Evaluation of the relationship between HbA1c values of pregnant women with gestational diabetes and anthropometric measurements of their newborn

Gestasyonel diyabetli gebelerin HbA1c değerleri ile yenidoğanlarının antropometrik ölçümleri arasındaki ilişkinin değerlendirilmesi

Birgül Deniz Doğan [1], Emin Pala [2], Süleyman Ersoy [2], Murat Doğan [3]

Abstract

Aim: In our study, we aimed to evaluate the relationship between the HbA1c values of pregnant women who were diagnosed with gestational diabetes mellitus (GDM) and the anthropometric measurements of their newborns.

Methods: 200 pregnant women with GDM between the ages of 18 and 43 with sufficient data were accepted to our study. Also, 200 healthy pregnant women formed the control group. The data of both groups were statistically compared.

Results: Gravidity of pregnant women was 1-8 and parity 1-7 and all between 27-42 gestational weeks. HbA1c values ranged from 4.3 to 8.3. The height of the babies was between 30 and 57 cm, birth weight between 800 and 4760 grams, and head circumference between 22 and 65 cm. While 1st minute apgar values varied between 2 and 9, 5th minute apgar values varied between 4 and 10. While 55.3% of the pregnant women had a normal birth, 44.7% of them had cesarean section. 95.5% of HbA1c values were less than 6.5 and 4.5% of them were at least 6.5. 45% of the newborns were girls and 55% were boys. 7% were low birth weight, 87% normal weight and 6% macrosomic. While 21.5% of newborns had complications, 78.5% had no complications.

Conclusion: The complication rate was higher in pregnant women with GDM and cesarean rate was higher due to increasing birth weight in our study. Further, multi-center and prospective studies may provide new perspectives for prevention of GDM and its complications.

Keywords: Gestational Diabetes Mellitus, HbA1c, Newborns

[1] **Mucur State Hospital Family Medicine Clinic, Kırşehir, Turkey.**
[2] **Health Sciences University, Ümraniye Training and Research Hospital, Department of Family Medicine, İstanbul, Turkey.**
[3] **Health Sciences University, Kırşehir Training and Research Hospital, Department of Family Medicine, Kırşehir, Turkey.**

BDD: 0000-0002-9197-2459
EP: 0000- 0001- 9189-4342
SE: 0000-0003-0001-9329
MD: 0000-0003-0776-3644

Sorumlu yazar / Corresponding author:
Emin Pala
Adres/Address: Sağlık Bilimleri Universitesi, Ümraniye E.A.H, Aile Hekimliği Kliniği, Ümraniye, İstanbul, Turkey.
e-mail: eminpala72@gmail.com
Tel/Phone: +90 505 832 63 62

Öz

Amaç: Çalışmamızda gestasyonel diyabetes mellitus (GDM) tanısı alan gebelerin HbA1c değerleri ile bebeklerinin antropometrik ölçümleri arasındaki ilişkiyi değerlendirmeyi amaçladık.

Yöntemler: Çalışmamıza yaşları 18 ile 43 arasında değişen, yeterli veriye sahip 200 GDM'li gebe kabul edildi. Rastgele seçilen 200 sağlıklı gebe de kontrol grubunu oluşturdu. Her iki grubun verileri istatistiksel olarak karşılaştırıldı.

Bulgular: 1 ile 8 arasında değişen gravide ve 0 ile 7 arasında değişen parite değerlerine sahip gebeler 27 ile 42 hafta arasındaydılar. HbA1c değerleri 4,3 ile 8,3 arasında değişmekteydi. Bebeklerin boyları 30 ile 57 cm, doğum ağırlıkları 800 ile 4760 gram, baş çevreleri ise 22 ile 65 cm arasındaydı. 1. dk apgar değerlerinin 2 ile 9 arasında değişmesine karşılık, 5. dk apgar değerleri 4 ile 10 arasında değişmekteydi. Gebelerin %55,3' ü normal doğum yaparken, %44,7' sine sezeryan uygulanmıştı. HbA1c değerlerinin %95,5' i 6.5' ten küçük, %4,5' inin ise en az 6,5 idi. Gebelerin %53,5' ine diyet yanında insülin verilirken, %46,5' ine sadece diyet önerilmişti. Bebeklerin %45' i kız, %55' i erkekti. %7' si düşük doğum ağırlıklı, %87' si normal ağırlıklı ve %6'sı makrozomikti. Yenidoğanların %21,5' inde komplikasyon görülürken, %78,5' inde komplikasyon tespit edilememiştir.

