Orijinal Araştırma / Original Investigation
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The Relationship Between Glycosylated Hemoglobin A1c (Hba1c) Levels and Pregnancy Complications in Diabetic Pregnant Women; Retrospective Case-control Study

Diabetik gebelerde glikolize hemoglobin A1c (HbA1c) düzeyi ile gebelik komplikasyonları arasındaki ilişki-Retrospektif vaka-kontrol çalışması

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ÖZET

AMAÇ: Diabetes mellitus (DM) tanılı gebelerde glikolize hemoglobin A1C (HbA1c) düzeyleri ile gebelikte meydana gelebilecek olan komplikasyonlar arasında ilişki olup olmadığını saptamak.

GEREÇ VE YÖNTEM: Çalışmamız retrospektif vaka-kontrol çalışmasıdır. Ocak 2013 ve Aralık 2017 tarihleri arasında Aydın Adnan Menderes Üniversitesi hastanesinde yapılmıştır. Çalışmamız 321 hasta üzerinde yapılmıştır. Hastalarda HbA1C düzeyine göre komplikasyon oranlarına bakılmıştır.

BULGULAR: HbA1c değerleri 66 gebede %4-5,9, 157 gebede %6-7.9 ve 91 gebede HbA1c≥%8'dir. Pregestasyonel DM tanılı gebelerde gestasyonel diabetes mellitus (GDM) tanılı gebelere kıyasla preeklampsi, fetal distres, preterm doğum, omuz distosisi ve yenidoğan hipoglisemisi daha sık saptanmıştır (p<0.05). Tip 1 DM tanılı gebelerde Tip 2 DM tanılı gebelere kıyasla erken doğum tehdidi (EDT), polihidroamnios, hiperbilirübinemi, yenidoğan hipoglisemisi ve yenidoğan kilo kaybı daha sık saptanmıştır (p<0.05). GDMA2 tanılı gebelerde GDMA1 tanılı gebelere kıyasla gestasyonel hipertansiyon (GHT), preeklampsi, EDT ve large for gestational age (LGA) daha sık saptanmıştır (p<0.05). GDMA1 tanılı gebelerde oligohidroamnios daha sık saptanmıştır (p<0.05). HbA1c≥%8 ve HbA1c %6-7,9 olan gebelerde HbA1c değeri normal olan gebelere kıyasla GHT, preeklampsi, EDT, oligohidroamnios, polihidroamnios, LGA, fetal distres, preterm doğum, yenidoğan hipoglisemisi, yenidoğan kilo kaybı, yenidoğan solunum sıkıntısı, respiratuar distres sendromu (RDS), hiperbilirübinemi ve intrauterin ex fetüs daha sık saptanmıştır (p<0.05). GDM tanılı HbA1c>%6 ve HbA1c %5-5,9 olan gebelerde HbA1c %4-4,9 arasında olan gebelere kıyasla GHT, preeklampsi, EDT, polihidroamnios, small for gestational age (SGA), LGA, fetal distres, preterm doğum, yenidoğan hipoglisemisi ve yenidoğan solunum sıkıntısı daha sık saptanmıştır (p<0.05).

SONUÇ: Pregestasyonel DM, Tip 1 DM, GDMA2 ve yüksek HbA1c değeri olan gebelerde obstetrik komplikasyon oranlarında artma olduğu saptanmıştır.

Anahtar Kelimeler: glikolize hemoglobin a1c (hba1c), gebelik komplikasyonu, gestasyonel diabetes mellitus, diyabette gebelik

ABSTRACT

OBJECTIVE: To determine whether there is a relationship between glycosylated hemoglobin A1C (HbA1c) levels and complications that may occur during pregnancy in pregnant women with diabetes mellitus (DM).

MATERIALS AND METHODS: This study was a retrospective case-control study. It was conducted in Aydın Adnan Menderes University hospital between January 2013-December 2017 and performed on 321 patients. Complication rates were evaluated according to the HbA1C level of the patients.

RESULTS: HbA1c values were pregnant women's 4-5.9% in 66, 6-7.9% in 157 HbA1c≥8% in 91. Compared to gestational diabetes mellitus (GDM), preeclampsia, fetal distress, preterm delivery, shoulder dystocia, and neonatal hypoglycemia were found more frequently in pregnant women with pregestational DM (p<0.05). Compared to type 2 DM, threatened premature birth (TPL), polyhydramnios, hyperbilirubinemia, neonatal hypoglycemia, and neonatal weight loss were found more frequently in pregnant women with type 1 DM (p<0.05). Compared to normal HbA1c values in pregnant women, GHT, preeclampsia, TPL, oligohydramnios, polyhydramnios, LGA, fetal distress, preterm birth, neonatal hypoglycemia, neonatal weight loss, neonatal respiratory distress, respiratory distress syndrome (RDS), hyperbilirubinemia and ex fetus were found more frequently in pregnant women with HbA1c≥8% and HbA1c between 6-7.9% (p<0.05). In pregnants with GDM diagnosis with HbA1c>6% and HbA1c between 5-5.9%, GHT, preeclampsia, TPL, polyhydramnios, small for gestational age (SGA), LGA, fetal distress, preterm birth, neonatal hypoglycemia, and neonatal respiratory distress were found more frequently compared to pregnants with HbA1c between 4-4.9%.

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CONCLUSION: Obstetric complication rates increased in pregnant women with pregestational DM, Type 1 DM, GDMA2, and high HbA1c values.

