestational diabetes, insulin levels, pregnancy

SUMMARY. ***Objective.*** The status of carbohydrate metabolism of pregnant women with positive glucose challenge test (GCT), but normal oral glucose tolerance test (OGTT) and their neonates are not defined clearly. ***Study Design.*** Pregnant women with normal GCT (n: 120), with abnormal glucose challenge test (AGCT) but normal OGTT (n: 67) and with gestational diabetes (GDM, n: 67) were included into the study. Insulin sensitivity was evaluated by fasting insulin level, homeostasis model assessment of insulin resistance index (HOMA-IR); quantitative insulin check index (QUICKI) and IS_{OGTT}. Serum insulin and glucose values during OGTT were documented. Perinatal outcome and delivery modalities were compared. ***Results.*** Both GDM (31.6±5.9 yrs) and AGCT groups (29.0±4.0 yrs) were older than controls (28.1±4.9 yrs). Body mass index (BMI) was the predominant factor affecting both AGCT and GDM groups (OR: 3.78 and 5.97 respectively). Despite there was no significance between insulin indices; serum glucose and insulin values were similarly different; macrosomic infant and caesarean section rates were higher than controls in both GDM and AGCT groups in favor of gestational diabetics (6.6% vs. 18.9%; p=0.0001 and 20% vs. 27.7% p=0.0001 respectively). ***Conclusion.*** Pregnant woman with abnormal glucose challenge test have impaired carbohydrate metabolism as in gestational diabetics with a lesser severe degree.

Izvorni članak

Ključne riječi: 50 g test probira glukozom, test opterećenja glukozom, blagi gestacijski dijabetes, gestacijski dijabetes, razina inzulina, trudnoća

SAŽETAK. ***Cilj istraživanja.*** Stanje metabolizma ugljikohidrata u trudnica s pozitivnim testom probira (glucose challenge test – GCT), a normalnim testom opterećenja glukozom (OGTT) te njihove novorođenčadi, nije jasno definirano. ***Način istraživanja.*** U studiju su uključene trudnice s normalnim GCT-om (n: 120), s abnormalnim GCT-om ali normalnim OGTT-om (n:67 te trudnice s gestacijskim dijabetesom (n: 67). Insulinska osjetljivost je vrednovana jutarnjiom vrijednošću insulina, modelom prosudbe homeostaze indeksom rezistencije na inzulin (HOMA-IR), kvantitativnim indeksom provjere insulina (QUICKI) i IS_{OGTT}-om. Vrijednosti serumske glukoze i inzulina su analizirane. Uspoređen je perinatalni ishod i način poroda. ***Rezultati.*** Trudnice s GDM (31,6±5,9 godina) i one s AGCT (29,0±4,0 godina) su bile starije dobi od kontrolnih trudnica (28,1±4,9 godina). Indeks tjelesne težine (BMI) je bio presudni čimbenik u skupini s AGCT i GDM (OR: 3,78 odnosno 5,97). Unatoč tome nije bilo značajnosti među inzuilinskim indeksima; serumske vrijednosti glukoze i inzulina su bile slično različite; makrosomna djeca i stopa carskih rezova su u trudnica s AGCT i OGTT bile češće, posebice u trudnica s GDM (6,6% prama 18,9%, p = 0,0001; 20% prama 27,7%, p = 0,0001). ***Zaključak.*** Trudnice s abnormalnim testom probira na glukozu (AGCT) imaju poremećaj metabolizma ugljikohidrata kao i trudnice s gestacijskim dijabetesom (GDM), ali u nešto manjoj mjeri.

Introduction

It is well documented that the pregnancy is the insulin resistant state which can be tolerated by most of the women with normal glucose metabolism. However, some pregnant women experience carbohydrate intolerance with various degrees during their pregnancies. Although the certain mechanism of this pregnancy dependent carbohydrate intolerance has not been well known yet, excessive insulin resistance, which means reduced insulin response to carbohydrates or low insulin sensitivity and beta cell dysfunction are the common characteristics of the subjects. Diagnostic methods of this heterogeneous group of pregnant women are also under debate. Gestational diabetes mellitus (GDM) affects the 1 to 14 percent of the pregnancies according to the diagnostic test which was preformed by their physician.[1,2] Today, one-step and two-step approaches are the common tests for the detection of gestational diabetes.[3] The 50-g, 1-hour oral glucose challenge test (GCT), fol-

