Özgün Araştırma / Original Article

Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology - Obstetrics and Neonatology

DOI: 10.38136/jgon.895195

Diyet ile takip edilen veya insülin ile tedavi edilen gestasyonel diyabetli kadınlarda neonatal ve maternal komplikasyonların karşılaştırılması

Comparative study of neonatal and maternal adverse outcomes in women with gestational diabetes mellitus followed or treated with insulin versus dietary regimen

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ÖZ

Amaç: Bu çalışmanın birincil amacı, insülin ile tedavi edilen veya diyetle takip edilen Gestasyonel Diabetes Mellitus (GDM) hastalarının neonatal ve maternal komplikasyonlarını karşılaştırmaktır. İkincil amaç ise sezaryen oranını ve endikasyonlarını değerlendirmektir.

Gereç ve Yöntemler: GDM'li kadınlar insülin (n = 120) ve diyet (n = 200) olarak iki gruba ayrıldı. Demografik veriler, antenatal takip ölçümleri, doğumda gebelik haftası ve doğum şekli kaydedildi. Yenidoğan komplikasyonları (yenidoğan yoğun bakım yatışı, omuz distosisi, hipoglisemi, düşük apgar skoru) ve maternal komplikasyonlar (tromboz, hipoglisemi ve selülit) kaydedildi. Toplam ve primer sezaryen oranları hesaplandı ve endikasyonlara göre gruplandı. Gruplar arasında istatistiksel analiz yapıldı.

Bulgular: Yaş ve vücut kitle indeksi açısındaniki grup arasından istatistiksel olarak anlamlı fark yok idi. Diyet grubuna göre insülin grubunda düşük apgar skoru, yenidoğan yoğun bakıma yatış, postpartum maternal komplikasyonlar ve primer sezaryen oranı istatistiksel olarak anlamlı yüksekti (tümü için p <0.05). Vajinal doğum oranı diyet grubunda istatistiksel olarak anlamlı derecede yüksekti (OR: 1.8, CI:% 95). Makrozomi ve buna bağlı sezaryen, insülin grubunda istatistiksel olarak anlamlı yüksek bulundu (p <0.05). Doğum indüksiyonu ve erken doğum oranları açısından **anlamlı fark yoktu.**

Sonuç: GDM'li kadınlarda normoglisemiye ulaşmak önemlidir. Ancak bu amaçla birincil yaklaşım olan diyet takibi, etkili bir medikal tedavi olarak bilinen insüline göre neonatal ve maternal komplikasyonlar açısından avantajlı görünmektedir.

Anahtar kelimeler: Gestasyonel diabetes mellitus, insülin, diyet rejimi, komplikasyon

ABSTRACT

Aim: Primary aim of this study is to compare the neonatal and maternal complications of women with Gestational Diabetes Mellitus (GDM) treated with insulin or followed by diet. Secondary aim is to evaluate the rate of cesarean section and indications of that.

Materials and Methods: Women with GDM were divided into two groups as insulin (n=120) and diet (n=200). Demographic data, antenatal follow-up measurements, gestational week at birth and type of delivery were recorded. Neonatal complications (neonatal intensive care admission, shoulder dystocia, hypoglycemia, low apgar score) and maternal complications (thrombosis, hypoglycemia and cellulitis) were recorded. Total and primary cesarean section rates were calculated by dividing them according to indications. Statistical analysis between groups was performed.

Results: Age and body mass index were not statistically significant in both groups. Low apgar score, admission to neonatal intensive care, postpartum maternal complications and primary cesarean section rate were statistically significantly higher in the insulin group compared to the diet group (p <0.05 for all). Vaginal delivery rate was statistically significantly higher in the diet group (OR: 1.8, CI: 95%). Macrosomia and related cesarean section were found to be statistically significantly higher in the insulin group (p<0.05). There was no significant difference in terms of induction of labor and preterm delivery rates.

Conclusion: It is important to achieve normoglycemia in women with GDM. However, dietary follow-up, which is the primary approach for this purpose, seems to be advantageous in terms of neonatal and maternal complications compared to insulin which is known as an effective medical treatment.