Sonuç: Çalışmamızda GDM'li gebelerde komlikasyon ve artan doğum kilosuna bağlı olarak sezaryan oranı daha yüksek bulunmuştur. Maternal ve fetal morbidite ve mortalite üzerindeki olumsuz etkilerinin daha iyi anlaşılabilmesi ve önlenebilmesi için çok merkezli ve prospektif çalışmaların yapılmasına ihtiyaç vardır.

Anahtar Kelimeler: Gestasyonel Diyabetes Mellitus, HbA1c, Yenidoğan

Introduction

GDM, is an intolerance to carbohydrates at second or third trimester of pregnancy in women without a history of diabetes mellitus, arising due to the hyperinsulinemia and insulin resistance caused by several hormones released from the placenta [1,2]. It occurs resulting from failure of pancreas to overcome insulin resistance [3].

Although the incidence is higher in countries where diabetes is more prevalent, usually it is seen in 2-4% of pregnant women. In our country the prevalence of diabetes is 13.7% in the population over 20 years old, thus GDM risk is medium. It is known that GDM may lead to many complications both in the mother and the fetus such as pre-eclampsia, hydramnios, macrosomia etc. [4]

One stage or two stage oral glucose tolerance test is the golden standard for diagnosis [5] and insulin is the golden standard in pharmacological therapy [6].

The objective of this study is, to evaluate the relationship between HbA1C values of pregnant women with GDM and anthropometric measurements of their newborn and compare them with normoglycemic pregnant women.

Material and methods

This was a retrospective case control study, and it was carried out by evaluation of the data that belong to pregnant women referring to University of Health Sciences, Umraniye Training and Research Hospital between December 2013 and December 2018.

Case group consists of pregnant woman who referred to our hospital for routine follow up and who met any of the following GDM diagnostic criteria:

50 g glucose challenge test 1-hr Plasma Glucose (PG) level ≥ 180 mg/dl,

50 g glucose challenge test 1-hr PG 140- 180 mg/dl and exceeding 2 of the 4 cut-off values after 100 g glucose challenge for OGTT to reach definitive diagnosis of GDM or in 75 g OGTT without any challenge test exceeded one of the fasting, 1-hr or 2-hr cut-off values.

The subjects who had Type I or Type II DM, any other endocrine disease or history of drug use, those with multiple pregnancy and under 18 years old and those with missing medical records were excluded from the study.

Case group was 200 pregnant women who met inclusion criteria regarding GDM diagnosis. A control group was selected randomly among pregnant women who do not have any comorbid disease or history of drug use.

The data of pregnant women with GDM and their newborns are compared with the control group.

Ethics approval

University of Health Sciences, Umraniye Training & Research Hospital Clinical Research Ethics Committee has approved the study on 22 May 2019 with B. 10. 1. TKH. 4. 34. H. GP. 0. 01/ 105 decision no and the study had clearance regarding ethical and scientific integrity of the study.

Statistical analysis

IBM SPSS Statistics 22 (IBM SPSS, Turkey) program is used for statistical analysis in assessment of data obtained from the study. Conformity of the parameters to normal distribution was tested by Shapiro Wilks test. For assessment of study data, in addition to descriptive statistical methods (mean, standard deviation, frequency) comparison of quantitative data and intergroup comparison of parameters with normal distribution were done by using one-way Anova test. Parameters with normal distribution were compared between two groups by

Student t test, parameters with non-normal distribution were compared between two groups by Mann Whitney U test. Qualitative data were compared by using Chi-square test, Fisher's Exact test, and Continuity (Yates) Correction. The correlation between parameters that are in conformity with normal distribution was studied by using Pearson correlation analysis. p < 0.05 is considered significant.

Results

Our study included 200 pregnant women with GDM diagnosis and 200 pregnant women who served as control group in an age range of 18-43 years and their newborns.

