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DETERMINING THE IMPORTANCE OF GLYCEMIC VARIABILITY IN GESTATIONAL DIABETES MELLITUS USING VARIOUS TECHNIQUES

GESTASYONEL DİABETES MELLİTUSTA GLİSEMİK DEĞİŞKENLİKLERİN ÖNEMİ VE FARKLI YÖNTEMLERLE ARAŞTIRILMASI

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ABSTRACT

Objective: The study aims to determine glycemic variation in patients with gestational diabetes mellitus (GDM) and to evaluate the effect on the fetal growth using a continuous glucose monitoring system (CGMS) and to investigate the correlation between glucose variation through biomarkers including HbA1c, fructosamine (FRM), and 1.5-Anhydroglucitol (1.5-AG).

Materials and Methods: The study involves 31 women with GDM at gestational week ≥35 who'd only had diet therapy. Blood glucose levels were monitored for three consecutive days using CGMS to evaluate mean blood glucose levels and mean absolute difference (MAD). Self-monitoring of blood glucose (SMBG) was required from the patients while having the CMGS on their body. Blood samples were collected to measure serum 1.5-AG, HbA1c, and FRM.

Results: The mean levels were HbA1c=5.0±0.3%, FRM=2.1±0.2 µmol/L, 1.5-AG=17.0±4.9 ng/ml, and 3-day average max-min glucose range=131.1±22.5 and 54.7±11.6 mg/dl (MAD=6.7±3.1%). The mean glucose levels measured using SMBG and CGMS were similar (82.9±10.2 vs 86.1±10.3 mg/dL). No correlation occurred between CMGS and biomarkers. The baby weight at birth and head circumference was determined to be lower for patients with glucose fluctuations.

Conclusion: Biomarkers do not reflect glycemic fluctuation, and regular SMBG is required to achieve the desired glucose

ÖZET

Amaç: Gestasyonel Diabetes Mellitus (GDM)'da gün içi glukoz dalgalanmaları ve bunun bebek üzerine etkisini belirlemek; ayrıca, glukozdaki dalgalanmaların HbA1c, fruktozamin (FRM) ve 1,5-Anhidroglucitol (1,5-AG) ile korelasyonunu saptamaktır.

Gereç ve Yöntem: Sadece diyetle takip edilen GDM tanısı alan ve ≥35 gebelik haftasındaki 31 hastada devamlı glukoz ölçüm sistemi (CGMS) ile 72 saatlik glisemik değişkenlikler (ortalama mutlak değer %MAD ve ortalama glukoz değeri) ölçüldü, ayrıca hastalardan, CGMS takılı olduğu günler, kendi kendine glukoz ölçüm sistemi (SMBG) her öğün öncesinde ve birinci saat sonrasında parmak ucundan kan glukoz düzeylerini ölçmeleri istendi. 1,5 AG, Hba1c ve FRM düzeyleri CGMS çıkarıldığı üçüncü gün hastalardan alındı.

Bulgular: Hastaların ortalama HbA1c, FRM ve 1,5-AG sırasıyla %5,0±0,3, 2,1±0,2 µmol/L, ve 17,0±4,9 ng/mL idi. Üç günlük izlemde maximum-minimum glukoz düzeyi ortalaması 131,1±22,5 ve 54,7±11,6 mg/dL iken %MAD değeri %6,7±3,1 idi. SMBG ve CGMS ile ölçülen ortalama glukoz değeri birbiri ile koreleyken (82,9±10,2 ve 86,1±10,3 mg/dL); glukoz dalgalanması ile FRM, HbA1c ve 1,5-AG arasında anlamlı korelasyon yoktu. Hastaların glikoz dalgalanmaları varsa doğumdaki bebek ağırlığının ve baş çevresinin düşük olduğu belirlendi.

Sonuç: Çalışmamızda biyobelirteçlerin glisemik dalgalanmayı yansıtmadığı; istenilen glukoz seviyesinin sağlanması için, diyet-

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level, even in diet-regulated GDM. Lower head circumference and birth weight were determined in GDM mothers with high glycemic fluctuations, and CGMS may be an alternative method despite its cost and application difficulties.