lowed by 100-g, 3-hour oral glucose tolerance test (OGTT) as the two-step approach, has gained widespread acceptance as a universal screening tool for GDM.[4] At present, the status of carbohydrate metabolism of pregnant women with high glucose levels, which exceeds the critical threshold value of GCT, but normal 100-g, 3-hour OGTT have not been evaluated clearly yet. In few studies the group of pregnants with positive GCT but normal OGTT has been described as either »borderline glucose intolerance«[5] or »mild gestational hyperglycemia«[6,7] Also some other studies focused on minor degrees of glucose intolerance which is not well defined with either »National Diabetes Data Group« or Carpenter and Coustan's criteria. Despite the increment of perinatal adverse outcomes were pointed out in these studies, a common treatment strategy to this group of pregnant women has not been defined yet. Current approach is to leave them untreated unless their blood glucose levels exceed defined cut-off values. The ideal threshold value for the GCT has also not been identified yet. Sensitivity of the test totally depends on the threshold value. Detection rate of GDM will be 99% and 80% with serum glucose values of 135 mg/dL and 140 mg/dL respectively.[8] In any case maternal and fetal, long and short-term adverse effects are the major concern for the early detection and the treatment of carbohydrate intolerance in pregnancy.[9,10]

Some mathematical relations between fasting insulin and glucose values are widely used to simplify the evaluation of the abnormality of carbohydrate metabolism during pregnancy. Homeostasis model of assessment of insulin resistance index (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) are simple and widely used formulations to evaluate the insulin resistance/sensitivity in pregnancy. Also IS_{OGTT} has been reported to estimate insulin sensitivity in pregnancy better than fasting glucose and insulin values.[11–13]

The aim of this study is to evaluate the carbohydrate intolerance and fetal outcomes in pregnant subjects with abnormal GCT and normal OGTT in Turkish population; by using insulin indexes and the insulin and glucose values during OGTT.

Materials and methods

This clinical trial was conducted at the Obstetrics and Gynecology Department at Inonu University between January 2005 and January 2006. The study was approved by the local ethical committee and the written informed consent was obtained from each subject.

Study subjects

Two hundred fifty-four pregnant subjects were selected from 441 pregnant women attended to the outpatient clinic between 24 and 28 weeks of gestation. The study population consisted of Turkish women living in Eastern Region of Turkey. Singleton and uncomplicated pregnancies with body mass index <30 kg/m^2 were included into the study. The control group was randomly selected from pregnant women with normal glucose challenge test. Gestational age was based on last menstrual period and according to a reliable menstrual history confirmed by ultrasonography before 20 weeks of gestation.

All the pregnant women underwent 50-g glucose challenge test as our routine antenatal screening protocol. Fifty grams of glucose was administered orally regardless of the time of the day or the fasting state. Venous plasma glucose was measured at the first hour of the glucose load. A value of plasma glucose ≥140 mg/dL (7.8 mmol/L) was accepted as the threshold value for the positive glucose challenge test. Pregnant women with a positive challenge test underwent 3-hour 100-g OGTT within 7 days.[11] According to Carpenter and Coustan criteria[10] at least two plasma glucose levels exceeding the cut-off values following OGTT were essential for the diagnosis of GDM. Women with one abnormal value were excluded from the study.

The subjects were classified into 3 groups according to the OGTT and GCT results: group 1 (n: 120) pregnant women with normal GCT served as control group; group 2 (n: 67) women with abnormal glucose challenge test (AGCT), and group 3 (n: 67) gestational diabetics. Blood samples were collected at 8:00 am after 12-hours fast and at 60, 120 and 180 minutes following the 100-g oral glucose load. Plasma glucose levels were measured by hexokinase method using Olympus autoanalyser (Olympus Diagnostica GmbH-Irish Branch-Lismeehan) and plasma insulin levels were measured by chemiluminescent enzyme immunoassay method using Immulite 2000 autoanalyser (Diagnostic Products Corporation, Los Angeles, CA, USA).

The insulin sensitivity index from the OGTT was calculated according to 3 mathematical equations. First equation was HOMA-IR which was derived from the product of fasting plasma glucose [HOMA-IR = (FPG × FPI)/22.5 mmol/L] and fasting plasma insulin (FPI μU/L) divided by a constant.[12]The second equation was QUICKI which was the inverse log sum of fasting insulin (I_0) and fasting glucose (G_o) (13). [QUICKI=1/ [log (I_o) + log(G_o)]. The third equation was IS_{OGTT} in which insulin sensitivity is estimated by dividing a constant (10.000) by the square root of the product of fasting plasma glucose (FPG) times fasting plasma insulin (FPI) times the mean glucose (G) times mean insulin (I) [IS_{OGTT}=10.000/√ (FPG × FPI) × (G × I)].[13]

Body mass index (BMI) was calculated as the ratio between weight (kg) and height (m^2).