Keywords: glycosylated hemoglobin a1c (hba1c), pregnancy complication, gestational diabetes mellitus, pregnancy in diabetes

INTRODUCTION

Diabetes mellitus (DM) poses a significant problem in pregnancy. Gestational diabetes mellitus (GDM) constitutes approximately 90% of diabetes seen in pregnancy and pregestational DM 10%. Pregestational DM, on the other hand, is divided into Type 1 DM and Type 2 DM. In addition, GDM is divided into two, GDM A1, which requires diet and exercise therapy, and GDM A2, which requires insulin in treatment, according to the need for insulin use (1,2). Glycated hemoglobin A1c (HbA1c) is a crucial parameter for clinicians in the diagnosis and follow-up of DM. The total blood hemoglobin (Hgb) of a normal adult individual consists of 97% hemoglobin A (HbAo), approximately 2.5% HbA2, and approximately 0.5% HbF. Hemoglobin, like many other proteins in the body, undergoes nonenzymatic glycosylation (3). The terms glycosylated hemoglobin (G-Hgb) or HbA1c are used to define Hgb with added glucose as a result of nonenzymatic glycosylation. (3,4). About 4-6% of Hgb in a healthy adult is in the form of HbA1c (4). HbA1c provides information about 8-12 weeks of glycemic control retrospectively. It is an important parameter used in both diagnosis and follow-up of DM. A diagnosis of DM is made if the HbA1c value is 6.5% or more in two different measurements. An HbA1c value of 8% or above indicates that blood sugar regulation is not good in DM. (4,5). Today, it is accepted that HbA1c not only gives information about glycemic control but also indicates the risk of developing complications related to DM and the quality of diabetic care. Thus, HbA1c is very important in obstetric practice, which will give an idea about possible maternal and fetal complications in patients diagnosed with DM during pregnancy (6). If HbA1c values tend to increase in the 3rd trimester during pregnancy, there is an increase in the risk of preeclampsia, macrosomia, and inutero ex fetus (IUEF). Hence, HbA1c is very important to predict possible complications in pregnancy. It is recommended in different publications that the HbA1c value should be below normal before pregnancy to prevent obstetric complications (7,8). For this reason, studies on HbA1c and possible pregnancy complications are vital. The benefits of HbA1c in predicting possible fetal/neonatal and obstetric complications were investigated in our study to contribute to the existing literature.

In our study, we aimed to determine whether there was a relationship between HbA1c levels, which show at least 60 days of retrospective blood sugar regulation, and obstetric complications that might occur during pregnancy in patients diagnosed with pregestational DM and patients diagnosed with GDM.

MATERIAL & METHODS

Research Place and Time

This research was a retrospective case-control study and conducted at Aydın Adnan Menderes University Application and Research Hospital between January 2013 and December 2017.

Population and Sample of the Research

This study was designed on 357 pregnant women who were diagnosed with pregestational DM and GDM and came to their follow-ups. However, 36 patients whose records could not be reached because they did not come to their follow-ups and gave birth in our hospital were not included in the present study. The population of this research consisted of 321 patients who were followed up in Aydın Adnan Menderes University Application and Research Hospital and gave birth. Women over the age of 18 who were diagnosed with DM or GDM before and/or during pregnancy, whose HbA1c values were checked, and who had a singleton pregnancy and gave birth in our hospital were included in the study. Patients under the age of 18, with multiple pregnancies and whose HbA1c values were not checked, were excluded from this study. The HbA1c values of the patients were measured at the end of the 2nd trimester (24-27 weeks of gestation) and the beginning of the 3rd trimester (28-30 weeks of gestation).

Study Design

This study was designed as a single-center, retrospective, multidisciplinary and controlled study. The ages of the patients included in this study, the history of their previous pregnancies, the total number of pregnancies, the number of live births, the number of stillbirths, the types of births, their CVs, drug use during pregnancy, and the total weight gained during pregnancy were recorded with the data collection form.

Weight and height measurement records were obtained from the obstetric follow-up form for each patient with the data collection form. Body mass index (BMI) was calculated as weight (kg)/height2 (m2). The gestational weeks of the patients were calculated by the Negele method according to the first day of the last menstrual period (LMP). In patients who do not know the LMP date and are in doubt, the gestational week was calculated according to the Crown-rump length (CRL) measurements in the first-trimester ultrasonography (USG).

A two-step method was used for the diagnosis of GDM. GDM screening was performed between 24-28 weeks of gestation in patients with no obvious risk of DM. Firstly, a 50 g glucose screening test (OGTT), which does not require fasting, was performed on the patients. Those with 50 gr OGTT 1st hour result of 180 mg/dl and above were accepted as GDM. On the other hand, 100 g or 75 g OGTT tests were performed on patients whose 50 g OGTT 1st hour result was between 140-180 mg/dl. Patients with at least 2 values higher in 100 g OGTT and a single value increase in 75 g OGTT were considered GDM. Patients who were diagnosed with GDM in their previous pregnancy and who had risk factors for overt DM were examined for DM at the beginning of pregnancy.

Patients with a diagnosis of pregestational DM included in this study were in the treatment and follow-up of endocrinology and metabolism diseases. These patients were using insulin and oral antidiabetic. Patients with GDM, on the other hand, receive diet/exercise and insulin therapy.

Premature birth was defined as birth occurring before 37 weeks of gestation. Threatened premature birth (TPL) was defined as pain, bleeding and active amniotic fluid discharge that would require hospitalization between 20-37 weeks of gestation. Intrauterine growth retardation (IUGR) is defined as a fetal weight below the 10th percentile of expected percentile values according to the week of gestation. Small for Gestational Age (SGA) is defined as a fetal weight less than 2500 grams in term deliveries. Large for Gestational Age (LGA) is defined as fetal development above the 90th percentile by the week of gestation.

Gestational hypertension (GHT) is defined as the detection of blood pressure above 140/90 mmHg at least twice at 6-hour intervals after the 20th week of pregnancy and its return to normal within 12 weeks postpartum. Preeclampsia, on the other hand, has been defined as a progressive multisystemic syndrome that progresses with the addition of organ dysfunctions without proteinuria or proteinuria.

Oligohydramnios was defined as the amniotic fluid index (AFI) value less than 5 cm. Polyhydramnios was defined as an AFI value of 25 cm or more. Intrahepatic cholestasis was defined as increased blood bile acid in the second half of pregnancy, abnormal liver function tests, and widespread itching throughout the body.