Keywords: Gestational diabetes, 1.5-anhydroglucitol, glycemic variability, HbA1c, fructosamine

le regüle GDM de bile, SMBG'un sık, düzenli olarak yapılmasının gerekliliği saptanmıştır; ancak glisemik dalgalanmaları fazla olan GDM'li annenin bebeğinde baş çevresi ve doğum kilosu daha düşük saptanmıştır ve glisemik dalgalanmayı daha yakından gösteren CGMS' in her ne kadar maliyet ve uygulama zorluğu olsa da, SMBG' ye alternatif yöntem olabileceği gösterilmiştir.

Anahtar Kelimeler: Gestasyonel diabetes, 1.5 anhidroglucitol, glisemik değişkenlik, HbA1c, fruktozamin

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as glucose intolerance resulting in maternal and fetal complications that first begin in pregnancy (1). Pancreatic beta cell defect and chronic insulin resistance are thought to be present in GDM pathophysiology (2). Multiple maternal and fetal complications can occur such as hydramnios, preeclampsia, macrosomia, hypertension, and neonatal respiratory problems in GDM (3). The oral glucose tolerance test (OGTT) is recommended between the 24th-28th week of pregnancy due to GDM's high risk of complications (4).

Poorly controlled blood glucose levels are known to correlate with microvascular complications, with post-prandial hyperglycemia being a significant risk factor for macrovascular complications in GDM (5). In the third trimester of pregnancy, the insulin effect decreases by 50-70%, with the insulin concentrations being twice as high compared to non-pregnant women. Additionally, total gluconeogenesis increases in late pregnancy (6). Blood glucose levels may fluctuate during the day, and fluctuations can define a glycemic variability that can cause an increase in free radicals through oxidative stress. Free radicals are well known to trigger tissue damage by causing endothelial dysfunction due to a wide variety of pathological pathways and different mechanisms (7). Although the correlation between glycemic variability and maternal/fetal complications is known, not enough information is found on this subject. Furthermore, no indicator is present that directly reflects glycemic variability (5). Therefore, markers that show glycemic variability are needed in clinical practice (8). Self-monitoring of blood glucose (SBMG) can be used for glycemic control but can only be used to identify symptomatic hypoglycemia. Most hyperglycemia variabilities should be known to be asymptomatic, and this situation can be overlooked when using SBMG (4, 9). The most ideal method for determining the amplitude of glycemic variability is a continuous glucose monitoring system (CGMS), which can determine the percentage of mean absolute difference (MAD%) and be used to evaluate glycemic variability in patients (10). However, the uses of CGMS in clinical practice are limited due to its expensive and invasive nature. In clinical practice, glycemic control monitoring occurs by Hemoglobin A1c (HbA1c) and fructosamine (FRM) in GDM. Although HbA1c reflects three-month glycemic control, it may test normal even in the presence of significant glycemic variability, as hypoglycemic episodes compensate for hyperglycemia. Studies have shown fetal complications to develop frequently, even at normal HbA1c levels (11). FRM is another marker that reflects the average glucose level over a 1-3week period and has been recommended due to its ability to reflect short-term glucose changes in cases where rapid therapy change may be required during pregnancy (12). Neither HbA1c nor FRM are sensitive indicators of glycemic variability in GDM. A more sensitive marker is needed in addition to these markers for evaluating variability. The literature has shown 1.5 Anhydroglucitol (1.5-AG) to reflect short-term glycemic control, variability, and postprandial hyperglycemia (13).

In line with this information, this study aims to investigate the fluctuations in daily glucose levels in the third trimester of pregnancy with GMD using CGMS and SMBG and to evaluate the correlation among the HbA1c, FRM, and 1.5 AG markers.