Keywords: Gestational diabetes mellitus, insulin, dietary regimen, outcome

INTRODUCTION

Approximately 7% of all pregnancies are complicated with any diabetes and 86% of these are diagnosed with gestational diabetes mellitus (GDM) (1). GDM is associated with a high risk of maternal, neonatal-fetal complications. Type 2 Diabetes mellitus develops at a rate of 40-60% in 5-10 years after delivery in women with GDM . It is an important pregnancy and general public health problem. The pathophysiology of GDM is pancreatic β-cell dysfunction accompanied by chronic insulin resistance. β-cells are poor to realize the increase in blood glucose level in the presence of insulin resistance, which is frequently present before and increases in severity with pregnancy, and they become unable to meet the increased insulin need (2). The direct effect of glucose (glucotoxicity)

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Başvuru tarihi : 11.03.2021
Kabul tarihi : 06.08.2021

also contributes to the dysfunction in the overloaded β-cells. Once β-cell dysfunction begins, a vicious cycle (hyperglycemia, insulin resistance and severe β-cell dysfunction) is inevitable (3). With the increased glucose passing from the placenta to the fetus, hyperinsulinemia develops in the fetus, fetal growth is triggered and thus negative effects such as macrosomia may occur.

For the diagnosis of GDM, it is recommended to screen high-risk patients (obesity, poor obstetric history, family history of diabetes) at the first antenatal visit, while screening is recommended between 24-28 weeks of gestation for low-risk patients. For diagnosis, the International Assoociation of Diabetes and Pregnancy Study Group (IADPSG) (4) recommends a one-step 2-hour 75-g oral glucose tolerance test (OGTT) based on the extensive Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (5) . These criteria have also been supported by the World Health Organization (WHO) (6) and the American Diabetes Association (ADA) (7). There are publications showing that the single-step test diagnoses gestational diabetes mellitus at a higher rate than the two-step test (8). In addition, especially in the United States , 50 g glucose loading for screening and 100 g OGTT for diagnosis, which is a two-stage test, continues (9).

It has become clear that maternal and fetal adverse outcomes increase in women with GDM. HAPO study found an increase in birth weight, primary cesarean section rate, neonatal hypoglycemia and cord blood c peptide levels with increased OGTT results (5). Furthermore, in the HAPO-FUS study, as the intrauterine exposure to glucose increased, it was found to be increased glucose level and insulin resistance in childhood regardless of BMI and family history (10). Therefore, GDM treatment is of great importance and it has been reported that poor perinatal outcomes decrease with treatment (9). Diet and nutritional therapy are recommended as the primary approach in GDM treatment, either alone or by adding moderate exercise three days a week. If the blood glucose levels of the women followed by diet remain above the target values pharmacological treatment is started (4, 7, 9). The safest drug used for GDM is insulin. In addition, among oral antidiabetic agents, metformin and glyburide, which have safe evidence that they are not teratogenic and do not cross the placenta, have been used in recent years (11).

Although there are studies reporting increased cesarean section rates in the delivery method, no significant difference was found in comparative meta-analyzes according to treatment options in the current Cohrane Library resources. General recommendations are that if glucose levels of women with GDM are normal and close to normal, the term should be waited, and if possible not exceeded. Elective cesarean sectiondoes not reduce birth trauma and is not cost effective. It is known that preterm labor planning will prevent macrosomia but will not reduce other complications. There is no difference in cesarean section rates in the analyzes of comparative studies such as diet and insulin, insulin and oral antidiabetic drugs, diet and exercise, and different insulin regimens. However, the Cohrane library reported that there was not enough robust data for insulin and diet comparative studies (11, 12).

The aim of our study is to compare maternal and neonatal complication rates in women with GDM in terms of diet and insulin therapy. The secondary aim is to evaluate cesarean section rates and indications. Although it has been reported that cesarean section rates and neonatal and maternal complications are seen at a higher rate in women with GDM, there are not enough studies to compare this comparison with insulin versus diet.