Premature rupture of membranes (PROM) was defined as active amniotic fluid discharge before the onset of labor. Placenta previa was defined as the closure of the internal cervical os by the placenta. Placenta accreta was defined as an invasion of the myometrium by chorionic villi.

In addition, fetal distress, shoulder fixation at birth, nerve and bone damage, prenatal examination findings, and neonatal problems were investigated.

The HbA1c values of the patients were measured at the end of the 2nd trimester (between 24-27 weeks of gestation) and the beginning of the 3rd trimester (between 28-30 weeks of gestation).

HbA1c measurements of the patients were made with the Adams HA-8160 (Arkray KDK, Shiga, Japan) HPLC device in the biochemistry laboratory of our hospital. In this method, data are calculated from the peak areas of different hemoglobin fractions as %HbA1c, %HbA1-%HbF and reported as a percentage (%) of total hemoglobin.

In our study, complication rates among pregnant women with pregestational DM-GDM, complication rates among pregnant women with Type 1 DM-Type 2 DM, complication rates between GDMA1-GDMA2 in pregnant women with GDM, and complication rates according to HbA1c levels of pregnants were examined.

Patients were divided into groups based on an 8% HbA1c level, which indicates poor glycemic regulation. Pregnant women with DM were divided into three different groups according to their HbA1c levels 4-5.9%, 6-7.9%, and 8% and above.

In the GDM group, based on the normal range of HbA1c of 4-6%, the patients were divided into three different groups according to their HbA1c levels as being between 4-4.9%, between 5-5.9%, and above 6%.

Ethical Approval

The research protocol was approved by Adnan Menderes University Faculty of Medicine Ethics Committee with the date 07.12.2017, number 53043469-050.04.04 and decision number 2017/1271. The present study was conducted according to the Declaration of Helsinki and informed consent was obtained from the patients.

Statistical Analysis

Categorical variables in our study were expressed as Numbers (N) and Percentages (%). With the Kolmogorov-Smirnov test of normality, it was concluded that the data had a normal distribution. The chi-square test was used to determine the relationship between DM groups and categorical variables. A confidence interval of 95% was determined in the calculations, and P-values of <0.05 were considered statistically significant. SPSS (IBM SPSS for Windows, Ver.24) statistical package program was used for the calculations.

RESULTS

The age of the patients included in this study ranged from 18 to 48 years. We did not have any patients under the age of 18. Given the age distribution of the patients, there were 53 patients (16.5%) between the ages of 18-25, 177 patients (55.1%) between the ages of 25-35, and 91 (28.3%) patients over the age of 35.

When the BMIs of the patients were examined, we did not have any patients with a BMI below 18.5. There were 32 patients (10%) with a BMI of 18.5-24.9, 11 patients (35.2%) with a BMI of 25-29.9, 127 patients (39.6%) with a BMI of 30-39.9, and 49 patients (15.3%) with a BMI of 40 and above.

Seventy three (22.7%) of the patients included in this study had a diagnosis of pregestational DM. 36 (49.3%) of the pregnant women with a diagnosis of pregestational DM had Type 1 DM and 37 (50.7%) had Type 2 DM. Two hundred forty-eight pregnant women (77.3%) were diagnosed with GDM. 31 (42.5%) of the pregnant women diagnosed with pregestational DM had DM between 1-5 years, 30 (41.1%) had 5-10 years, and 12 (16.4%) had DM for 10 years or more.

Of the pregnant women diagnosed with GDM, 126 (50.8%) received diet and exercise therapy. One hundred twenty-two pregnant women (49.2%) diagnosed with GDM received insulin therapy. When the blood sugar follow-ups of the pregnant women were examined, it was seen that the blood sugars of 153 patients (47.7%) were regulated, and the blood sugars of 168 patients (52.3%) were unregulated. When the HbA1c values of the patients are examined, the HbA1c value was between 4-5.9% in 66 (21%) patients, between 6-7.9% in 157 (50%) patients, and 8% and above in 91 (29%) patients.

GHT in 137 patients (42.7%), preeclampsia in 131 patients (40.8%), intrahepatic cholestasis in eight patients (2.5%), placenta accreta in two patients (0.6%), placenta previa in three patients (0.9%), TPL in 80 patients (24.9%), PROM in 17 patients (5.3%), oligohydramnios in 33 patients (10.3%), polyhydramnios in 46 patients (14.3%), IUGR in 42 patients (13.1%), SGA in 10 patients (3.1%), LGA in 55 patients (17.1%) and fetal distress in 102 patients (31.8%) was detected.

28 (8.7%) of the patients were delivered vaginally, and 293 (91.3%) were delivered by cesarean section. Ninety patients (28%) had preterm delivery (<37 weeks), 230 patients (71.7%) had term delivery (38-41 weeks), and one patient (0.3%) had post-term delivery (>42 weeks). Shoulder dystocia was detected in 10 (3.1%) patients at birth. Brachial plexus injury developed in one (0.3%) patient. Obstetrics complications are shown in Table 1.

Table 1. *The incidence of obstetric complications*

	n	%
Preeclampsia	131	40.8
GHT	137	42.7
İntrahepatic Cholestasis	8	2.5
Placenta Accreta	2	0.6
Placenta Previa	3	0.9
TPL	80	24.9
PROM	17	5.3
Oligohydramnios	33	10.3
Polyhydramnios	46	14.3
IUGR	42	13.1
SGA	10	3.1
LGA	55	17.1
Fetal Distress	102	31.8
Preterm Labor	90	28
Post-term Pregnancy	1	0.3
Shoulder Dystocia	10	3.1
Brachial Plexus İnjury	1	0.3
Cesarean Birth	293	91.3
Vaginal Birth	28	8.7

GHT: Gestational Hypertension, TPL: Threatened Preterm Labor, IUGR: Intrauterine Fetal Growth Retardation, SGA: Small For Gestational Age, LGA: Large For Gestational Age, PROM: Premature Rupture of Membranes, n: Number, %: Percent

The development of preeclampsia was 1.39 times, fetal distress 1.49 times, preterm delivery 1.6 times, shoulder dystocia 3.4 times, and neonatal hypoglycemia 1.4 times

more common in pregnant women with pregestational DM compared to pregnant women with GDM. The incidence of existing complications was statistically significant in the pregestational DM group (95% CI, p<0.05). Complication rates between pregestational DM and GDM are given in Table 2.