MATERIALS AND METHODS

Study design and patient selection

The study involves 33 pregnant women with GDM undergoing follow-up in Istanbul University Adult Endocrinology Clinic after the 35th week of pregnancy. GDM was diagnosed in accordance with the Turkish Society of Endocrinology and Metabolism Diabetes Mellitus guidelines (4). The patients' demographic and clinical characteristics include questions about family history, gestational week, pre-gestational weight, weight during pregnancy, pre-gestational body mass index (BMI), comorbidity, previous abortion history, stillbirth, or large baby history. A physical examination of each patient was performed by the physician conducting the study, and each patient consulted with the gynecology clinic in terms of the fetal exam. Pregnant women who'd been diagnosed with GDM in previous pregnancies or have GDM and receive insulin therapy were excluded from the study in order to prevent iatrogenic glycemic variability. In addition, those with GDM and hemoglobin levels <12 gr/dL were also excluded from the study to prevent false low readings regarding HbA1c.

This study was approved by the local institution's ethics committee (Date: 21.02.2014, No: 04) and was conducted with the funding through the Istanbul University Scientific Research Project (Project No. 44800). Written informed consent was obtained from all study participants.

Evaluating glycemic variability

In order to evaluate the daily glucose level in each patient, a 72-hr CMGS (brand name Enlite Glucose Sensor®) was applied to all patients' extensor side of the upper arm, and all glucose measurements over the 72 hours were recorded on the Medtronic recorder®. At the end of the 72 hours, the patients were called in to have the sensor removed. The data from the CGMS was uploaded over the Internet to the software program CareLink iPro® specially organized by Medtronic®. To correlate the CMGS measurement with the SMBG, patients were asked to measure and keep a dairy of their blood glucose levels using their own blood glucose meters six times daily (pre- and 1-hr post-breakfast, pre- and 1-hr post-lunch, and pre- and 1-hr post-dinner). The patients' total number of glucose measurements during the 72 hours with CGMS; the highest, lowest, and mean glucose levels over the three days; standard deviation; daily absolute mean variability in glucose (MAD%); and number of high, low, and total fluctuations in glucose level were determined using the CGMS. In addition, the time interval below, between, and above the limit glucose values of 70-140 mg/dL, as well as the areas under the curves above the limit glucose values of 140 mg/dL (AUC -above limit) and below 70 mg/dL (AUC-below limit) were detected by the CGMS. The MAD% value was used for the 72-hr glucose variability in patients with GDM.

To determine the correlations between CMGS and SMBG using the 1.5-AG, HbA1c, and FRM, a blood sample was taken from the patients on the day of CGMS insertion. For the 1.5-AG level, the plasma was separated from the blood samples and kept at -80°C.The 1.5-AG measurements were studied collectively once all samples had been collected using the ELISA technique (Cusabio, Wuhan, China). The reference value for 1.5-AG is 14.4-30.2 mg/L in healthy subjects (14).

To evaluate the correlation 1.5-AG has with HbA1c and FRM, the HbA1C levels were measured using cation-exchange high performance liquid chromatography (HPLC; Bio-Rad, Richmond, California, USA), and FRM levels were determined using the colorimetric method within the Roche modular system (Roche, Mannheim, Germany).

Evaluating the effect of mothers' glycemic levels during pregnancy on their babies postpartum

To determine the effect of mother's glucose level on their baby when labor occurred, the patients were contacted by the physician conducting the study to record information about the date of birth; gestational week at the time of birth; delivery type; baby's birth weight, height, and head circumference; neonatal complications; and birth complications.

Statistical analysis

The data were analyzed and figures obtained using the program Statistical Package for Social Sciences (SPSS Inc., Armonk, NY, USA) v25.0. Demographic and clinical features were shown as percentages and means (±SD) or as a median with min-max levels in accordance with the data distribution. Spearman and Pearson correlation analyses were used for intercorrelations in accordance with the data distribution, with $p<0.05$ being considered significant for all analyses.