Subjects in Group 2 and 3 had diet or diet and insulin therapy as indicated. Daily caloric intake was arranged by a registered dietitian according to the pregestational BMI varying between 25–35 kcal per kg per day of actual weight; as 3 meal and 4 snacks.[14] Insulin therapy with short acting insulin lispro as intensive insulin therapy (3 premeal doses lispro and 1 bedtime NPH insulin)

has been started when the capillary blood glucose levels exceed 95 mg/dl (5.3 mmol/L) in the fasting state or 120 mg/dl (6.7 mmol/L) 2 hours after meal despite dietary recommendations.[15–16]

All study subjects were educated for nutrition, exercise, capillary blood glucose monitorisation and hypoglycemia by a team including an obstetrician, an endocrinologist, a dietitian and a nurse. Pregnant women treated with insulin and diet therapy were followed up by home blood glucose monitoring system using reflectancemeter. The goal of the therapy was maintaining capillary blood fasting glucose levels ≤95 mg/dl, 2-hour values ≤120 mg/dl and during the night ≥60 mg/dl (3.3 mmol/L) with an average 100 mg/dl (5.5 mmol/L) (14).

Fetal well-being was monitored by clinical assessment and non-stress CTG test (NST) and detailed ultrasound scan for estimated fetal weight, polyhydramnios and other anomalies. Beginning from 28 weeks of gestation all study subjects had NSTs and ultrasonographic examination every 2 weeks until 40 weeks of gestation unless there has been any abnormality. Patients either with AGCT or GDM treated with diet were followed until 40 weeks of gestation. If there was associated macrosomia and a history of previous cesarean section, elective cesarean section was planned. Cesarean section rate, stillbirth, perineal lacerations and pre-eclampsia, were considered as maternal adverse outcomes.

Intrapartum electronic fetal monitoring was done for all pregnant women during labor. Birth weight, 5-minute Apgar score, umbilical artery pH values and base excess, hypoglycemia, neonatal intensive care unit stay (NICU) were recorded for all newborns. Macrosomia was defined as a birth weight exceeding or equal to 4000 grams. Fetal hypoxia was assessed as umbilical artery pH value ≤7.10 and base deficit ≤–12. Neonatal hypoglycemia was diagnosed if any of two consecutive blood glucose value was <35 mg/dl (1.7 mmol/L) in term offsprings.[17]

Statistical Analysis

Statistical analyses were performed by SPSS® for Windows version 13.0 (Chicago, IL, USA). Data are expressed as means ± SD (standard deviation). Normality for continued variables in groups was determined by the Shapiro Wilk test. The ANOVA was used to compare parametric data and Least significant difference (LSD) test was used for comparison of variables. Pearson chi-squared test was used for the evaluation of categorical data; i.e. age, history, pregestational BMIs. Fisher's exact test was used for comparison of fasting glucose values of the groups. A *p* value of less than 0.05 was considered significant. To quantify the prediction of developing both AGCT and GDM based on patients characteristics, logistic regressions were performed to select the significant factors when the characteristics were considered jointly.

Results

Demographic characteristics of the pregnant women were given on *Table 1.* The pregnants in both AGCT and GDM groups were similarly older than control subjects. Both pregestational and in the course of GCT, BMIs were higher in AGCT and GDM groups compared to controls; GDM group was more obese than AGCT group. The groups were matched for parity and diabetic family history: the history of gestational diabetes in previous pregnancies was significantly higher in GDM group.

The baseline metabolic charactheristics of the three groups were documented on *Table 2.* In both AGCT and GDM groups GCT insulin values were significantly and similarly higher than control subjects. There was no significant difference for fasting insulin, HOMA-IR, QUICKI and IS_{OGTT} values between groups; but fasting glucose values were higher in both AGCT and GDM groups compared to controls in favor of GDM group (p=0.0001).