Table 2. *Complication rates between GDM and Pregestational DM*

	GDM	PDM	P
	n (%)	n (%)	
Preeclampsia	93 (37.5)	38 (52.1)	**0.026***
GHT	104 (41.9)	33 (45.2)	0.620
İntrahepatic Cholestasis	6 (2.4)	2 (2.7)	0.877
Placenta Accreta	2 (0.8)	0 (0)	0.441
Placenta Previa	2 (0.8)	1 (1.4)	0.660
TPL	56 (22.6)	24 (32.9)	0.074
PROM	12 (4.8)	5 (6.8)	0.500
Oligohydramnios	28 (11.3)	5 (6.8)	0.272
Polyhydramnios	32 (12.9)	14 (19.2)	0.179
IUGR	34 (13.7)	8 (11)	0.540
SGA	7 (2.8)	3 (4.1)	0.578
LGA	42 (16.9)	13 (17.8)	0.862
Fetal Distress	71 (28.6)	31 (42.5)	**0.026***
Preterm Birth	61 (24.6)	29 (39.7)	**0.037***
Shoulder Dystocia	5 (2)	5 (6.8)	**0.037***
Brachial Plexus İnjury	1 (0.4)	0 (0)	0.587
Neonatal Hypoglycemia	68 (27.4)	29 (39.7)	**0.044***
Newborn Weight Loss	23 (9.3)	11 (15.1)	0.157
Newborn Respiratory Distress	37 (14.9)	16 (21.9)	0.157
RDS	13 (5.2)	8 (11)	0.083
Hyperbilirubinemia	9 (3.6)	5 (6.8)	0.236

GDM: Gestational Diabetes Mellitus, PDM: Pregestational diabetes Mellitus, DM: Diabetes Mellitus, GHT: Gestational Hypertension, TPL: Threatened Preterm Labor, PROM: Premature Rupture of Membranes, IUGR: Intrauterine Fetal Growth Retardation, SGA: Small For Gestational Age, LGA: Large For Gestational Age, RDS: Respiratory Distress Syndrome, n: Number, %: Percent

**Chi-Square Test, 95% confidence interval was determined in the calculations and P values <0.05 were considered statistically significant.*

TPL was found 2.05 times, polyhydramnios 3.77 times, neonatal hypoglycemia 2.28 times, newborn weight loss 4.62 times, and hyperbilirubinemia five times more common in pregnant women with Type 1 DM compared to pregnant women with Type 2 DM. The incidence of existing complications was statistically significant in the Type1 DM group (95% CI, p<0.05). Complication rates between Type 1 DM and Type 2 DM are given in Table 3.

GHT was found 1.72 times, preeclampsia 1.56 times, TPL 1.85 times, and LGA 2.07 times more in the group using insulin therapy (GDMA2) compared to the group given diet/exercise treatment (GDMA1) in pregnant women with GDM. The incidence of existing complications was statistically significant in the GDMA2 group (95% CI, p<0.05).

Table 3. *Complication rates between Type 1 DM and Type 2 DM*

	Type 1 DM	Type 2 DM	P
	n (%)	n (%)	
Preeclampsia	22 (61.1)	16 (43.2)	0.127
GHT	20 (55.6)	13 (35.1)	0.080
İntrahepatic Cholestasis	2 (5.6)	0 (0)	0.146
Placenta Accreta	0 (0)	0 (0)	-
Placenta Previa	0 (0)	1 (2.7)	0.321
TPL	16 (44.4)	8 (21.6)	**0.038***
PROM	3 (8.3)	2 (5.4)	0.620
Oligohydramnios	4 (11.1)	1 (2.7)	0.155
Polyhydramnios	11 (30.6)	3 (8.1)	**0.015** *
IUGR	5 (13.9)	3 (8.1)	0.429
SGA	1 (2.8)	2 (5.4)	0.572
LGA	9 (25)	4 (10.8)	0.113
Fetal Distress	18 (50)	13 (35.1)	0.119
Preterm Birth	17 (47.2)	12 (32.4)	0.197
shoulder dystocia	4 (11.1)	1 (2.7)	0.155
Brachial Plexus İnjury	0 (0)	0 (0)	-
Neonatal Hypoglycemia	20 (55.6)	9 (24.3)	**0.006***
Newborn Weight Loss	9 (25)	2 (5.4)	**0.019***
Newborn Respiratory Distress	11 (30.6)	5 (13.5)	0.078
RDS	4 (11.1)	4 (10.8)	0.967
Hyperbilirubinemia	5 (13.9)	0 (0)	**0.019***

DM: Diabetes Mellitus, GHT: Gestational Hypertension, TPL: Threatened Preterm Labor, PROM: Premature Rupture of Membranes, IUGR: Intrauterine Fetal Growth Retardation, SGA: Small For Gestational Age, LGA: Large For Gestational Age, RDS: Respiratory Distress Syndrome, n: Number, %: Percent

** Chi-Square Test, 95% confidence interval was determined in the calculations and P values <0.05 were considered statistically significant.*

Oligohydramnios was found 2.4 times more frequently in pregnant women with a diagnosis of GDMA1 compared to pregnant women with a diagnosis of GDMA2. The detection of oligohydramnios in pregnant women with GDMA1 was statistically significant (95% CI, p<0.05). Complication rates between GDMA1 and GDMA2 in patients with GDM according to the treatment method are given in Table 4.