MATERIALS AND METHODS

Study design . The study was designed retrospectively and approved by Baskent University Institutional Review Board (Project no: KA20/13). Women diagnosed with GDM at Başkent University Gynecology and Obstetrics Department between January 2015 and January 2020 will be included. Women were divided into two groups, followed by dietary regimen and lifestyle changes (n= 200) and treated with insulin (n= 120). The following values will be taken as reference as GDM criteria; Women who have one or more results above the threshold value after 75 g OGTT (4-6) or who have two or more values above the threshold value after 100 g OGTT (7-8). Women with GDM primarily take a calorie diet suitable for the body mass index. Following this, blood glucose monitoring is required 4 times a day and 3 days a week. Insulin treatment is initiated in women with results of two or more values above the threshold value during weekly follow-up. It is recommended to monitor blood glucose 4 times a day for women who are started on insulin therapy. According to this approach, women whose blood glucose was regulated by diet or treated with insulin were collected in two separate groups.

Data collection: Demographic characteristics, age, body mass index (BMI) obstetric history, HbA1c levels, time and type of birth, and indications, if delivered by cesarean section, will be

recorded for women with GDM. Primary and repeated cesarean section rates will be calculated and their indications will be recorded. Admission to neonatal intensive care unit, apgar score, hypoglycemia and shoulder dystocia were recorded in terms of neonatal complications. Thrombophilia-related pathologies, maternal hypoglycemia, and cellulitis as postoperative wound infection were recorded as maternal complications. Obstetric parameters (amnion fluid measurement, umblical artery doppler, gestational week at birth, preeclampsia development) were recorded antenatally. Multiple pregnancies, women with pre-gestational diabetes or overt diabetes during pregnancy (fasting plasma glucose> 126 mg/dl or random plasma glucose > 200 mg/dl), and known cervical insufficiency will be determined as exclusion criteria.

Statistical Analysis: SPSS 25.0 (Başkent University licensed, IBM Corporation, Armonk, New York, United States) program was used in the analysis of variables. The compliance of the data to normal distribution was evaluated with Shapiro-Wilk francia test and variance homogeneity with Levene test. Independent-Samples T test was used together with Bootstrap results, while Mann-Whitney U test was used with Monte Carlo simulation technique in comparing two independent groups with each other according to quantitative data. In comparison of categorical variables with each other, Pearson Chi-Square Exact and Monte Carlo simulation results were used, while Fisher-Freeman-Holton test was tested using only Monte Carlo Simulation technique. Column ratios from the significant results were compared with each other and expressed according to the Benjamini-Hochberg corrected p value results. Odds ratio was used with 95% confidence intervals. Quantitative variables are mean ± SD in tables. (standard deviation) and Median (25% Percentile / 75% Percentile), while categorical variables were shown as n (%). Variables were examined at a 95% confidence level, and a p value of less than 0.05 was considered significant.

RESULTS

The mean age of the women included in our study was 32.1 ± 4.9 and 31.1 ± 5.2 for the insulin and diet groups, respectively. Median BMI values were not statistically significant in the insulin group compared to the diet group. While 75% of the women in the insulin group were multiparous, this rate was 64% in the diet group (p <0.05). Median gestational ages at the time of delivery were 39 weeks in the diet group and 38 weeks in the insulin group, and a statistically significant difference was observed (p <0.05). When the gestational age was categorized according to weeks, no statistically significant difference was observed. There was no statistically significant difference between the two groups in terms of weight gain during pregnancy, smoking status, amniotic fluid levels, and umblical artery doppler blood flow measurements at the time of delivery. The incidence of macrosomia was significantly higher in the insulin group (p <0.05). When the results of OGTT (in the second trimester) were examined, fasting plasma glucose levels were 96.4 mg/dL in the insulin group and 93 mg/dL in the diet group that is not statistically significant. However, HbA1c levels were 5.6 mg/dL in the insulin group and 5.36 mg/dL in the diet group and statistically significant difference was observed (p<0.05) (Table 1).

