The effect of treatment on pregnancy outcomes in women with one elevated oral glucose tolerance test value

Wpływ leczenia ciężarnych z powodu nieprawidłowego testu obciążenia glukozą na wyniki położnicze

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Abstract

Objective: *The aim of the study was to evaluate whether dietary intervention could reduce maternal and perinatal morbidity in pregnancies with one elevated 100g oral glucose tolerance test (OGTT) value.*

Material and methods: *The study was conducted among patients with positive 50g glucose challenge test (GCT) and one elevated 100g OGTT value. Plasma glucose value of 140 mg/dL was used as the threshold to define an abnormal GCT result. Carpenter and Coustan criteria were used to evaluate the OGTT results. Seventy-four women with normal GCT values comprised group I. Ninety-nine women with one elevated 100g OGTT value who were given a caloric diet and 102 women with one elevated OGTT value in group III who received antenatal care with no special diet were randomly assigned to groups II and III, respectively. All women were followed up until the end of pregnancy. Poor maternal outcome was defined as: cesarean delivery performed due to cephalopelvic disproportion, failure to progress or fetal distress, preeclampsia, and/or preterm labor. Poor perinatal outcome was defined as: small for gestational age, large for gestational age or admission to a neonatal intensive care unit. The groups were compared in terms of maternal and perinatal outcomes.*

Results: *The rates of macrosomia and large for gestational age incidence were significantly higher in group III as compared to groups I and II. When we examined the multivariate effects of the risk factors considered to be predictive of poor maternal outcomes, group III was the only statistically significant risk factor (OR=3.90, 95% CI:1.95-7.84; p=<0.001). In terms of poor perinatal outcome, one elevated OGTT value (group III) was the only significant risk factor (OR=2.92, 95% CI:1.56-5.46; p=<0.001).*

Conclusion: *Women with one elevated OGTT value benefit from a structured program of diet therapy aimed to reduce adverse maternal and perinatal outcomes.*

Key words: **diabetic diet** / **gestational diabetes mellitus** / **glucose tolerance test** /

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Streszczenie

Cel pracy: *Celem badania była ocena czy zastosowanie diety może zmniejszyć matczyną i perinatalną śmiertelność u ciężarnych z nieprawidłowym wynikiem testu obciążenia 100g glukozy (OGTT).*

Materiał i metoda: *Badanie przeprowadzono wśród pacjentek z dodatnim testem z 50g glukozy (GCT) oraz jedną podwyższona wartością testu 100g OGTT. Poziom odcięcia nieprawidłowego testu GCT wynosił 140mg/dl glukozy we krwi. Kryteria Carpentera i Coustan użyto dla oceny testu OGTT. Do grupy I należały 74 kobiety z prawidłowym wynikiem GCT. Do grupy II losowo przydzielono 99 kobiet z jednym podwyższonym wynikiem testu OGTT ze 100g glukozy, które otrzymały zalecenia dietetyczne. Natomiast do grupy III losowo przydzielono 102 kobiety z podwyższonym wynikiem testu OGTT, które nie otrzymały zaleceń dietetycznych w trakcie opieki prenatalnej. Wszystkie kobiety podlegały kontroli aż do ukończenia ciąży. Za gorsze wyniki położnicze uznano: cięcie cesarskie ze względu na dysproporcję matczyno-płodową, brak postępu porodu lub objawy zagrożenia życia płodu, stan przedrzucawkowy i/lub poród przedwczesny. Za gorsze wyniki perinatalne uznano: SGA, LGA lub przyjęcie do oddziału intensywnej opieki neonatalnej. Badane grupy porównano pod względem matczynych i perinatalnych wyników.*