GHT was found 1.8 times, preeclampsia 2.1 times, TPL 3 times, polyhydramnios 2.4 times, LGA 2 times, fetal distress 2.17 times, preterm labor 2.67 times, neonatal hypoglycemia 1.73 times, newborn weight loss 2.09 times, neonatal respiratory distress 2.18 times, respiratory distress syndrome (RDS) 3.62 times and, hyperbilirubinemia 4.82 times more in pregnant women with HbA1c value between 6-7.9% compared to pregnant women with HbA1c value between 4-5.9%. The incidence of existing complications was statistically significant in the patient group with HbA1c values between 6-7.9% (95% CI, p<0.05).

GHT was found 1.84 times, preeclampsia 2.53 times, TPL 4.76 times, oligohydramnios 2.65 times, polyhydramnios 2.65 times, LGA 2.8 times, fetal distress 2.72 times, preterm labor 3.81 times, neonatal hypoglycemia 1.81 times, neonatal weight loss 2.98 times, neonatal respiratory

distress 1.8 times, RDS 1.12 times and hyperbilirubinemia 7.55 times in pregnant women with HbA1c value of 8 and above compared to pregnants with an HbA1c value of 4-5.9%. The incidence of existing complications was statistically significant in the patient group with an HbA1c value of 8% and above (95% CI, p<0.05).

Table 4. *Complication Rates in GDM Patients by Treatment Type*

	Diet/Exercise (GDMA1)	İnsulin (GDMA2)	P
	n (%)	n (%)	
GHT	39(31%)	65(53.3%)	**0.001***
Preeclampsia	37(29.4%)	56(45.9%)	**0.007***
İntrahepatic Cholestasis	3 (2.4%)	3 (2.5%)	0.968
Plasenta Accreta	0(%0)	2(1.6%)	0.149
Plasenta Previa	2(1.6%)	0(%0)	0.162
TPL	20(15.9%)	36(29.5%)	**0.010***
PROM	4 (3.2%)	8 (6.6%)	0.215
Oligohydramnios	20(15.9%)	8 (6.6%)	**0.020***
Polyhydramnios	13(10.3%)	19(15.6%)	0.217
IUGR	21(16.7%)	13(10.7%)	0.169
SGA	3 (2.4%)	4(3.3%)	0.670
LGA	14(11.1%)	28(23%)	**0.013***
Fetal Distress	31(24.6%)	40(32.8%)	0.154
Preterm Birth	29(23%)	32(26.2%)	0.490
Shoulder Dystocia	1 (0.8%)	4(3.3%)	0.164
Brachial Plexus İnjury	0(%0)	1 (0.8%)	0.309
Neonatal Hypoglycemia	31(24.6%)	37(30.3%)	0.312
Newborn Weight Loss	11(8.7%)	12(9.8%)	0.764
Newborn Respiratory Distress	19(15.1%)	18(14.8%)	0.943
RDS	4 (3.2%)	9(7.4%)	0.138
Hyperbilirubinemia	4 (3.2%)	5(4.1%)	0.697

GDM: Gestational Diabetes Mellitus, HbA1c: Glycosylated HemoglobinA1c, GHT: Gestational Hypertension, TPL: Threatened Preterm Labor, PROM: Premature Rupture of Membranes, IUGR: Intrauterine Fetal Growth Retardation, SGA: Small For Gestational Age, LGA Age: Large For Gestational, RDS Respiratory Distress Syndrome, n: Number, %: Percent

** Chi-Square Test, 95% confidence interval was determined in the calculations and P values <0.05 were considered statistically significant.*

IUEF was found 24.46 times more frequently in the patient group with an HbA1c value of 8% and above. A statistically significant correlation was found between the occurrence of IUEF and high HbA1c (95% CI, p<0.05). Complication rates according to HbA1c are given in Table 5.

GHT was found 2.95 times, preeclampsia 4.31 times, TPL 14 times, polyhydramnios 2.01 times, LGA 1.65 times, fetal distress 2.17 times, preterm birth 1.94 times, neonatal hypoglycemia 2.35 times, and neonatal respiratory distress 1.79 times in the patient group with HbA1c value between 5-5.9% in pregnant women diagnosed with GDM, compared to the patient group with an HbA1c value between 4-4.9%. The incidence of existing complications was statistically significant in the patient group with HbA1c values between 5-5.9% (95% CI, p<0.05).

Table 5. *Complication rates by HbA1c*

HbA1c	Between %4-5.9 n (%)	Between %6-7.9 n (%)	%8 and Above n (%)	P
GHT	77 (34.5)	44 (63.8)	14 (63.6)	**0.001***
Preeclampsia	68 (30.5)	44 (63.8)	17 (77.3)	**0.001***
İntrahepatic Cholestasis	4 (1.8)	3 (4.3)	1 (4.5)	0.414
Placenta Accreta	1 (0.4)	1 (1.4)	0 (0)	0.611
Placenta Previa	3 (1.3)	0 (0)	0 (0)	0.539
TPL	32 (14.3)	37 (47.8)	15 (68.2)	**0.001***
PROM	11 (4.9)	5 (7.2)	1 (4.5)	0.746
Oligohydramnios	23 (10.3)	4 (5.8)	6 (27.3)	**0.016***
Polyhydramnios	23 (10.3)	17 (24.6)	6 (27.3)	**0.003***
IUGR	29 (13)	12 (17.4)	1 (4.5)	0.291
SGA	6 (2.7)	3 (4.3)	1 (4.5)	0.737
LGA	23 (13)	18 (26.1)	8 (36.4)	**0.002***
Fetal Distress	52 (23.3)	35 (50.7)	14 (63.6)	**0.001***
Preterm Birth	40 (17.9)	33 (47.8)	15 (68.2)	**0.001***
Shoulder Dystocia	4 (1.8)	5 (7.2)	1 (4.5)	0.073
Brachial Plexus İnjury	0 (0)	1 (1.4)	0 (0)	0.168
Neonatal Hypoglycemia	56 (25.1)	30 (43.5)	10 (45.5)	**0.004***
Newborn Weight Loss	17 (7.6)	11 (15.9)	5 (22.7)	**0.022***
Newborn Respiratory Distress	28 (12.6)	19 (27.5)	5 (22.7)	**0.010***
RDS	9 (4)	10 (14.5)	1 (4.5)	**0.007***
Hyperbilirubinemia	4 (1.8)	6 (8.7)	3 (13.6)	**0.003***
Ex Fetüs	3 (1.3)	1 (1.5)	7 (31.8)	**0.001***