Table 1. Comparison of antenatal parameters and follow-up measurements between two groups

	Diet (n=200)	Insulin (n=120)	P
Age, mean ± SD.	31.1 ± 5.2	32.1 ± 4.9	0,082 [t]
BMI, first visit, median (Q1/Q3)	31 (28/34)	32 (27/36)	0,190 [u]
Parity, n (%)			
Primiparous	72 (36)	29 (24.2)	**0.027** [pe]
Multiparous	128 (64)	91 (75.8)	
Gestational week at birth , median(Q1/Q3)	39 (37/40)	38 (37/39)	**0,013** [u]
Gestational week at birth, n(%)			
<34	12 (6)	8 (6.7)	0,989 [pm]
34- 36[6]	34 (17)	21 (17.5)	
37- 38[6]	110 (55)	66 (55)	
>39	44 (22)	25 (20.8)	
Fasting plasma glucose at OGTT mg/dL (Q1/Q3)	93 (82.5/93)	96.4 (88.7/104.4)	0,064 [u]
HbA1c at OGTT time (%) median (Q1/Q3)	5.36 (5.1-5.9)	5.6 (5.24-6.2)	**0,003** [u]
intake of weight, median (Q1/Q3)	11 (9 / 15)	11 (8 / 14)	0,391 [u]
Smoking, n(%)			
No	175 (87,5)	103 (85.8)	0,733 [pe]
Yes	25 (12,5)	12 (14.2)	
Amniotic Fluid, n(%)			
Normohydramnios	154 (77)	83 (69.2)	0,198 [pm]
Oligohydramnios	18 (9)	11 (9.2)	
Polyhydramnios	28 (14)	26 (21.7)	
Umb. Artery Doppler S/D, median(Q1/Q3)	2,1 (1,8 / 2,5)	2,17 (1,8 / 2,7)	0,419 [u]
Macrosomia, n(%)	36 (18)	30 (25)	**0,026** [pe]

[t] Independent Samples t test(Bootstrap), [u] Mann Whitney u test (Monte Carlo), [p] Pearson Chi Square Test ([e] Exact, [m] Monte Carlo), Q1: %25 Percentile, Q3: %75 Percentile, SD.:Standard Deviation, bold values means p<0.05

When both groups were compared in terms of type of birth, the cesarean section rate was 59.5% in diet group and 72.5% in insulin group, and a statistically significant difference was observed (p <0.05, odds ratio: 1.8, 95% CI). The primary cesarean section rate was 48.3% in the insulin group and 35.5% in the diet group and this difference was statistically significant too (p <0.05). When the indications of cesarean section were compared, macrosomia was found to be statistically significantly higher in the insulin group compared to the diet group (23%, 7.6%, respectively, p <0.05). There was no statistically significant difference in terms of women who underwent cesarean section with the indications of labor arrest and CPD, recurrent cesarean, malpresentation, fetal distress, cord prolapse and

severe preeclampsia. The preterm delivery rate did not differ statistically between the insulin and diet groups (24.2%, 23%, respectiveley). Fetal birth weight and percentege of induction of labor were similar in both groups. When neonatal results were analyzed, low apgar score, intensive care unit acceptance was statistically significantly higher in the insulin group, while the ratio of shoulder dystocia was similar in both groups . Maternal complications were satisticaly significantly higher in the insulin group than the diet group (14.2%, 4.5%, respectively, p <0.001) (Table 2).

Table 2. Comparison of delivery type, cesarean rate and postpartum adverse outcomes between the groups