Wyniki: *Odsetek makrosomii i LGA był znacząco wyższy w grupie III w porównaniu do grupy I i II. W analizie wieloczynnikowej, spośród czynników ryzyka uznanych za niekorzystne predykcyjnie dla wyników matczynych, tylko grupa III okazała się być istotnym statystycznie czynnikiem ryzyka (OR=3,90, 95%CI: 1,95-7,84, p<0,001). Pod względem wyników perinatologicznych, jedynym czynnikiem ryzyka był pojedynczy podwyższony wynik OGTT (grupa III), (OR=2,92, 95%CI: 1,56-5,46, p<0,001).*

Wnioski: *Kobiety z pojedynczym nieprawidłowym wynikiem testu OGTT mogą odnieść korzyść z zastosowania diety celem zmniejszenia niekorzystnych wyników matczynych i perinatalnych.*

Słowa kluczowe: **dieta cukrzycowa** / **cukrzyca ciążowa** / **test obciążenia glukozą** /

Introduction

The American College of Obstetricians and Gynecologists (ACOG) defines the term 'gestational diabetes mellitus' (GDM) as the onset or first recognition ofan abnormal glucose tolerance during pregnancy and recommends to screen pregnant women with a two-step approach which begins with a 50g oral GCT and continues with a 100g oral OGTT for definitive diagnosis [1]. The diagnosis of GDM is made if any two out of four threshold values at 100g OGTT are met or exceeded. One elevated value of 100g OGTT is defined as borderline GDM, impaired glucose tolerance, or mild gestational hyperglycemia [2-4]. Although certain amount of controversy regarding adverse maternal and fetal outcomes in cases of one elevated 100g OGTT value has recently been noted [4-8], the need for surveillance and treatment of women with one elevated 100g OGTT value remains the subject of much debate [9].

We aimed to design a prospective randomized controlled study to determine maternal and perinatal outcomes of pregnant women with one elevated 100g OGTT value and investigate whether dietary intervention can reduce maternal and perinatal morbidity.

Material and methods

We conducted this prospective randomized study at Zekai Tahir Burak Women's Health and Education Hospital, Ankara, Turkey. During the study period, 411 pregnant women between 24 and 28 weeks of gestation were screened for GDM. Gestational age was calculated using the date of the last menstrual period and confirmed by the first trimester sonography. Smokers and women with systemic diseases, multiple gestations, and history of uterine operations were excluded from the study. All study participants gave their informed consent and the study protocol was approved by the Hospital Research Ethics Committee.

The screening test of GDM was performed in all women using the 1-hour, 50g GCT with a subsequent 3-hour, 100g OGTT for confirmation, if screened positive. Women, who showed a 50g GCT level of more than 140 mg/dL, but less than 200 mg/dL, took the 100g OGTT. Elevated OGTT values were defined as venous plasma glucose of >95, 180, 155, or 140 mg/dL for fasting, 1-hour, 2-hour, and 3-hour tests after the 100g glucose load, respectively [10].

Among 411 pregnant women, there were 74 cases with normal 50g GCT (group I) and 201 with one elevated OGTT value. Subjects with one elevated OGTT value were randomized into two groups by using 'the toss of a coin' method in which 99 women were assigned to group II and received personalized dietary advice from a qualified dietitian. The remaining 102 women (group III) received only routine antenatal care with no diet therapy. Meal plans consisted of a total daily caloric intake of 22-35 kcal/kg according to a woman's body mass index (BMI) and daily routine activation with a minimum of 1800 kcal and maximum of 2200 kcal. Meals were divided into 3 main meals and 3 snacks with a daily total caloric distribution of approximately 40% carbohydrates, 30% proteins, and 30% fat. The diet therapy was continued if fasting blood glucose was <95 mg/dL, and 1-hour post prandial <140 mg/dL. The women with fasting blood glucose ≥95 or 1-hour post prandial≥140 mg/dl were deemed eligible for insulin regimen. All women were followed up until the end of pregnancy and they all delivered in our hospital.

