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Original Article

The role of fetal adipose tissue thicknesses measured ultrasonographically in the prediction of gestational diabetes

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ABSTRACT

Objective: This study aims to investigate whether second-trimester fetal adipose tissue components reflect glycemic control in diabetic pregnancies and their role as an auxiliary method in predicting gestational diabetes.

Materials and Methods: This study was designed prospectively, cross-sectionally in 300 pregnant women 24-28 weeks of gestation between April 2020 and July 2020. The adipose tissue thickness of the humerus, femur, scapula, and abdominal circumference was examined by transabdominal ultrasound. The age, body mass index, family history of diabetes, and diabetes history in previous pregnancies of the groups were questioned.

Results: The anterior abdominal wall adipose tissue thickness of the fetuses we included in the study was 5 ± 0.8 mm, femur adipose tissue thickness was 4 ± 0.7 mm, humerus adipose tissue thickness was 3.7 ± 0.7 mm, scapula adipose tissue thickness was 4.1 ± 2,2 mm. The total adipose tissue thickness was 16.9 ± 2.9 mm. A statistically significant correlation was found between femoral adipose tissue thickness (p = 0.001) and humeral adipose tissue thickness (p = 0.023) in gestational diabetes groups. Patients with a diagnosis of Gestational Diabetes Mellitus (n = 60) constituted the first group, patients without GDM (n =240) constituted the second group. In our independent analysis of two groups, femur and humerus adipose tissue thickness were found to be statistically significantly different between both groups (p= 0.002, p = 0.043, respectively). Other parameters did not differ significantly between groups. Between three groups (healthy, impaired glucose tolerance, and gestational diabetes groups). Femoral adipose tissue thickness was statistically significant among the three groups (p = 0.005). As a result of binary logistic regression, if the femoral adipose tissue thickness was above 4.1 mm, the possibility of developing GDM was observed with 63.8% sensitivity and 65% specificity.

Conclusion: In the prediction of gestational diabetes, fetus femoral adipose tissue thickness may be significant.

Keywords: fetal soft tissue thickness; gestational diabetes mellitus; 50 gr oral glucose; 100 gr oral glucose

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Introduction

Diabetes, which progresses with disorders in insulin production, secretion, or both, is a metabolic disease. It causes damage and dysfunction of the eyes, nerves, kidneys, blood vessels, and heart. (1) Abnormal conditions occur in carbohydrate adipose protein metabolism due to insulin deficiency in target tissues. From decreased tissue sensitivity to insulin, insufficient insulin secretion is caused by complex pathways in hormone secretion. Insulin secretion disorder and impaired perception of insulin in the cellular dimension often coexist in the same patient. It is often not possible to predict the primary cause of hyperglycemia. (2)

The encounter with diabetes during pregnancy occurs in two different ways. Patients have diabetes before pregnancy, referred to as Pregestational Diabetes, or diagnosed during pregnancy, called Gestational Diabetes Mellitus (GDM) (3)

GDM is defined as any glucose intolerance noticed for the first time during pregnancy or starts during pregnancy. In addition to its relationship with increased fetal-maternal morbidity, it can affect mothers and children in the long term. (4)

GDM increases perinatal and neonatal complications, including macrosomia, hypocalcemia, hypoglycemia, polycythemia, hyperbilirubinemia, respiratory distress syndrome (RDS), and congenital malformations. (5)

By affecting the physiological adaptation of both the fetus and the mother, diabetes can lead to undesirable conditions such as shoulder dystocia and other obstetric severe complications during delivery. (6)

GDM also may have long-term effects on mothers. These include cardiovascular diseases, obesity, and the development of type 2 DM. (7)

According to the current screening program of ACOG (American College of Obstetrics and Gynecology) and ADA (American Diabetes Association), screening is routinely performed on pregnant women at 24 and 28 weeks of gestation. Screening is performed before 50 grams of oral glucose loading; if high, 100 grams of oral glucose tolerance test (OGTT) for 3 hours. According to WHO, FIGO, NICE guidelines, it can be applied directly as 75 g OGTT. (8,9)

In this study, we considered a supplemental method to the glucose tolerance test, an easy and inexpensive method used in gestational diabetes screening. We examined the relationship between fetal subcutaneous adipose tissue measurements, which we evaluated ultrasonographically, between 24-28 weeks of gestation, and gestational diabetes.

Material and methods

Our study was conducted in Health Sciences University Bursa Yüksek İhtisas Training and Research Hospital, Gynecology and Obstetrics Department, between April 2020 and July 2020.

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According to the last menstrual period confirmed by first trimester ultrasounds, a 50 g GCT screening test was performed on pregnant women between 24 and 28 weeks. It was designed prospectively with a total of 300 volunteers.
The study was initiated following the approval by the local ethics committee with the numbered 2011-KAEK-25 2019 / 06-27; the participants were informed, and the "Informed Volunteer Consent Form" was read and signed.