Table 1. Maternal and neonatal characteristics of control, AGCT and GDM groups
Tablica 1. Majčinske i novorođenačke karakteristike kontrolne, AGCT i GDM skupine

	Control	AGCT	GDM	p value
Maternal characteristics				
Age (yrs)	28.1±4.9	29.0±4.0*	31.6±5.9†	0.0001
Parity				NS
Primipara (%)	29.8	34.4	37.7	
Multipara (%)	70.2	65.6	62.3	
History				
Family history of diabetes (%)	40	34	23	NS
Gestational diabetes (%)	0	0	12‡	0.002
Prepregnancy BMI (kg/m^2)	22.7±2.7	24.0±2.7§	25.5±3.0$^{\&\$}$	0.0001
GCT BMI(kg/m^2)	25.0±2.8	27.5±3.0$^{\#}$	29.8±3.4$^{\dagger\$}$	0.0001
Neonatal characteristics				
Gestational age at birth	39 weeks	38 weeks 2 days	38 weeks 2 days	NS
Birth weight	3186.3±567.0	3330.0±524.5	3135.1±587.2	NS

GCT BMI: Body mass index during glucose challenge test
* AGCT *vs.* control p=0.02; † GDM *vs.* control p=0.001; ‡ GDM *vs.* AGCT and control p=0.002; § AGCT *vs.* control p=0.04; $^{\&}$ GDM *vs.* control p= 0.04; $^{\$}$ GDM *vs.* AGCT p=0.001; $^{\#}$ AGCT *vs.* control p= 0.001

Table 2. The baseline metabolic parameters of control, AGCT, and GDM groups
Tablica 2. Temeljni metabolički pokazatelji kontrolne, AGCT i GDM skupine

	Control	AGCT	GDM	p value
Fasting glucose mg/dl	79.0 (74.0–86.0)	81.0 (77.7–86.2)‡	90.0 (84.2–96.5)†*	0.0001
Fasting insulin μU/ml	8.3 (5.2–12.7)	8.4 (6.1–12.9)	10.1 (6.6–11.9)	NS
HOMA-IR	6.5 (2.6–8.6)	6.6 (2.3–10.5)	6.8 (2.9–13.1)	NS
QUICKI	0.128 (0.122–0.132)	0.127 (0.119–0.334)	0.127 (0.116–0.344)	NS
ISOGTT	6.5 (3.4–11.6)	6.1 (4.4–8.3)	4.8 (2.4–6.6)	NS
GCT glucose mg/dl	107.5 (91.0–123.0)	142.5 (142.7–162.2)‡	201.0 (177.0–221.0)†*	0.0001
GCT insulin μU/ml	38.1 (22.9–53.2)	49.4 (33.5–63.7)‡	58.8 (41.7–75.17)†	0.0001

All the parameters are presented as median followed by interquartile ranges in parentheses. GCT: glucose challenge test.
* GDM *vs.* AGCT p=0.0001; † GDM vs. control p=0.0001; ‡ AGCT vs. control p=0.0001

Table 3. The predictive factors for AGCT and GDM
Tablica 3. Pretkazativni čimbenici za AGCT i GDM

	Odds ratio (95% CI)	p value
AGCT Group	3.127 (1.22–8.02)	0.01
Age (≥25 yrs)	1.86 (0.96–3.58)	NS
Family history for DM	3.78 (1.86–7.70)	0.0001
Pregestational BMI	1.33 (0.34–5.24)	NS
Fasting glucose		
GDM Group		
Age (≥25 yrs)	1.91 (0.81–4.54)	NS
Family history for DM	1.62 (0.81–3.24)	NS
Pregestational BMI	5.97 (2.87–12.42)	0.0001
Fasting glucose	6 (1.63–22.07)	0.003

After adjustment for maternal age (≥25 years), pre-pregnancy BMI, family history for diabetes and fasting glucose values, pre-pregnancy BMI was the common and most predictive factor for the development of both AGCT and GDM (p=0.0001 for both). The odds ratios (OR) and confidence intervals (CI) of the parameters are documented on *Table 3.*

Blood glucose and insulin values of OGTT were shown in *Figure 1* and *Figure 2.* Glucose levels in whole OGTT intervals were significantly higher in GDM group compared to both AGCT, and control groups but only the 60 minute value was significantly higher in AGCT group compared to the controls. The insulin levels were similarly high in both GDM and AGCT groups compared to controls in all time intervals. Additionally, except for 60-minute value, insulin levels were significantly higher in GDM group compared to AGCT group.