Time span was 27-42 gestational weeks. Gravidity was 1-8 and parity was 0-7 and HbA1c values ranged between 4,3 - 8,3. and in 82 pregnant women the values ranged between 5,7-6,4. Complications were observed in 21.5% of the newborns and the remaining newborns were free from complications.

Table 1. Distribution of study parameters.

	Min-Max	Mean±SD
Age at pregnancy	18-43	29.14±5.79
Gestational week (median)	27-42	38.08±2.26(38)
Gravidity(median)	1-8	2.81±2.32 (3)
Parity(median)	0-7	1.33±1.14 (1)
HbA1c (n=200)	4.3-8.3	5.61±0.54
Height at birth (cm)	30-57	50.22±2.89
Weight at birth (g)	800-4760	3300.68±540.95
Head circumference (cm)	22-65	34.63±2.79
Apgar 1 (median)	2-9	8.73±0.8 (9)
Apgar 5 (median)	4-10	9.8±0.65 (10)

	n	%
Gestational week group		
Preterm (under 37 weeks)	44	11
Term (37-42 weeks)	334	83.5
Post-term (over 42 weeks)	22	5.5
Type of birth		
Normal	221	55.3
Caesarian	179	44.8
HbA1c group (n=200)		
<6.5	191	95.5
≥ 6.5	9	4.5
Treatment (n=200)		
Insulin +Diet	107	53.5
Diet	93	46.5
Sex		
Female	180	45
Male	220	55
Birth weight (g) group		
Low (under 2500)	28	7
Normal (2500- 4000)	348	87
Macrosomia (above 4000)	24	6
Presence of complication		
Yes	314	78.5
No	86	21.5

Table 2. Intergroup assessment of study parameters.

	GDM group (Min-Max)-(Mean±SD)	Control group (Min-Max)-(Mean±SD)	p
Age at pregnancy (y)	(20-42)-(30.93±5.21)	(18-43)-(27.36±5.81)	[1]0.000*
Gestational week (median)	(27-42)-(37.62±2.22 (38))	(19-42)-(38.54±2.21 (39))	[2]0.000*
Gravidity (median)	(1-40)-(3.2±2.92 (3))	(1-8)-(2.43±1.41 (2))	[2]0.000*
Parity (median)	(0-6)-(1.49±1.03 (1))	(0-7)-(1.18±1.23 (1))	[2]0.000*
HbA1c	(4.3-8.3)-(5.61±0.54)	-	-
Height at birth	(30-57)-(49.79±3.17)	(36-56)-(50.66±2.51)	[1]0.002*
Birth weight	(800-4760)-(3315.72±599.04)	(1265-4310)-(3285.65±476.88)	[1]0.579
Head circumference	(22-65)-(34.87±3.55)	(29.5-46)-(34.4±1.72)	[1]0.092
Apgar 1 (median)	(2-9)-(8.63±0.94 (9))	(5-9)-(8.82±0.62 (9))	[2]0.002*
Apgar 5 (median)	(4-10)-(9.74±0.74 (10))	(6-10)-(9.86±0.53 (10))	[2]0.014*
	n (%)	n (%)	
Gestational week			
Preterm	30 (15)	14 (7)	
Term	164 (82)	170 (85)	[3]0.005*
Postterm	6 (3)	16 (8)	
Type of birth			
Normal	87 (43.5)	134 (67)	[3]0.000*
Caesarian	113 (56.5)	66 (33)	
HbA1c			
≤6.5	193 (96.5)	-	-
>6.5	7 (3.5)	-	
Treatment			
Insülin+Diet	107 (53.5)	-	-
Diet	93 (46.5)	-	
Sex			
Female	98 (49)	82 (41)	[3]0.108
Male	102 (51)	118 (59)	
Birth weight			
Low	15 (7.5)	13 (6.5)	
Normal	168 (84)	180 (90)	[3]0.094
Macrosomia	17 (8.5)	7 (3.5)	
Presence of complication			
Yes	141 (70.5)	173 (86.5)	[3]0.000*
No	59 (29.5)	27 (13.5)	

[1] Student t Test, [2] Mann Whitney U Test, [3] Ki-Kare Test, * p<0.05

The height of the newborns was between 30 and 57 cm, birth weight between 800 and 4760 grams, and head circumference between 22 and 65 cm. While 1st minute apgar values varied between 2 and 9, 5th minute apgar values varied between 4 and 10. Pregnancies have ended at preterm in 11%, term in 83.5% and post-term in 5.5% of the pregnant women. 55.3% of the pregnant women had a normal birth and 44.7% of them had cesarean section. Only diet was recommended as treatment in 46.5% of the subjects diagnosed as GDM and the remaining subjects had additional insulin injections. 45% of the babies were girls and 55% were boys. 7% were low birth weight, 87% normal weight and 6% had macrosomia (Table 1).