HbA1c: Glycosylated HemoglobinA1c, GHT: Gestational Hypertension, TPL: Threatened Preterm Labor, PROM: Premature Rupture of Membranes, IUGR: Intrauterine Fetal Growth Retardation, SGA: Small For Gestational Age, LGA: Large For Gestational Age, RDS: Respiratory Distress Syndrome, n: Number, %: Percent

** Chi-Square Test, 95% confidence interval was determined in the calculations and P values <0.05 were considered statistically significant.*

GHT was found 4.05 times, preeclampsia 7.02 times, TPL 34.7 times, polyhydramnios 3.87 times, SGA 1.06 times, LGA 3.5 times, fetal distress 4.37 times, preterm birth 4.6 times, neonatal hypoglycemia 3.32 times, and neonatal respiratory distress 3.37 times İn the patient group with an HbA1c value of 6% and above in pregnant women diagnosed with GDM, compared to the patient group with an HbA1c value between 4-4.9%. The incidence of existing complications was statistically significant in the group of patients with an HbA1c value of 6% and above (95% CI, p<0.05). Complication rates according to HbA1c in patients with GDM are given in Table 6.

Table 6. *Complication rates according to HbA1c in GDM Patients*

HbA1c	**Between %4-4.9**	**Between %5-5.9**	**%6 and Above**	
	n (%)	**n (%)**	**n (%)**	**P**
GHT	10 (15.9)	63 (47)	29 (64.4)	**0.001***
Preeclampsia	6 (9.5)	55 (41)	30 (66.7)	**0.001***
Intrahepatic Cholestasis	3 (4.8)	1 (0.7)	2 (4.4)	0.154
Placenta Accreta	0 (0)	1 (0.7)	1 (2.2)	0.448
Placenta Previa	1 (1.6)	1 (0.7)	0 (0)	0.660
TPL	1 (1.6)	30 (22.4)	25 (55.6)	**0.001***
PROM	1 (1.6)	9 (6.7)	2 (4.4)	0.298
Oligohydramnios	6 (9.5)	16 (11.9)	6 (13.3)	0.814
Polyhydramnios	4 (6.3)	17 (12.7)	11 (24.4)	**0.023***
IUGR	6 (9.5)	20 (14.9)	8 (17.8)	0.434
SGA	4 (6.3)	0 (0)	3 (6.7)	**0.011***
LGA	6 (9.5)	21 (15.7)	15 (33.3)	**0.004***
Fetal Distress	8 (12.7)	37 (27.6)	25 (55.6)	**0.001***
Preterm Birth	7 (11.1)	29 (21.6)	23(51.1)	**0.001***
Shoulder Dystocia	1 (1.6)	1 (0.7)	3 (6.7)	0.052
Brachial Plexus Injury	0 (0)	0 (0)	1 (2.2)	0.111
Neonatal Hypoglycemia	8 (12.7)	40 (29.9)	19 (42.2)	**0.002***
Newborn Weight Loss	3 (4.8)	14 (10.4)	5 (11.1)	0.377
Newborn Respiratory Distress	5 (7.9)	19 (14.2)	12 (26.7)	**0.025***
RDS	2 (3.2)	6 (4.5)	4 (8.9)	0.374
Hyperbilirubinemia	2 (3.2)	2 (1.5)	4 (8.9)	0.056
Ex Fetus	1 (1.6)	2 (1.5)	3 (6.8)	0.350

GDM: Gestational Diabetes Mellitus, HbA1c: Glycosylated HemoglobinA1c, GHT: Gestational Hypertension, TPL: Threatened Preterm Labor, PROM: Premature Rupture of Membranes, IUGR: Intrauterine Fetal Growth Retardation, SGA: Small For Gestational Age, LGA Age: Large For Gestational, RDS Respiratory Distress Syndrome, n: Number, %: Percent

** Chi-Square Test, 95% confidence interval was determined in the calculations and P values <0.05 were considered statistically significant.*

GHT was found 4.05 times, preeclampsia 7.02 times, TPL 34.7 times, polyhydramnios 3.87 times, SGA 1.06 times, LGA 3.5 times, fetal distress 4.37 times, preterm birth 4.6 times, neonatal hypoglycemia 3.32 times, and neonatal respiratory distress 3.37 times in the patient group with an HbA1c value of 6% and above in pregnant women diagnosed with GDM, compared to the patient group with an HbA1c value between 4-4.9%. The incidence of existing complications was statistically significant in the group of patients with an HbA1c value of 6% and above (95% CI, $p<0.05$). Complication rates according to HbA1c in patients with GDM are given in Table 6.

DISCUSSION

Tight glycemic control is essential to minimize maternal and fetal morbidity and mortality in pregnancies complicated with diabetes. HbA1c is a useful parameter in the metabolic control of DM, in addition to home blood glucose measurement, which may not always reflect the true average blood glucose level. High HbA1c levels are associated with increased obstetric complications during pregnancy (9).

In our study, the relationship between the HbA1c value measured between 24-30 weeks of pregnancy and obstetric complications was investigated. This study aimed to identify patients who might be at risk according to HbA1c, predict and manage complications early. In the normal population, an average of 90% of pregnant women with DM is GDM and 10% are pregestational DM (10).