	Diet (n=200)	**Insulin (n=120)**	**P**
Induction of labor, n(%)	61 (30.5)	31 (25,8)	0,445 [pe]
Preterm Delivery, n(%)	46 (23)	29 (24.2)	0.892 [pe]
Fetal birth weight , median (Q1,Q3)	3400 (3000/3727)	3400 (3130/3825)	0,241 [u]
Type of Delivery, n(%)			
Vaginal birth	81 (40.5)	33 (27.5)	**0,037** [pe]
Ceasear section	119 (59.5)	87 (72.5)	**1.8 (1.1-2.9)** [or]
Primary Ceasear section, n(%)	71 (35.5)	58 (48.3)	**0,042** [pe]
Indication of ceasear section, n(%)			
Repeat ceasearen	48 (40.3)	29 (33.3)	**0,021** [ff]
Malpresentation	15 (12.6)	7 (8)	
Labor arrest or CPD	26 (21.8)	12 (13.8)	
Macrosomia	9 (7.6)	20 (23)*	
Fetal Distress or Cord prolaps	17 (14,3)	13 (14.9)	
Severe preeklampsia	4 (3,4)	6 (6.9)	
Low Apgar Score, n(%)	15 (7.5)	22 (18.3)	**0.006**[pe]
Intensive care unit, n(%)	21 (10.5)	30 (25)	**<0.001**[pe]
Shoulder dystocia, n(%)	3 (1.5)	1 (0.8)	0.603[pe]
Postpartum maternal complication, n(%)	9 (4.5)	17 (14.2)	**0.001**[pe]
Cellulitis	6 (3)	5 (4.2)	
Deep venous thrombosis	1 (0.5)	2 (1.7)	
Severe hypoglisemia	1 (0.5)	9 (7.5)*	
Sinus venous thrombosis	0 (0)	1 (0.8)	

[u] Mann Whitney u test(Monte Carlo), [p] Pearson Chi Square Test([e] Exact, [m]Monte Carlo), [ff] Fisher Freeman Halton Test (Monte Carlo); Posthoc test: Benjamini Hocgberg Test, Q1: %25 Percentile, Q3:%75 Percentile, [or] odds ratio, bold values means p<0.05, *significant compare to other group

Neonatal fetal death was recorded in one neonate in both groups. One of them in the diet group was related to intracranial hemorrhage developing after preterm delivery. The other was due to pulmonary immaturity after preterm delivery in the insulin group.

DİSCUSSİON

It is known that the treatment of GDM reduces complications in pregnancy. The following questions come to mind in treatment; Does glycemic control prevent complications or is there an increase in complications even if the glycemic index is preserved with insulin which we consider as a pharmacological approach? In line with this hypothesis, our primary aim is to compare the maternal and neonatal complication rates by dividing women who are followed up with diet and insulin into separate groups. Our secondary aim is to examine cesarean section rates and indications.

GDM causes some changes in the mother, fetus and placenta. Fetal endogenous hyperinsulinemia secondary to maternal hyperglycemia causes overgrowth and placentomegaly in the fetus. The placenta which tries to provide support to the overgrown fetus by growing in the same way, becomes relatively inadequate after a while. A hypoxic environment occurs and may lead to fetal and maternal complications. The subject that is the basis of our study and that is striking in the literature is the role of exogenous insulin applied for GDM treatment. In some studies, the incidence of placentomegaly is higher in women with GDM who are applied exogenous insulin compared to the diet and exercise group only. In other words, exogenous insulins have a direct or indirect effect on the placenta. The increase in fetal endogenous insulin secretion triggered by postprandial hyperglycemia and post-insulin hypoglycemia attacks is blamed for these effects (13, 14). The important role of the glycemic index on neonatal and maternal health is clear. However, an important point we want to touch upon in our study; neonatal and maternal complications, macrosomia and related cesarean section rates are higher in women with exogenous insulin regulated GDM compared to diet group. This may be related to the use of exogenous insulin. While providing glycemic index control, this issue can be discussed in order not to rush to start insulin administration and to direct women to correct and effective diet and exercise. Rasmussen et al. published a comprehensive article on diet and healthy lifestyle for women with GDM. They reported that professional nutritional counseling and advice should be given to all women with GDM according to their optimal calory and energy needs, and also that knowing the effect of diet on blood glucose is the cornerstone in preventing the risk of birth complications (cesarean section and macrosomia) and in the development of type 2 DM in the future. They noted that promoting moderate-intensity physical activity for at least 30 minutes a day or 150 minutes a week provides great benefit in achieving glycemic control (15).