The most common complications were hyperbilirubinemia (36%) and transient tachypnea of the newborn (30,2%) followed by ASD (8.1%), prematurity (8.1%), sepsis (7.0%), congenital pneumonia (5.8%) and VSD (4.7%).

Mean age, gravidity values, parity values and birth by cesarean section were statistically significantly higher in pregnant women with GDM compared to the control group (p<0.001). However, gestational week values and height of the newborns at birth were significantly lower than the control group (p<0.001) (Table 2).

In the newborns of the group with GDM transient tachypnea of the newborn and early neonatal sepsis rates were statistically significantly lower compared to the control group regarding complications. (p<0.05) However, rate of hyperbilirubinemia was statistically significantly higher compared to the control group (p<0.05) (Table 3).

Table 3. Intergroup complication rates.

Complications	GDM group n (%)	Control group n (%)	p
Transient tachypnea of newborn	13 (22)	13 (48.1)	[1]0.028*
Atrial septal defect	5 (8.5)	2 (7.4)	[2]1.000
Hypoglycemia	6 (10.2)	0 (0)	[2]0.170
Small for gestational age	1 (1.7)	0 (0)	-
Large for gestational age	2 (3.4)	0 (0)	-
ventricular septal defect	3 (5.1)	1 (3.7)	[2]1.000
Hyperbilirubinemia	28 (47.5)	3 (11.1)	[1]0.003*
Pulmonary hypoplasia	1 (1.7)	0 (0)	-
Congenital cardiac defects	1 (1.7)	0 (0)	-
Intrauterine growth retardation	3 (5.1)	1 (3.7)	[2]1.000
Patent ductus arteriosus	4 (6.8)	2 (7.4)	[2]1.000
Sepsis	2 (3.4)	1 (3.7)	[2]1.000
Tricuspid insufficiency	1 (1.7)	1 (3.7)	-
Inguinal hernia	1 (1.7)	0 (0)	-
Prematurity	5 (8.5)	2 (7.4)	[2]1.000
Brachial plexus injury	1 (1.7)	0 (0)	-
Low birth weight	2 (3.4)	1 (3.7)	[2]1.000
Intubation	1 (1.7)	0 (0)	-
Pneumothorax: decreased aeration of lungs	3 (5.1)	0 (0)	[2]0.549
Asphyxia	1 (1.7)	0 (0)	-
Congenital pneumonia	3 (5.1)	2 (7.4)	[2]0.647
Exitus	2 (3.4)	0 (0)	-
Respiratory distress syndrome	2 (3.4)	1 (3.7)	[2]1.000
Early neonatal sepsis	1 (1.7)	5 (18.5)	[2]0.011*
Urinary tract infection	1 (1.7)	0 (0)	-
Thrombocytopenia	1 (1.7)	1 (3.7)	-
Clavicular fracture	1 (1.7)	0 (0)	-
Aorta coarctation	0 (0)	1 (3.7)	-
Down syndrome	0 (0)	1 (3.7)	-
Spina bifida: nerve damage in spinal cord	0 (0)	1 (3.7)	-
Other complications	0 (0)	3 (11.1)	[2]0.029*

[1] Continuity (Yates) Correction, [2] Fischer's Exact Test, *: p<0,05, Chi Square

Presence of complications, type of birth and birth weight did not affect HbA1c values statistically in both groups (Table 4).

In subjects with GDM, there was no statistical correlation between HbA1c values and age, gravidity, parity of the subjects and birth weight of the newborns (p>0.05).