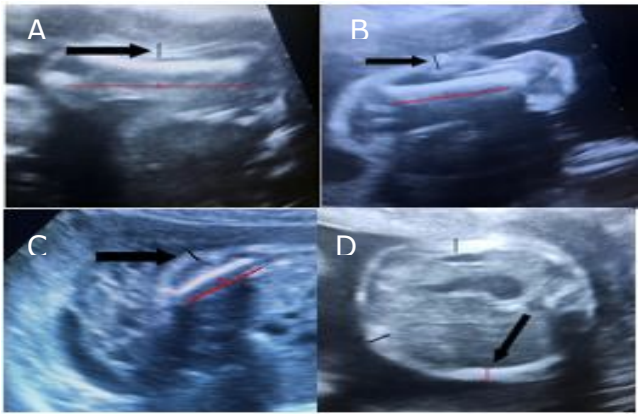
Patient selection

We performed a 50-g glucose challenge test on pregnant women between 24-28 weeks of gestation following the ACOG guideline. We applied the 100 g oral glucose tolerance test as the diagnostic test to those found to be positive for this test. (10) According to the 2020 diabetes guide of the Turkish Endocrinology and Metabolism Association, we divided the patients into three groups. (11) Pregnant women with an average of 50 gr OGTT results constituted the first group, those with 50 gr OGTT positive and impaired glucose tolerance according to 100 gr OGTT formed the second group, and those with GDM results according to 100 gr OGTT formed the third group. Before the study, the patient did not meet the inclusion criteria, multiple pregnancies, those with comorbid diseases (Type 1 and Type 2 Diabetes, pregestational diabetes, thyroid diseases, hypertension, heart diseases), and those who did not consent to participate in the study were out of the study.

Conceptual design

Three hundred pregnant women between 24-28 weeks of gestation were included in the groups. Before performing ultrasonography, the pregnant information and consent document was read to each pregnant, and written consent was obtained. Smoking, family history, history of previous pregnancies (gestational diabetes diagnosis in previous pregnancies, macrosomia baby birth) were noted.

As ultrasonographic parameters, we measured the thickness of the subcutaneous adipose tissue of the fetal abdominal anterior wall, femur, humerus, and scapula bone. In addition, the total adipose tissue thickness was evaluated according to the sum of these four measurements, as in the literature examples. (12,13)
Fetal abdominal adipose tissue thickness was measured from the standard abdominal circumference plane. During the imaging, fetal skin and subcutaneous tissues were evaluated clearly. Then the distance between the outer skin edge and the inner edge of the anterior abdominal wall was measured 2 cm away from the entry of the umbilical cord. Three measurements were taken, and the average was recorded. Fetal scapula, humerus, and femur adipose tissue thicknesses based on similar measurements in the literature was the distance between the outer edge of the skin and the outer edge of the bone in the midline plane of the bones (Figures 1,2,3,4).
Figure-1. Adipose Tissue Thickness Measurements



A, Humerus; B, Femur; C, Scapular; D, Abdominal Wall

All dimensions were applied by an experienced sonographer (K.S.S.) on the same ultrasound with a 5-MHz transabdominal transducer (Ultrasound System Voluson S6; Europe - EAGM). Therefore, all measures were standardized.

Statistical analysis

Windows-based SPSS 24.0 statistical analysis program was used for appropriate statistical analysis (SPSS Inc, USA). We used visual (histograms, probability plots) and analytical methods (Shapiro-Wilk and Kolmogorov-Smirnov test) to determine whether the variables are normally distributed. Variables were defined as mean, standard deviation, mean difference between groups, 95% confidence interval, median (minimum-maximum), u value, frequency, and percentage.
We applied Pearson tests for normally distributed data and Spearmen tests for non-normally distributed or nominal data. The significance level was determined as $p<0.05$. We used the student's t-test for normally distributed variables in comparison and the Mann-Whitney-U test for non-normally distributed variables. In comparing three groups, One Way ANOVA for normally distributed data and Kruskal Wallis tests for non-normally distributed data were performed.
Binary logistic regression analysis was used to predict the study's results, which were significantly different from the two-group analysis's previous analyses. The Hosmer Lemeshow result was used to evaluate the model fit of the analysis. The 5% type-1 error level was considered statistically significant.
Receiver operating characteristic curves (ROC curves) were constructed, and areas under the curve (AUC) and sensitivity (sen.) and specificity (spe.) were calculated and a cut-off value was determined according to the group without gestational diabetes.