RESULTS

Results from the patients' demographics and clinical characteristics

The study involved 33 patient; however, due to data missing in the CGMS for two patients, the study had to dismiss these two and finish with data from 31 patients with GDM. The patients' mean age was 31.9±6.9 years, with a mean gestation period of 35.8±0.7 weeks. Additionally, the mean pre-pregnancy BMI was 26.2±5.9 kg/m^2, with a mean weight increase during pregnancy of 12.2±3.5 kg. When examining the patients' obstetric histories, 16.1% were seen to have a history of stillbirth, 67.7% a history of miscarriage, and 3.2% a history of large babies regarding the previous pregnancy duration. Patients' demographics and clinical characteristics are summarized in table 1.

Results from the patients' laboratory findings

While the patients' mean HbA1c level was 5.0±0.3%, their mean level of FRM was 2.1±0.2 µmol/L. Additionally, their mean 1.5-AG level was 17.0±4.9 ng/mL. All of the patients' laboratory findings are summarized in table 2.

Results from the patients' CGMS and SMBG

While the mean number of patients' glucose measurements during the 72-hr CGMS was 788.8±46.5, their mean highest glucose level during that span was 131.1±22.5 mg/dL and their mean lowest glucose level during that span was 54.7±11.6 mg/dL. Additionally, the mean glucose level for the 72-hr CGMS was 86.1±10.3 mg/dL. The 72-hr mean MAD%, which is the marker of daily glucose variation, was 6.7±3.1%. The mean glucose value measured by SMBG six times daily over the 72 hours was 82.9±10.2 mg/dL. The patients' CGMS and SGMS values are summarized in table 3.

A significant positive correlation was found between the mean glucose level for the 72-hr CGMS (86.1±10.3 mg/dL), and the mean glucose level as measured by SMBG six times a day for 72 hours (82.9±10.2 mg/dL; $r=0.767$, $p<0.001$) (figure 1).

Table 1: Demographics and clinical characteristics of the patients

Features	Median (min-max)	mean±SD	n, (%)
Age (years)	32 (20-47)	31.9±6.9	
DM history in the family			20 (64.5%)
Pregnancy duration (weeks)	36 (35-38)	35.8±0.7	
BMI (kg/m²)	26.4 (17.3-44.1)	26.2±5.9	
Weight before pregnancy (kg)	66 (46-110)	67.0±15.0	
Increase in the weight during pregnancy (kg)	13 (5-19)	12.2±3.5	
Obstetric examination findings during pregnancy			
Polyhydraamnios			2 (6.4%)
Oligohydroamnios			1 (3.2%)
Suspicion of trizomy 21			2 (6.4%)
Cleft palate-lib			1 (3.2%)
Number of pregnancy			
I			5 (16.1%)
II			10 (32.3%)
III			8 (25.8%)
IV			3 (9.7%)
V			4 (12.9%)
VI			1 (3.2%)
History of having stillbirth			5 (16.1%)
History of having miscarriage			10 (32.3%)
History of having large baby			1 (3.2%)
Concomitant disease			4 (12.9%)

BMI: Body mass index, DM: Diabetes mellitus, n: patient number; kg: kilogram, SD: standard deviation, min: minimum, max: maximum

Table 2: Laboratory findings of the patients

Laboratory features	
HbA1c (%) (mean±SD)	5.0±0.3
FRM (µmol/L) (mean±SD)	2.1±0.2
1,5-Anhydroglucitol (ng/mL) (mean±SD)	17.0±4.9
Triglyceride (mg/dL) (mean±SD)	204.3±72.3
HDL (mg/dL) (mean±SD)	65.5±17.3
LDL (mg/dL) (mean±SD)	151.5±38.7

HbA1c: Hemoglobin A1c, HDL: High density lipoprotein, LDL: Low density lipoprotein, SD: standard deviation, FRM: Fructosamine

At the end of the study, the glucose level of three of the patients whose CGMS data were examined was found to have been above 140 mg/dL during the 1st hour, and insulin therapy was requested. While one patient did not accept the use of insulin and continued diet therapy, basal-bolus insulin therapy was started in these other two patients. Existing diet therapy was continued in the remaining 28 patients.