The demographic and clinical features of patients and newborns were compared. The demographic features included maternal age at delivery, obstetric history, gestational period, pregestational BMI, total pregnancy weight gain, family history for diabetes mellitus in first degree relatives, history of macrosomic infants (birth weight ≥4000g), and gestational diabetes mellitus during previous pregnancy.

Table I. Demographic features of groups.

	Group I	Group II	Group III	P
Age (years)	26.20±4.67	27.89±5.79	27.91±5.81	0.079
Gravida	2.18±1.37	2.08±1.35	2.04±1.29	0.796
Parity	0.97±1.11	0.72±0.97	0.73±0.95	0.183
Pregestational BMI (kg/m^2)	26.10±2.70	26.41±2.74	26.69±3.35	0.518
Weight gain (kg)	11.77±1.88	10.38±2.22	12.46±2.30	0.059
Obstetric history for GDM	4 (5.4)	12 (12.1)	16 (15.7)	0.108
Macrosomia history	8 (10.8)	4 (4.0)	9 (8.8)	0.215
Family history for GDM	20 (27.0)	30 (30.3)	29 (28.4)	0.892
Gestational Period (days)	272.1±9.84	269.1±12.45	268.8±13.38	0.169
Values are given as mean ±standard deviation or number (percentage); Group I: normal 50g GCT; Group II: one elevated value of 100g OGTT with diet therapy; Group III: one elevated value of 100g OGTT without diet therapy				

Table II. Pregnancy complications, delivery route of women and clinical features of newborns in groups.

	Group I	Group II	Group III	P
Cesarean section	21 (28.4)	33 (33.3)	43 (42.2)	0.148
Preeclampsia	3 (4.1)	5 (5.1)	9 (8.8)	0.364
Preterm labor	2 (2.7)	5 (5.1)	7 (6.9)	0.464
Birth weight(g)	3288±424	3222±542	3350±661	0.279
Macrosomic infants	9 (12.2)	15 (15.1)	26 (25.5)	0.048*
LGA infants	7 (9.5)	10 (10.1)	21 (20.6)	0.044#
SGA infants	1 (1.4)	2 (2.0)	3 (2.9)	0.768
NICU admission	4 (5.4)	6 (6.1)	7 (6.9)	0.923
Neonatal hypoglysemia	1 (1.4)	1 (1.0)	2 (2.0)	0.850
5. min Apgar score <7	2 (2.7)	3 (3.0)	4 (3.9)	0.891
Neonatal polycythemia	1 (1.4)	2 (2.0)	1 (1.0)	0.824
Values are given as mean ±standard deviation or number (percentage) *difference between the groups is significant; p=0.704 for group I-II, p=0.029 for group I-III, p=0.044 for group II-III # difference between the groups is significant; p=0.888 for group I-II, p=0.046 for group I-III, p=0.040 for group II-III				

Table III. The incidence of poor maternal and perinatal outcomes.

	Group I	Group II	Group III	p*	p*		
					I-II	I-III	II-III
Poor maternal outcome	26 (35.1)	43 (43.4)	59 (57.8)	0.009	0.270	0.003	0.041
Poor perinatal outcome	12 (16.2)	18 (18.2)	31 (30.4)	0.040	0.735	0.031	0.044
Values are given as number (percentage) *p<.0.05 is considered statistically significant							

Neonatal birth weights were also recorded. Birth weight below the 10th percentile and above the 90th percentile was categorized as small-for-gestational-age (SGA) and large-for-gestational-age (LGA), respectively [11]. The incidence of cesarean delivery due to cephalopelvic disproportion, failure to progress or fetal distress, preterm delivery (before 37 weeks), preeclampsia (elevation in blood pressure together with proteinuria), and other maternal complications were noted. Adverse neonatal events, such as the 5-min. Apgar score <7, hypoglycemia (blood glucose level below 40mg/dl within 2 hours from birth), polycythemia (venous hematocrit level above 65%, 4 hours after birth), admission to a neonatal intensive care unit (NICU), and other complications were also recorded.