Wong et al. showed higher birth weight and percentage values in women with GDM treated with insulin compared to the diet-treated group. However, there was no difference in nenonatal morbidity. Similarly, in our study, we reported higher macrosomia in the insulin group. In addition, there was a significant increase in cesarean section rates due to macrosomia. Also, in our results, we saw that there was a significant increase in neonatal and maternal complications in the insulin group (16). Arshad et al. reported higher intrauterine exitus in GDM group treated with insulin compared to diet group. They suggested that the reason for this might be the overgrowing fetus and developing hypoxia due to relatively insufficient placental transport (13, 17). Although not statistically significant as reported in another study, women treated with insulin have a higher rate of placental fibrinoid necrosis, which may cause fetal hypoxia. (18). Adverse changes in the placental and umbilical cord due to insulin therapy are not expected in women followed by a diet and exercise regimen. Therefore, besides the benefits obtained by providing normoglycemia, the negative effects of factors other than glucose on the fetus and newborn should be considered. These negative effects may increase with insulin therapy. Comparative studies on diet, exercise and insulin regimen are few in the literature and there are different results. In a study, it was reported that the newborns of 95.7% of the women who were followed up with the diet regimen and 85.7% of the women who treated with insulin regimen were uncomplicated, and the complication rate was less in the diet group alone. Also, the neonatal fetal mortality rate was similar (19). Giuffrida et al. reported that there was no statistically significant difference between insulin therapy and diet regimen subjects with other fetal poor outcomes other than macrosomia (hyperbilirubinaemia, hypoglycemia, hypocalcemia, conjenital malformation), in terms of macrosomia, insulin therapy was more beneficial than diet regimen alone (20). These results suggest that insulin therapy may have negative effects other than maintaining the glycemic index, but it should be considered that women who receive insulin therapy are more difficult to control hyperglycemia or have severe GDM, so there may be more complications.

Insulin is held responsible for increased risk of preeclampsia, cesarean section delivery and type 2 diabetes development for women with GDM compared to oral antidiabetic drugs. However, there was insufficient evidence comparing insulin and dietary regimen (21). In our study, we found that maternal

complications were higher in the insulin group. Among these, deep vein thrombosis and severe hypoglycemia were very serious problems. In addition, vaginal delivery was significantly higher in the diet group and the leading reason for this was that women who used insulin had more cesarean section due to macrosomia. The reason for the higher rate of neonatal and maternal complications in the insulin group may be the use of insulin. However, it should be considered that the difficulty in achieving normoglycemia, higher levels of hba1c and fasting glucose in this group, in other words, the severity of GDM, may have caused this. In the Cohrane review, it is reported that lifestyle interventions as a non-pharmacological approach reduce the rate of LGA babies (22). Another review reported that lifestyle change was the only intervention that showed better health improvement for maternal and fetal health (12).

Induction of labor and cesarean section rates of women with GDM are also an important subject of discussion. In a study conducted in this area, it was reported that primigravida, obesity and previous cesarean section history increase the probability of cesarean section in these women. In the same study, it was reported that insulin, diet, metformin or combined therapies did not correlate with the cesarean section rate. However, in that study, there was no control group without GDM as in our study (23). On the contrary, we found that women who used insulin had satatisticaly higher cesarean section rates (OR:1.8). In addition primary cesarean section rates were also high. There was no difference in terms of labor induction and preterm labor rates. Inocencio et al. reported that starting insulin therapy early in pregnancy and macrosomia history in women with GDM increased the cesarean section rate (24). Grabowska et al. reported that women with GDM were more likely to undergo cesarean, but similar to our study, induction of labor at term did not increase this risk more. According to their results, the main risk factors for cesarean section were advanced maternal age, high pregestational BMI and insulin therapy in women with GDM (25).

Our article has some limitations. Since oral antidiabetic agents were not used routinely during the retrospective screening period in our clinic, this group could not be included in the study. The correlation between the insulin dose used and the complications could not be evaluated.

In conclusion, the diet group, which includes lifestyle interventions followed without pharmacological treatment, showed fewer complications and better fetal and maternal outcomes than women with GDM using insulin. Although it is observed that women using insulin have more severe GDM, the increase in cesarean section rates due to macrosomia, increased need for neonatal intensive care and maternal poor outcomes should be considered in this group. For this reason, we make an emphasis on preventing GDM and treating it with effective and well-followed lifestyle changes and diet when it occurs.

Acknowledgments

The author thanks Hüseyin Candan for his support in statistical analysis.

Disclosure

The author of this manuscript declares that there is no conflict of interest

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