Mean age of the mothers of newborns with complications was higher than the mothers of newborns without complication; birth weight of newborns with complications was lower than newborns without any complications (p<0.001).

Insulin treatment in subjects with HbA1c <5.7 (45%) was statistically significantly lower than subjects with HbA1c 5,7 - 6,4(59,8%) and HbA1c >6,5(100%) (p=0.024).

There was no statistically significant difference regarding the rate of complications and birth weights of the newborns in mothers with GDM who are treated with insulin or not (Table 5).

Table 4. Assessment of HbA1c values in GDM group according to the presence of complication, type of birth and birth weight.

GDM group	HbA1c		p
	Min-Max	Mean±SD	
Presence of complication			0.459[1]
No	4.5-7.2	5.59±0.49	
Yes	4.3-8.3	5.65±0.65	
Type of birth			0.523[1]
Normal	4.3-8.3	5.58±0.56	
Caesarian	4.5-7.4	5.63±0.53	
Birth weight group			0.167[2]
Low	5.1-8.3	5.77±0.78	
Normal	4.3-7.2	5.58±0.5	
Macrosomia	4.6-7.4	5.78±0.68	

[1] Student t test, [2] Oneway Anova Test

There is no significant correlation between HbA1c and height and head circumference of the newborns (r=0.118, p=0.096 and r=0.020, p=0.774 respectively).

Table 5. Assessment of presence of complications according to insulin treatment in subjects with GDM.

	Insulin treatment		
	Yes (n%))	No (n%))	p
Presence of complication			
No	70 (65.4)	71 (76.3)	[1]0.091
Yes	37 (34.6)	22 (23.7)	
Birth weight. *Mean±SD*	3303.74±659.94	3329.49±523.51	[2]0.763

[1] Ki-kare Test, [2] Student t test

Discussion

In the literature it is reported that advanced age is a risk factor for GDM in pregnancy. In a Canadian study by Denice et al. 1,109,605 pregnant women were assessed and GDM prevalence was found as 10% in women older than 30 [7]. In Finland, Lamminpää et al. studied 230,003 pregnant women over 35 years old with GDM and 5532 non-diabetic pregnant women younger than 35 years old and have found that GDM risk increases by increasing age [8]. In our study, mean age, gravidity, and parity values of women with GDM were found to be statistically significantly higher than the control group.

GDM is a significant health issue since it substantially impacts maternal and perinatal morbidity. In a study by Carolan M et al. it is observed that maternal hypertension, pre-eclampsia rates and interventions such as caesarian have increased in women with GDM [9] Also in our study C/S ratio (56.5%) of pregnant women with GDM was significantly higher than the control group (33%).

Measuring HbA1c in GDM patients is a controversial issue. The International Experts Committee on diabetes has reported that individuals with a HbA1c value 5.7-6.4% (39-46 mmol/mol) are at high risk for diabetes and should be included into the prevention programs [3]. In our study, HbA1c was 5.7-6.4% in 82 (41%) pregnant women and ≥ 6.5 in 9 (4.5%) of them. Mean value of HbA1c was 5.61 in pregnant women with GDM.

Macrosomia is a common complication observed in newborns of diabetic mothers and described as birth weight over 4000 g or more than 90th percentile in population-based growth charts. In the study of Figueroa et al., it is reported that in newborns of patients with borderline gestational diabetes LGA and macrosomia incidence have increased 2 and 1.6 times, respectively. In the study by Bonomo et al. it is reported that even slight alterations in glucose intolerance [10] may lead to excessive growth of the fetus [11]. In our study there was no significant difference between newborns regarding birth weight.

In the literature, correlation between fetal birth weight and maternal is a debated issue. In the study by Coen et al., it is concluded that there is no correlation between maternal HbA1c and birth weight [12]. In a comprehensive HAPO study, it is stated that plasma glucose level is more relevant in determining birth weight compared to HbA1c values [13]. In another study carried out in Turkey, it is reported that there is a positive and independent correlation between 2nd trimester maternal HbA1c values and birth weight [14]. In our study, we could not find any significant relationship between HbA1c values and birthweight, height at birth and head circumference of the newborns. This may be associated with strict antenatal follow up, proper insulin therapy, diet and exercise.