Table IV. Multivariate logistic regression analysis of risk factors for poor maternal or perinatal outcomes.

Dependent Variables *Independent Variables*	OR	Wald	p	95% CI
Maternal Outcome				
Age >30 years	2.25	3.11	0.053	1.03-4.95
GDM History	0.29	2.72	0.099	0.07-1.26
Macrosomia history	0.53	1.35	0.245	0.18-1.55
Family History	0.58	2.88	0.090	0.31-1.09
BMI ≥27	1.75	3.47	0.063	0.97-3.15
Weight gain>10kg	0.44	2.01	0.115	0.18-1.44
Group I	1.00	-	-	-
Group II	1.39	0.94	0.333	0.71-2.73
Group III	3.90	14.69	**<0.001***	1.95-7.84
Perinatal Outcome				
Age >30 years	1.62	1.87	0.172	0.81-3.24
GDM History	1.78	1.33	0.248	0.67-4.74
Macrosomia history	1.10	0.03	0.858	0.39-3.06
Family History	0.43	3.35	0.061	0.21-0.88
Weight gain>10kg	1.89	2.14	0.222	0.46-4.86
Group I	1.00	-	-	-
Group II	0.87	0.14	0.708	0.42-1.80
Group III	2.92	11.27	**<0.001***	1.56-5.46
*p<.0.05 is considered statistically significant				

Poor maternal outcome was defined as: cesarean delivery due to cephalopelvic disproportion, failure to progress or fetal distress, and pregnancy complications (preeclampsia, preterm labor). Poor perinatal outcome was defined as: SGA, LGA or NICU admission.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, Version 76, Chicago, IL). Normality testing (Kolmogorow-Smirnow test) was performed to determine if data were sampled from a normal distribution. For normally distributed quantitative variables, the difference between the groups was evaluated by one-way Anova test. For the quantitative variables that were not normally distributed, the difference between the groups was evaluated by the Kruskal Wallis test. The chi-square test was used to evaluate qualitative variables. The multivariate logistic regression model and odds ratios (with 95% confidence intervals) were used to assess the independent value of the factors associated with poor maternal and perinatal outcomes. P <0.05 was accepted as statistically significant.

Results

Seventy-four women with normal 50-g GCT value constituted group I, while 99 subjects who received diet therapy and 122 who did not receive any diet therapy comprised groups II and III, respectively. Demographic features of the study participants are shown in Table I. There were no significant differences between the groups regarding maternal age, gravidity, parity, pregestational BMI, total pregnancy weight gain, historical status and gestational period.

Although the rates of primary cesarean section, preeclampsia, and preterm labor were higher in group III as compared to I and II, the differences between the groups were not statistically significant (Table II). As far as neonatal data were concerned, mean birth weight in group I was 3288±424 g, in group II 3222±542 g and in group III 3350±661 g without significant differences (p=0.279). The incidence of macrosomic infants was the highest in group III (25.5%; Table II). Group III was significantly different from groups I and II in terms of incidence of macrosomia (p=0.029, p=0.044, respectively; Table II). Groups I and II were similar with regard to incidence of macrosomia (p=0.704). Incidence of LGA was the highest also in group III (20.6%; Table II).

Group III was significantly different from groups I and II with regard to the incidence of LGA infants (p=0.046, p=0.040, respectively; Table 2). Groups I and II were similar with regard to the incidence of LGA infants (p=0.888). We found no differences in the number of SGA infants, NICU admission, neonatal metabolic complications and 5-min. Apgar score<7 between the groups. There were no cases of neonatal birth injury or fetal anomaly, either.

The groups were also compared in terms of poor maternal and perinatal outcomes and the results revealed significant differences: 57.8% of the 'no diet' group (III) had poor maternal outcome. The result was significantly higher than the 'diet therapy' group (II) or the 'normal GCT' group (I) (p=0.009; Table III).