Correlation analysis of CGMS measurements and laboratory parameters

Upon performing the correlation analyses of the CGMS measurements and laboratory findings for 1.5-AG, HbA1c, and FRM, no significant correlation was determined to exist between the CGMS measurements and laboratory findings (table 4). Additionally, no significant correlation was found among the laboratory measurements regarding 1.5-AG, HbA1c, and FRM.

Results regarding labor and newborns

Fourteen patients (45.2%) delivered vaginally, and 17 patients (54.8%) delivered by cesarean section. While the babies' mean birth weight was 3,142.9±366.2 gr, the babies' mean birth length (height) was 47.7±2.6 cm and mean head circumference was 34.3±1.3 cm. Thirteen infants had neonatal jaundice, with one having prolonged jaundice. Postnatal respiratory distress occurred in two babies. One of these babies had a cleft palate (lip defect). Neonatal hypoglycemia was not detected in any of the babies.

Table 3: Results of CGMS and SGMS values of the patients

Features	
Number of the glucose measurements in patients during 72 hours (mean±SD)	788.8±46.5
The highest glucose level for 72 hours with CGMS (mg/dL) (mean±SD)	131.1±22.5
The lowest glucose level for 72 hours with CGMS (mg/dL) (mean±SD)	54.7±11.6
Mean glucose level for 72 days with CGMS (mg/dL) (mean±SD)	86.1±10.3
MAD % (mean±SD)	6.7±3.1
AUC Above-140 mg/dL (median/min-max)	0.0 (0-1.5)
AUC Below-70 mg/dL (median/min-max)	1.0 (0-3.7)
Mean glucose level as measured by SMBG (mg/dL) (mean±SD)	82.9±10.2

AUC: Area under the curve, MAD%: Percentage of mean absolute differences, CGMS: Continuous glucose monitoring system, SMBG: Self-monitoring of blood glucose; SD: Standard deviation, min: minimum, max: maximum

Table 4: Correlation analysis between CGMS measurements and laboratory findings including HbA1c, FRM and 1,5 AG

CGMS Measurements		HbA1c	FRM	1,5- Anhydroglucitol
The highest glucose level for 72 hours with CGMS	r	-0.188	0.108	0.088
	p	0.310	0.565	0.640
The lowest glucose level for 72 hours with CGMS	r	0.096	-0.193	-0.059
	p	0.609	0.298	0.754
Mean glucose level for 72 days with CGMS	r	-0.154	0.153	-0.038
	p	0.409	0.413	0.839
MAD%	r	-0.036	-0.009	0.023
	p	0.849	0.961	0.904
AUC Above-140 mg/dL	r	-0.185	-0.078	0.113
	p	0.318	0.676	0.545
AUC Below-70mg/dL	r	-0.071	0.121	0.121
	p	0.703	0.517	0.518

CGMS: Continuous glucose monitoring system, AUC: Area under curve, MAD%: Percentage of mean absolute differences, HbA1c: Hemoglobin A1c, FRM: Fructosamine

A negative correlation was found between the AUC>140 mg/dL and mean birth weight (r=-0.428, p=0.016). A negative correlation was also determined between MAD% and babies' mean head circumference (r=-0.459, p=0.009). The babies of three patients (9.7%) who had post-prandial glucose levels > 140 mg/dL as measured by CGMS had lower birth weights (2,949.9±316.1 gr) and head circumferences (30.3±1.1 cm) compared to the other mothers' babies' birth weights (3,042.9±326.2 gr) and head circumferences (32.1±1.2 cm). However, these weight differences were not statistically significant (p>0.05).

Subgroup analysis of the patients

When dividing the patients into two groups according to the presence of a family history of DM, while 20 patients had a family history of diabetes, 11 patients had no family history. While the CGMS measurements and laboratory findings did not different between these two groups, infants' heights and weights were found to be significantly lower in the group with a family history (p=0.043 and p=0.029, respectively).