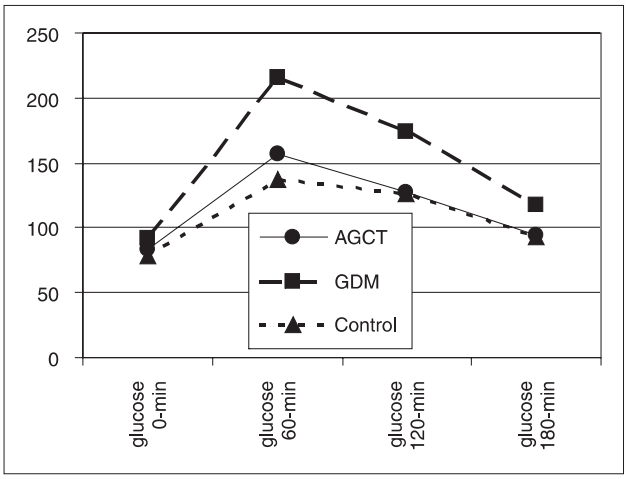

Figure 1. Line graphics of glucose levels during a 3 hour 100 g OGTT in control, AGCT and GDM groups
Slika 1. Grafikon razine glukoze tijekom 3-satnog 100 g OGTT-a u kontrolnoj, AGCT i GDM skupini

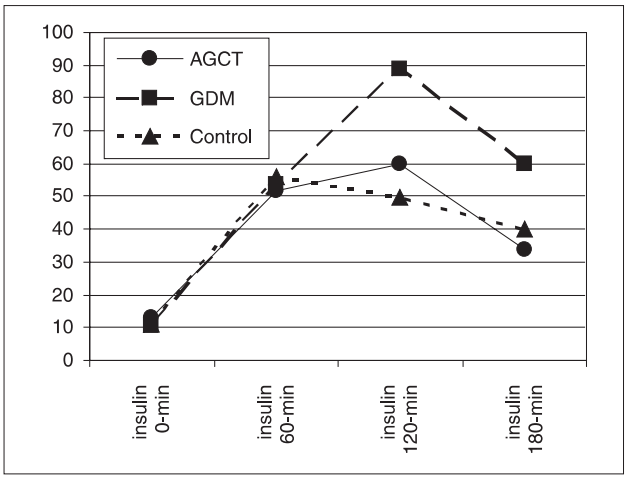

Figure 2. Line graphics of insulin levels during a 3 hour 100 g OGTT in control, AGCT and GDM groups
Slika 2. Grafikon razine inzulina tijekom 3-satnog 100 g OGTT-a u kontrolnoj, AGCT i GDM skupini

The rate of macrosomia was significantly higher in both AGCT and GDM groups compared to controls in favor of GDM group (6.6% vs. 18.9%; p=0.0001). In addition, the rate of caesarean section due to macrosomia was significantly higher in both AGCT and GDM groups compared to controls; in favor of GDM group (20% vs. 27.7%; p=0.0001 respectively). One of the patients in GDM group experienced severe preeclampsia. The complications of neonatal hypoglycemia, low Apgar score (5 min <7), low umbilical artery pH (≤7.10) and base excess (≥12) and NICU stay were all seen in the unique neonate of these mothers. The neonates were comparable for gestational age at birth; and mean birth weight for all the three groups *(Table 1)*.

As reflecting the increment of insulin resistance with advanced age and increased body fat mass, maternal age was significantly and positively correlated with fasting

Table 4. The correlating parameters with age and prepregnancy BMI
Tablica 4. Usporedbeni pokazatelji dobi i BMI prije trudnoće

	r value	p value		r value	p value
Age			*BMI*		
Fasting glucose	0.237	0.003	Fasting glucose	0.266	0.001
GCT glucose	0.327	0.0001	Fasting insulin	0.171	0.035
GCT insulin	0.158	0.018	QUICKI	–0.281	0.001
HOMA-IR	0.225	0.009	GCT glucose	0.423	0.0001
			GCT insulin	0.132	0.048

GCT: Glucose challenge test

glucose, HOMA-IR, glucose and insulin values during the course of GCT. Pregestational BMI was also positively correlated with fasting glucose-insulin; and glucose-insulin concentrations during the course of GCT; and negatively correlated with QUICKI. The correlation coefficients and p values are documented on *Table 4.*

Discussion

To our knowledge, this is one of the first prospective clinical trials evaluating the charactheristics of the carbohydrate metabolism in pregnant women with abnormal glucose challenge test, but normal 100-g 3-hour OGTT in Turkish population.