Emma L.J. et al. found the rate of GDM at 28.8% in their study on 466 women in Australia (11). Our study was conducted on 321 pregnant women and we have a 77.3% GDM and 22.7% pregestational DM rate. In our study, the rate of preeclampsia was 52.1% in patients with pregestational DM, and this rate was 61.1% in the Type 1 DM patient group and 43.2% in the Type 2 DM patient group.

Murphy HR et al. found the rate of preeclampsia to be 7.8% in patients with Type 1 DM and 5.2% in patients with Type 2 DM in a study they conducted in 2011 in patients with Type 1 DM and Type 2 DM (12). In our study, the rate of preeclampsia was 37.5% in patients with GDM. In a study conducted by Bodmer-Roy et al. on patients with GDM in Canada between 2008 and 2010, the rate of preeclampsia was 6.5%. Again, in the study conducted by Bodmer-Roy et al., the rate of preeclampsia was 2.7% in patients in the control group (13). In the HAPO study, the rate of development of preeclampsia was 4.8% in pregnant women diagnosed with GDM (2). The reason for the high rate of preeclampsia in our study is the fact that we are a tertiary center.

GHT and preeclampsia were found in 63.8% of pregnant women whose HbA1c values were between 6-7.9%. 63.6% GHT and 77.3% preeclampsia were found in pregnant women with an HbA1c value of 8% and above. In the pregnant women diagnosed with GDM, on the other hand, 47% of GHT and 41% of preeclampsia were found in the patient group whose HbA1c value was between 5 and 5.9%.

In the patient group with an HbA1c value of 6% and above in pregnant women with GDM, 64.4% of GHT and 66.7% of preeclampsia were detected. Sibai reported that preeclampsia rates varying between 9-66% were found in a study conducted in England on patients with pregestational DM. It was reported that this rate increased as the severity of DM increased according to White's classification, and the highest rate was seen in women with pregestational DM and nephropathy. Again, Sibai reported that as the severity of DM increases in women with Type 1 DM, the rates of preeclampsia and adverse neonatal outcomes increase (14).

Holmes et al. investigated the relationship between glycemic control, preeclampsia, and GHT in women with Type 1 DM in their study in 2011. This is a prospective study conducted on 749 pregnant women with Type 1 DM. They found preeclampsia in 17% of the patients and GHT in 11%. They found that women who developed preeclampsia had significantly higher HbA1c values before and during pregnancy compared to women who did not develop preeclampsia ($P<0.05$). Patients with HbA1c≥8.0% in early pregnancy were associated with a significantly increased risk of preeclampsia (Odds ratio 3.68 [95% CI 1.17-11.6]) compared with patients with optimal control (15).

Lapolla et al. conducted a 33-centered study in Italy between 1999-2003. They found the rates of TPL, GHT, and preeclampsia to be significantly higher in patients with HbA1c value of 8% and above compared to the control group. In addition, they found the rates of stillbirth and neonatal death in pregnant women with DM higher than in the normal population (16). Yin B. et al. found the rate of preeclampsia to be 1.7% in a recent study conducted on 8585 women between 2018 and 2019. Again, in this study, it was reported that there was an increased risk of preeclampsia in patients with an HbA1c value between 5.5-5.9% (17). Temple R. et al. conducted a study in which they examined the relationship between monthly HbA1c level, pre-pregnancy care, parity, duration of DM, microvascular complications, and maternal age to determine the risk of preeclampsia in 290 pregnant women with Type 1 DM. In this study, it was determined that week 24th-week HbA1c levels of patients who developed preeclampsia increased significantly compared to patients who did not develop preeclampsia (18).

Odsæter IH. et al. found a significant relationship between first-trimester HbA1c values and the development of preeclampsia (19). Maresh MJ. et al. found an increased risk of preeclampsia at HbA1c values of 6.0-6.4% (42-47 mmol/mol) during pregnancy (20). In our study, a significant relationship was found between high HbA1c levels and the development of GHT and preeclampsia. Current literature information supports our study.

In our study, polyhydramnios was found at a rate of 30.6% in pregnant women with Type 1 DM and 8.1% in pregnant women with Type 2 DM. Polyhydramnios was found at a rate of 24.6% in the patient group with an HbA1c value between 6-7.9% and at 27.3% in the patient group with an HbA1c value of 8% and above. Polyhydramnios was found at a rate of 12.7% in the patient group with an HbA1c value between 5-5.9% in pregnant women diagnosed with GDM and 24.4% in the patient group with an HbA1c value of 6 and above. Idris N. et al. found the incidence of polyhydramnios as 18.8% in a study on polyhydramnios in pregnant women with pregestational DM between 1996 and 2006 at the Maternal-Fetal Medicine Department of Mater Mothers Hospital. The HbA1c values of patients with polyhydramnios were significantly higher, and it was found in patients with poor glycemic control (21). Deniz K. et al., who investigated the relationship between HbA1c and the development of polyhydramnios, found the incidence of polyhydramnios as 2.9%. In this study, they stated that HbA1c was a positive independent predictor for AFI and that AFI value at 32-34 weeks of gestation was associated with mid-pregnancy HbA1c level (22).

In our study, no relationship was found between PROM and DM. The study by Sun B. et al. found the rate of PROM development to be higher in patients with GDM and IGT compared to the normal population (23).

In our study, the incidence of preterm labor was higher in patients with high HbA1c values compared to patients with normal HbA1c values. Murphy HR et al. reported the rate of preterm birth as 37.1% in pregnant women with Type 1 DM and 17.5% in pregnant women with Type 2 DM (12). Ho Yi-Ran et al. conducted a prospective study on 1989 pregnant women. As a result of this study, they reported that high HbA1c levels (7% and above) lead to an increase in the risk of GHT, preeclampsia, premature birth, increased need for neonatal intensive care, low birth weight, and macrosomia (24).