The incidence of poor perinatal outcome was also higher in group III as compared to groups I and II (p=0.040; Table III).

When we examined the multivariate effects of risk factors considered to be effective in predicting poor maternal outcomes, the results from group III were statistically significant (OR=3.90, 95% CI:1.95-7.84; p=<0.001). Also, group III was the only significant risk factor (OR=2.92, 95% CI:1.56-5.46; p=<0.001) for poor perinatal outcome (Table IV).

Discussion

The fact that untreated GDM and lesser degrees of hyperglycemia during pregnancy are associated with increased maternal and neonatal complications is well-established [12]. Thus, the correct diagnosis is extremely important. However, there is no consensus about the appropriate screening/diagnostic test or

diagnostic thresholds. At present, much of the world uses a one-step 75g, 2-hour test, which was supported by the International Association of Diabetes and Pregnancy Study Groups in 2010 [13] and the American Diabetes Association in 2011 [14]. On the other hand, the American College of Obstetricians and Gynecologists showed that there is no evidence that the identification and treatment of women based on one-step 75g test will lead to clinically significant improvement in maternal and neonatal outcomes. Also, it would lead to a significant increase in healthcare costs. The diagnosis of GDM should be based on a two-step approach in which the initial 50g glucose challenge test (GCT) is followed by a 3-hour 100g OGTT, if the GCT exceeds the thresholds [1].

In our study, the two-step approach was used. The women were initially screened by measuring plasma glucose 1 hour after a 50g glucose load. Patients with glucose concentration ≥140 mg/dL, underwent a 100g OGTT on another day and the diagnosis of GDM was established by the Carpenter and Coustan criteria, as recommended by ACOG [15]. We were able to determine that women with one elevated 100g OGTT value are still at risk for increased maternal morbidities and neonatal complications that are associated with GDM, although they do not meet diagnostic criteria for GDM. Our results also showed that proper diet therapy reduces the risk of poor maternal and perinatal outcomes in women with one elevated 100g OGTT value.

The effect of one elevated 100g OGTT value on maternal outcome is not clear. Increased risk of primary cesarean delivery among patients with mild gestational hyperglycemia has been recently confirmed in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study, which is a large multicenter trial (15 centers with approximately 25.000 women) using the 75g OGTT [16]. The incidence of primary cesarean delivery or preeclampsia was reported to be higher in women with one elevated 100g OGTT value by Lindsay et al. [6]. However, Vambergue et al., and Forest et al., showed in their studies that the incidence of cesarean delivery and preeclampsia was not statistically increased in patients with only one elevated value, regardless of the treatment [4,7]. In another study by Fassett et al., cesarean delivery incidence was reported to not be significantly reduced with diet therapy in women with one elevated 100g OGTT value [17]. In our study, no difference was observed between the groups in terms of primary cesarean delivery or preeclampsia incidence. Also, our results are in agreement with those of Fassett et al., because there was a tendency of increased incidence of cesarean delivery in women with no diet therapy (42.2%) as compared to the two other groups (28.4% and 33.3%), being without statistically significant difference.

The rate of preterm labor in women with one elevated OGTT value has been somewhat inconsistent in the literature. Lao et al., and Jensen et al., showed that the incidence of preterm birth correlated significantly with increasing glucose intolerance according to 75g OGTT [18,19]. A Taiwanese study indicated a significantly increased risk for preterm labor as the abnormal value of the OGTT increased according to the two-step approach [20]. However, a Turkish study including 2029 singleton pregnancies found that the incidence of preterm labor was similar between normal GCT and one elevated OGTT value groups [21]. Our study demonstrated that preterm labor incidence was not statistically increased in patients with only one elevated value, regardless of treatment, as compared to women with normal 50g GCT value.