The close relationship between impaired carbohydrate metabolism and increased age and BMI are reported by several authors.[18–20] In our study fasting glucose, glucose-insulin levels of GCT, and HOMA-IR values were found to be strongly and positively correlated with age. Additionally in both of our GDM and AGCT groups the patients were older than control subjects, as supporting the hypothesis that advanced age detoriates the carbohydrate metabolism.[7] Also, age over 25 years was one of the affecting factors for development of AGCT (odds ratio 3.12).

Although our study groups were consisted of women with BMI<30 kg/m^2 – to exclude the effect of obesity- the severity of carbohydrate intolerance was found to be increased correlated with BMI. Furthermore BMI was the common and significant predictive factor for development of both AGCT and GDM (odds ratios were 3.78 and 5.97 respectively). Normal pregnancy is accompanied by an ascending insulin resistance that increases as gestation proceeds. It can be concluded that, on the basis of this physiology, the increased BMI has an additive and worsening effect on the process. but not enough to predict the subsequent AGCT or GDM during the current pregnancy.

As supporting the previous data,[21] parity was found to be insignificant as an predictive factor for both subsequent AGCT and GDM in our study groups.

Chronic insulin resistance in GDM has been documented by various studies.[3,22,23] Also, a compensatory pancreatic insulin production leading to a state of hyperinsulinemia which is an essential event preceding the development of GDM during pregnancy has been well documented. In the present study fasting glucose values were significantly higher in both AGCT and GDM groups compared to controls, while the fasting insulin levels were similar in all 3 groups. Additionally GCT insulin and glucose values were similarly high in both AGCT and GDM groups compared to control group. Significant increments have been detected in insulin levels at the second hour of glucose load during OGTT both in AGCT and GDM groups. Putting together, our data supports the hypothesis of increased tissue resistance to insulin secretion together with reduced early insulin response in the pathogenesis of glucose intolerance in AGCT group similar but in lesser degree to GDM.[24,25]

We have measured three indices to evaluate insulin resistance and insulin sensitivity in our study subjects. HOMA-IR model was the first index that we used to evaluate insulin resistance based on liver and pancreatic β-cell interactions related to plasma glucose and insulin levels. Although HOMA-IR has some limitations to reflect the peripheral insulin sensitivity, it was proven to be a good predictor of the total insulin sensitivity.[26] We used QUICKI as the second index to measure insulin sensitivity, which is preferred in clinical trials, since single blood sample is enough for the mathematical calculation.[14] We also calculated IS_{OGTT} to asses and compare the peripheral insulin sensitivity. IS_{OGTT} is considered more informative index for prediction of peripheral insulin sensitivity, since it reflects the insulin-mediated glucose uptake after glucose load.[14] However none of these indexes were statistically different between our study groups. As reflecting the increased insulin resistance, insulin levels were found to accelerate during OGTT but not in fasting state; this could be the possible result of insignificant indexes; HOMA-IR and QUICKI which root from fasting values. Despite showing no statistical significance IS_{OGTT} values were found to decrease parallel to severity of carbohydrate intolerance.[11–13,25,26]

According to our follow up protocol we treated our patients no matter with AGCT or GDM, until achieving the goals for defined glucose values:[14] either with diet or if needed with insulin. However the macrosomic infant rates were significantly higher in both of the groups compared to controls with a higher rate in GDM group. The caesarian section rates due to macrosomia were similarly high in both AGCT and GDM groups. But the subjects could be preserved from other well known

complications. There was no difference for gestational age at birth and mean birth weight of the newborns. Tight diet and insulin therapy prevented the maternal and neonatal adverse outcomes except macrosomia in AGCT and GDM groups.

The limitation of this study is the lack of an untreated AGCT group i.e. of comparing their outcomes with normal pregnant women. But for avoiding both maternal and fetal complications, we could not consist such an untreated group ethically.

In conclusion, data obtained from this Turkish pregnant women based study, demonstrate that pregnant women with abnormal glucose challenge test have impaired carbohydrate metabolism as in gestational diabetics. Decreased insulin sensitivity and increased insulin resistance in AGCT group is similar with the gestational diabetics, with a less severity. So, it would be appreciable to these pregnants to be followed up and treated as gestational diabetics. Comparable results with new studies will allow us to define and treat the pregnant women with abnormal glucose challenge test thoroughly.

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