In a study conducted by Barbry F et al. on 4383 women between 2011 and 2018, they found high preterm birth rates in pregnant women with HbA1c>5.9% (25). In our study, a higher rate of preterm delivery was found in pregestational DM patients, which is consistent with the literature.

In our study, SGA was found at a rate of 6.7% in the group with an HbA1c value of 6% and above in pregnant women diagnosed with GDM. Pedersen et al. reported that 10 pregnant women with HbA1c of 8.9% and above had fetuses smaller than normal (26).

Fetal distress was found at a rate of 50.7% in the patient group with an HbA1c value between 6-7.9% and in 63.6% in the patient group with an HbA1c value of 8% or more. Fetal distress was found at a rate of 27.6% in the patient group with an HbA1c value between 5 and 5.9% in pregnant women with GDM and 55.6% in the patient group with an HbA1c value of 6% and above. In a study conducted by Teramo K. et al. on 145 pregnant women, they found the 3rd-trimester average HbA1c values of pregnant women with DM who had fetal heart rate (FHR) abnormalities to be 7.63±0.87%. This value was significantly higher than pregnant women with DM who were included in the study and had normal FHR records (P<0.02) (27). In our study, fetal distress was detected in pregnant women with high HbA1c levels, which is consistent with the literature.

LGA was found at a rate of 26.1% in the patient group with an HbA1c value between 6-7.9% and in 36.4% in the patient group with an HbA1c value of 8% or more. In the pregnant women diagnosed with GDM, 15.7% of the patients with HbA1c values between 5 and 5.9%, and 33.3% of the patients with HbA1c values of 6% and above were found to have LGA. Murphy HR et al. found the LGA rate as 52.9% in pregnant women with Type 1 DM and 37.6% in pregnant women with Type 2 DM (12). The study conducted by Emma L. J. et al. showed that there is an increase in LGA risk in pregnant women with HbA1c≥5.6% (≥38 mmol/mol) at early gestational weeks (11). Lemaitre M. et al. retrospectively analyzed the birth records of 678 pregnant women at Lille Hospital between 1997 and 2019. In this study, the mean HbA1c of the patients before pregnancy was 7.2% (55 mmol/mol). Consistent with Lemaitre M. et al.'s findings, in the present study, LGA was found in 361 (56%), SGA in 29 (4.5%), and preterm delivery (76.1%) in 504 patients. In this study by Lemaitre M. et al., it was stated that high HbA1c was associated with maternal and fetal complications (28).

Cordero L et al. conducted a study on neonatal problems in 530 pregnant women with GDM and pregestational DM. Considering the results of 530 newborns in this study, 76 (14%) were born before 34 weeks of gestation, 115 (22%) were born between 34-37 weeks of gestation, and 339 (64%) were born at term. Again, 233 (47%) infants were reported to be admitted to the neonatal intensive care unit due to RDS, prematurity, hypoglycemia, or congenital malformation. In addition, hypoglycemia was found in 137 (27%) newborns, and RDS of varying severity was found in 182 (34%) newborns in this study. Polycythemia was found in 5%, hyperbilirubinemia in 25%, hypocalcemia in 4%, LGA in 36%, and SGA in 2% of newborns (29). The most common metabolic complications seen in infants of mothers with DM are listed as hypoglycemia, hypocalcemia, and hypomagnesemia (30). In our study, preeclampsia, fetal distress, preterm delivery, shoulder dystocia, and neonatal hypoglycemia were found more frequently in pregnant women with pregestational DM. TPL, polyhydramnios, hyperbilirubinemia, neonatal hypoglycemia, and neonatal weight loss were found more frequently in pregnant women with type 1 DM.

GHT, preeclampsia, TPL, oligohydramnios, polyhydramnios, LGA, fetal distress, preterm delivery, neonatal hypoglycemia, neonatal weight loss, respiratory distress, RDS, hyperbilirubinemia, and IUEF were found more frequently in pregnant women with an HbA1c value of 8% and above. GHT, preeclampsia, TPL, polyhydramnios, SGA, LGA, fetal distress, preterm delivery, neonatal hypoglycemia, and neonatal respiratory distress were found more frequently in pregnant women with GDM diagnosis and high HbA1c values. Our present findings are compatible with the literature information.

CONCLUSION

As a result of our study, it was observed that there was an increase in the rates of existing complications in pregnant women with high HbA1c levels. In conclusion, HbA1c is an important DM follow-up and treatment indicator in pregnancy. It is useful to be careful about complications in patients with high HbA1c. If we look at the additional results of our study, the complication rates are higher in patients with pregestational DM. In patients with a diagnosis of pregestational DM, the rates of existing complications were

higher in patients with a diagnosis of Type 1 DM. HbA1c should be reduced to acceptable ranges before pregnancy in patients with a diagnosis of pregestational DM and at the earliest time in patients with GDM. It should not be forgotten that a high HbA1c value indicates possible complications.

Limitations of the Study

As a result of our study, it was determined that there was an increased complication rate in pregnant women with high HbA1c. In our study, we have obtained data that may be useful in managing pregnant women with DM. Our retrospective study was a single-center study. It was also conducted in a small population and a tertiary center. If all these reasons are considered, prospective, multicenter studies in larger populations are needed.

Etik: Bu çalışmanın etik kurulu alınmıştır.

Ethics committee approval had been taken.

Yazar katkı durumu; Çalışmanın konsepti; İK, SDS, MK, dizaynı; İK, SDS, MK, Literatür taraması; İK, SDS, MK, verilerin toplanması ve işlenmesi; İK, SDS, MK, istatistik; İK, SDS, MK, yazım aşaması; İK, SDS, MK,

Author contribution status; The concept of the study; İK, SDS, MK, design; İK, SDS, MK, literature review; İK, SDS, MK, collecting and processing data; İK, SDS, MK, statistics; İK, SDS, MK, writing phase; İK, SDS, MK,

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