Patients were additionally divided into two different groups: those with a bad obstetric history and those without a bad obstetric history in terms of having a history of miscarriage, large baby, or stillbirth. While 12 patients had a history of large baby, stillbirth, or abortion in their previous pregnancies, 19 patients had no history. Upon considering both groups, their data regarding HbA1c, FRM, 1.5-AG, baby birth height, baby birth weight and head circumference were found to be similar.

The mean MAD% of the current study's group is the glycemic fluctuation parameter and was found to be 6.7%.

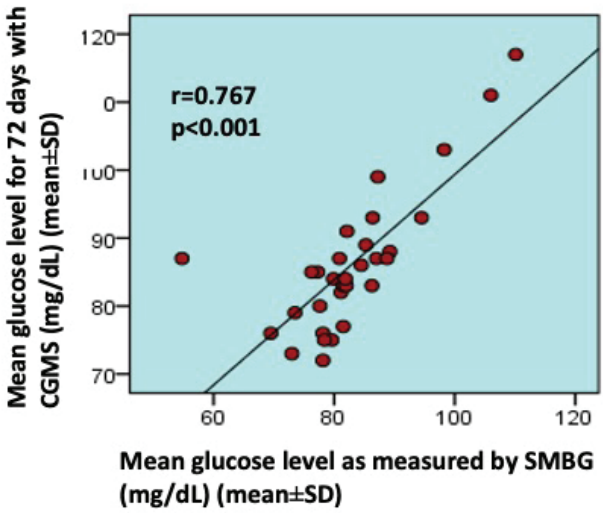

Figure 1: Correlation analysis between mean glukoz level for 72 days with CGMS and mean glucose level as measured by SMBG.

Upon separating patients into those with a MAD%>6.7 and those with MAD%<6.7, while 17 patients had a MAD%<6.7, 14 had a MAD%≥6.7. No significant difference was determined to occur between these two groups in terms of their demographics or clinical and laboratory findings, nor in terms of their babies' weight, height, or head circumference.

DISCUSSION

This prospective study has demonstrated that biomarkers HbA1c, FRM, and 1.5 AG do not determine the glycemic variability in patients with GDM during pregnancy. As a result of CGMS measurements, the patients were additionally observed to be able to experience glycemic variability throughout the day, even when their biomarkers were normal. Furthermore, the mean glucose level calculated as a result of the SBMG measurements showed a correlation with those calculated using the CGMS. When considering how simple, inexpensive, and easily applicable the SBMG measurement is compared to CGMS, this study can speculate that GDM complications can be minimized if the importance of self-monitoring glucose during pregnancy is emphasized.

Glycemic variability is important in pregnant women because complications can develop in both the pregnant woman and her fetus, and this means experiencing more episodes of hyperglycemia and hypoglycemia throughout the day (15). Furthermore, postprandial glycemia level is the biggest contributor to this glycemic fluctuation (16). Although the effect of glycemic variability on fetal complications is known, no indicator has been found yet that directly reflects these fluctuations (5). Neither A1C nor FRM are sensitive indicators of glycemic variability, and a more sensitive indicator is needed in addition to these (5). Studies have shown 1.5-AG to better reflect short-term glycemic control and postprandial hyperglycemia (16-18). With regard to the literature, Nowak et al. reported 1.5-AG to be a better marker than HbA1c for reflecting the glucose profiles of patients with gestational Type 1 DM and 1.5-AG to decrease in the third trimester (19); they argued it to be a highly predictive indicator for the development of macrosomia and thus the 1.5-AG measurement should be used in the clinic for pregnant women with Type 1 DM. However, in contrast to Nowak et al.'s study, the current study observed no correlation between glycemic variability determined using CGMS and the 1.5-AG levels of patients with GDM. The reason for the difference in two studies' result may be that the current study's patient group was made up of diet-regulated patients with GDM, while Nowak et al.'s study group involved pregnant women with Type 1 DM. Glycemic variability may be seen more frequently in patients with Type 1 DM due to the use of insulin and therefore they may have found lower 1.5-AG levels in Type 1 DM patients (19).