In some research it is observed that in pregnant women with previous diabetes diagnosis or with high HbA1c values during first trimester, risk of hazardous outcomes such as miscarriage, premature birth, neonatal mortality, fetal anomaly is higher compared to normal pregnancy. And it is reported that risk increases proportionally by increasing HbA1c values [15,16]. In different studies, the incidence of congenital anomalies was found higher in pregnant women with higher HbA1c values [17,18]. In our study as well, HbA1c values were significantly higher in diabetic pregnants who had complications compared to those without complications.

It is known that GDM may cause a lot of complications. In a study carried out in Poland the most common complications observed in newborns of the pregnant women with GDM were hyperbilirubinemia (17.3%), hypoglycemia (15.6%), congenital defects (4.3% - most commonly cardiac anomalies) [19]. In our study the most common complications among those with GDM were hyperbilirubinemia (47.5%), transient tachypnea of the newborn (22%), hypoglycemia (10.2%)

Advanced maternal age is among risk factors for GDM. In the study of Lamminpää et al.; it was observed that the advanced age of the mother increased the risk of prematurity, fetal mortality, and admission of the newborn to neonatal intensive care unit [9]. Based on this information we have compared the mean age of the pregnant woman with GDM who had complications (32.27 years) and those who did not have any complications (30.36 years). Mean age or the mothers with GDM was significantly higher in those who had complications compared to the ones without complications.

Preterm birth is defined as births occurring before 37th gestational age and GDM is a risk factor for preterm birth. In a study by Beigelman et al. incidence of preterm birth was found as 10% among 3841 pregnant women with GDM [20]. Moreover, in a study carried out by Heddeson et al. glucose intolerance is found to be related with spontaneous preterm births. In our study preterm birth rate was significantly higher in pregnant women with GDM (15%) compared to the control group (7%).

Due to various metabolic disorders occurring in newborns because of maternal diabetes the newborns of diabetic mothers may have lower apgar scores at birth. There are studies also on the contrary. In Israel Bental et al. investigated newborns of 120 pregestational diabetic and 825 gestational diabetic mothers prospectively and have found that APGAR score was higher in newborns of diabetic mothers compared to the newborns of non-diabetic mothers [21]. In our study 1st minute (8.63) and 5th minute (9.74) mean APGAR scores of the newborns of mother with GDM were found to be statistically lower than the mean APGAR scores of the newborns of non-diabetic mother group (8.82-9.86).

In a study carried out in Turkey it is suggested that HbA1c value >5,4 in pregnant women with GDM may be a predictor for starting insulin treatment [22]. In our study rate of insulin use in those with HbA1c <5.7 was 45%, it was 58.8% when the value is between 5.7-6.4 and 100% when it is ≥6.5.

According to these results it is observed that need for insulin increase as HbA1c value increases.

In our study there was no significant difference in terms of occurrence of complications between pregnant women with GDM who use insulin and who do not. However, in a randomized, multi-center study performed in the USA two groups with slight GDM were compared and in one of the groups normal gestational follow up was sustained and the other group was treated (diet, blood glucose monitoring and insulin when needed). In the treatment group complications such as macrosomia, shoulder dystocia and incidence of sectio was lower [23].

Anthropometric measurements of the newborns were compared in terms of treatment applied to the mothers with GDM diagnosis in Italy by Mello et al.; LGA rate was 18.8% in mothers treated only by diet; 9.9% in mothers treated with both diet and insulin and 8.3% in the control group [24]. Fetal macrosomia is a common adverse infant outcome of GDM if unrecognized and untreated in time. For the infant, macrosomia increases the risk of shoulder dystocia, clavicle fractures and brachial plexus injury and increases the rate of admissions to the neonatal intensive care unit [25] It may be suggested that proper follow up and treatment may decrease macrosomia. In our study, we could not find any significant difference between the birth weights of newborns who were born from pregnant women with GDM who were treated with insulin or not.

Consequently, the complication rate was higher in pregnant women with GDM and cesarean rate was higher due to increasing birth weight in our study. The negative impact of GDM on maternal and fetal morbidity and mortality may be mitigated by diet, insulin treatment and strict antenatal follow up. Further, multi-center and prospective studies may provide new perspectives for prevention of GDM and its complications.

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