Mean birth weight of newborns in all groups was similar. However, the rates of macrosomic and LGA infants were significantly increased in the 'no diet' group (III) as compared to normal GCT (I) and diet (II) groups. It is possible that one elevated 100g OGTT value may predict increased insulin resistance (that can cause fetal macrosomia) in later stages of pregnancy. Therefore, diet therapy and close monitoring of blood glucose levels may be useful. Our findings are in agreement with those of Langer et al., who reported that the incidence of macrosomic and LGA infants is significantly higher in patients with one abnormal OGTT value and that the use of diet and insulin therapy is beneficial in reducing the rate of macrosomic and LGA infants [5]. The HAPO Study has recently determined that the risk of having an LGA infant is greater than the risk of having a macrosomic infant among patients with gestational hyperglycemia and these associations were present at glucose levels currently lower than those used to diagnose GDM [6]. In contrast, Fassett et al., stated that medical nutrition therapy and self-blood glucose monitoring did not reduce the incidence of macrosomia in women with one elevated 100g OGTT value [17].

In our study population, a policy of routine treatment of women with one elevated OGTT value with diet therapy did not reduce the incidence of NICU admission and neonatal metabolic complications. This is in contrast to the findings of Langer et al. [5], but similar to Fassett et al. [17]. Langer et al., used the higher National Diabetes Data Group criteria for the diagnosis of GDM, and thus examined a group of women with higher degrees of hyperglycemia who would benefit more from the treatment. The participants of the study by Fassett et al., and our group, diagnosed using the lower Carpenter and Coustan criteria, would have less hyperglycemia and thus show less or no benefit from treatment.

Recently, the World Health Organization (WHO) has defined pregnant women who meet the criteria for diabetes mellitus or impaired glucose tolerance as having GDM [22]. It has been well-established that diabetes-complicated pregnancy is associated with adverse maternal and perinatal outcomes and lesser degrees of glucose intolerance have also been shown to be harmful [22, 23]. The treatment for gestational diabetes also reduces the odds of adverse pregnancy outcomes [22]. Thus, the importance of diagnosis and treatment approaches for GDM has been highlighted in several previous studies. Szymanska et al., presented a study in which they aimed to examine the influence of diagnostic time on the pregnancy outcome among patients with gestational diabetes and found that diagnosis of GDM during the recommended period (between 24 and 28 weeks of gestation) decreases the prevalence of LGA as compared to later diagnosis [24]. In another study that was conducted in Poland over a 10-year period, it was suggested that as no reliable method of identifying subjects at increased GDM risk was found, all pregnant women should undergo screening for GDM [25] and that proper nutrition therapy plays an important role in managing GDM. Most women with GDM are treated by diet therapy alone. In a prospective randomized trial reported by Cypryk et al., the authors concluded that both high- and low-carbohydrate diets were effective, safe and tolerable treatment in GDM [26]. Similarly, in a recent review comparing the effectiveness of GDM treatment with usual

antenatal care, Falavigna et al., stated that treatment of GDM was effective in reducing adverse pregnancy outcomes [27].

Conclusion

In conclusion, although women with one elevated OGTT value do not meet diagnostic criteria for GDM, they are probably at risk of increased maternal morbidities and neonatal complications associated with GDM. Diet therapy and close monitoring of the blood glucose levels may be enough in women with one elevated 100g OGTT value to decrease poor maternal and perinatal outcomes to near baseline levels. Further studies with larger sample are needed to determine the significance of this follow-up program for antenatal care of women with one elevated 100g OGTT value.

Authors' Contribution:

1. Mahmut Kuntay Kokanalı – concept, study, design, analysis and interpretation of data, article draft, corresponding author.
2. Aytekin Tokmak – concept, assumptions, acquisition of data, analysis and interpretation of data.
3. Oktay Kaymak – concept, assumptions, study design, article draft, revised article critically.
4. Sabri Cavkaytar – concept, acquisition of data, analysis and interpretation of data, revised article critically.
5. Ümit Bilge - concept, study design, acquisition of data, analysis and interpretation of data, revised article critically.

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