Another study determined glycemic variability with CGMS in patients with Type 2 DM, investigated the relationship this variability has with 1.5-AG, and also aimed to determine the correlations among 1.5-AG, A1C, and FRM (20). They found 1.5-AG to be negatively correlated with MAD% and to not be correlated with HbA1c and FRM. As a result, that study concluded 1.5-AG to better reflect glycemic fluctuations, especially during the postprandial period, compared to A1C and FRM. The current study also accordingly was unable to determine a correlation among the HbA1c, FRM, or 1.5-AG biomarkers. Also similar to the literature, no correlation was able to be observed between MAD% and 1.5-AG. Meanwhile, two studies were designed, one around pregnant women with Type 1 DM and the other around pregnant women with Type 2 DM; however, the current study was designed around pregnant women whose GDM was diet regulated (19-20). One can speculate that the reason no correlation was able to be detected was due to the current study's patient population being different, with a lower number of patients compared to other studies.

CGMS is well-known as a technique that is useful for managing patients with DM and especially for determining glycemic variability. Its use is even advocated for children and teens with Type 1 DM in accordance with the American Diabetes Association recommendations; however, no strong recommendations are found for this usage in people with Type 2 DM without insulin therapy or for women with GDM (21, 22). Although CGMS is an expensive and invasive technique for DM management and care, it can detect glycemic variabilities in patients with DM more sensitively due to the measurement frequency (21). SMBG has been published many times as

being a much cheaper method compared to CGMS, and daily blood glucose monitoring can be done correctly with SBMG once users are properly educated about it (23, 24). The current study found a significant correlation between the mean daily glucose level determined by CGMS and the mean glucose level determined by SBMG. In line with this result, one can consider SBMG to be an effective and sufficient method for blood glucose monitoring in pregnant women with GDM due to being both inexpensive and easily accessible. Meanwhile, this study also determined three patients (9.7%) who'd undergone CGMS to have had normal HbA1c and FRM levels and, despite having no abnormal measurement from the SBMG, their average postprandial blood glucose level was greater than 140 mg/dL after the CGMS measurement. Additionally, the study determined the patients with glucose levels>140 mg/dL as measured by CGSM to have a baby with lower birth weight and head circumference compared to the others. No other reason was found to explain low birth weight or small head circumferences in these patients. With these findings, one can speculate that, although SBMG is inexpensive, easy to use, and measures mean glucose levels similar to CGMS, fetuses suffering from growth retardation (e.g., low weight, small head circumference) whose mother may have high blood glucose levels may want to consider CGMS over SBMG for monitoring their glucose more closely.

When separating the patients into two subgroups according to having a bad obstetric history regarding their previous pregnancy or not, no difference was observed between the groups with regard to the laboratory findings or fetal/maternal complications. While approximately half of this study's patients had previously bad obstetric histories (n=12), these patients did not experience any complications during their current pregnancy. Maybe these patients also had GMD in their previous pregnancies; still, they may have had complications because the diagnosis and follow-up had not been done closely in their previous pregnancies. These findings from the current study are thought to show how the diagnosis and close monitoring of GDM can significantly prevent pregnancy and fetal complications.

This study has some limitations. Unfortunately, no healthy control group occurred for comparing the glucose variability and biomarkers. Also, this study's patients had GMD that was regulated by diet. Glucose variability is known to be more common in people who use insulin therapy or have Type 1 DM. The reason why glucose variability and biomarkers were not significant in the patients here may be due to the study having been conducted with a patient group that was considered to be well-monitored. Therefore, further studies can include a larger number of patients, and checks should be done to support this thesis.

In conclusion, the biomarkers in this study did not reflect glycemic fluctuation. The study did find frequent and regular SMBG to be required to achieve the desired glucose level, even in diet-regulated GDM. Meanwhile, head circumference and weight were found to be lower in the babies of mothers with GDM and high glycemic fluctuations; this shows that CGMS, which measures glycemic fluctuations more closely, may be an alternative method despite its cost and application difficulties.

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 21.02.2014, No: 04).

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