Results

Demographic and clinical characteristics and descriptive analyses are available in Table-1. Accordingly, 300 volunteers took part in the study. The mean age of the pregnant women was 28.1 (18-45 years). The gestational week of the pregnant women included in the study was between 24-28 weeks. Body mass index was 27.9 ± 3.8. Of the volunteers participating in the study, 60 (19.9%) were classified as gestational diabetes, and 70 (23.2%) had impaired glucose tolerance. The fetal mean anterior abdominal wall adipose tissue thickness was 5 ± 0.8 mm, the femur 4 ± 0.7 mm, the humerus 3.7 ± 0.7 mm, the scapula 4.1 ± 2.2 mm, and total adipose tissue thickness was determined as 16.9 ± 2.9 mm (Table-1). As shown in Table-2, humeral adipose tissue thickness, scapula adipose tissue thickness, and total adipose tissue thickness were positively correlated with body mass index (p values= 0.052; 0.024; 0.013, respectively). Femoral adipose tissue thickness (p=0.001) and humerus adipose tissue thickness (p=0.023) were statistically significantly correlated in the gestational diabetes groups. Adipose tissue thickness of the anterior abdominal wall (p=0.421), scapula adipose tissue thickness (p=0.418), and total adipose tissue thickness (p=0.356) did not differ significantly with gestational diabetes. The age of the pregnant women did not show a statistically significant correlation with any of the adiposity measurement parameters (p>0.05) (Table-2). We divided the patients into two groups. Patients diagnosed with Gestational Diabetes Mellitus (n=60) constituted the first group, and patients without GDM (n=240) constituted the second group. In the analysis of two independent groups, the thickness of the femoral and humeral adiposity was statistically significantly different between the two groups (p=0.002, p=0.043, respectively). Other parameters did not differ significantly between groups (Table-3).

Table-1. Descriptive characteristics analysis table of pregnant women and fetuses

	Pregnant women, (n=300)
Characteristics of the mother	***X±SD or Median (min-max)***
Age (years)	28.1 ±6.2 (18-45)
Pregnancy Week (week)	26 (24-28)
Body mass index (kg/m2)	27.9 ± 3.8
Nulliparous (n; %)	86; 28.5
Cigarettes (n; %)	33; 10.9
History of Gestational Diabetes (n; %)	59; 19.5
History of immunity (n; %)	16; 5.3
Healthy group (n; %)	170; 56.3
Impaired Glucose Tolerance (n; %)	70; 23.2
GDM (n; %)	60; 19.9
Characteristics of the fetus	***X±SD or Median (min-max)***
Fat tissue thickness of the anterior abdominal wall (mm)	5.0 ± 0.8
Femur fat tissue thickness (mm)	4.0 ± 0.7
Humeral fat tissue thickness (mm)	3.7 ± 0.7
Scapula fat tissue thickness (mm)	4.1 ± 2.2
Total fat tissue thickness (mm)	16.9 ± 2.9

mm: millimeter, kg: kilogram, m2: square meters, n: number, %: percent, X: mean, SD: standard deviation, min: minimum, max: maximum
Descriptive analyzes were defined as mean±standard deviation (X±SD) and median (min-max) for numerical variables, and as n (%) for categorical variables.

We divided the patients into three groups and analyzed the variables. The first group included pregnant women in the control group (n=170), the second group included pregnant women with impaired glucose tolerance (n=70), and the third group included pregnant women diagnosed with gestational diabetes mellitus (n=60). One Way ANOVA and Kruskal Wallis tests were applied in the three-group analysis. Accordingly, only the femoral adipose tissue thickness among the study parameters was statistically significant between the three groups (p=0.005). Abdominal, humerus, scapula, and total adipose tissue measurements did not differ between the three groups. Groups were analyzed post-doc in pairs. Accordingly, a statistically significant difference was found between the control group and pregnant women with gestational diabetes mellitus in the femoral adipose tissue thickness (p=0.010) (Table-4).

Table-3. Comparison of results in groups with and without gestational diabetes

Parameters	GDM (n=60)	Healthy (n=240)		
	X±SD/Median (min–max)	X±SD/Median (min–max)	Confidence interval (%95 CI) / U values	p
Age (years)	27 (18-45)	28 (18-43)	7026	0.77#
Body mass index (kg/m^2)	28.05±4.02	27.9±3.7	0.09 [(-0.99) - (1.17)]	0.87*
Gestational Diabetes history	n=14	n=45	6870	0.42#
Anterior abdominal wall adipose tissue thickness (mm)	5.1±1	4.9±0.7	0.13 [(-0.14) - (0.40)]	0.35*
Femur adipose tissue thickness (mm)	4±0.5	3.7±0.7	-0.33 [(-0.54)-(-0.12)]	0.002*
Humeral adipose tissue thickness (mm)	3.5±0.6	3.7±0.6	-0.19 [(-0.39)-(-0.06)]	0.043*
Scapula adipose tissue thickness (mm)	4.25 (2.4-6.8)	4 (2-4.9)	6713	0.42#
Total adipose tissue thickness (mm)	16.2 (10.7-22.4)	16.9 (10.5-17.3)	6638	0.35#

mm: millimeter, kg: kilogram, m2: square meters, n: number, %: percent, X: mean, SD: standard deviation, min: minimum, max: maximum, CI: confidence interval.
*Descriptive analyzes were prepared using the median (min-max) for normally distributed variables (X±SD) and non-normally distributed variables. Student's t-test *p<0.05 and Mann-Whitney U test #p<0.05 were accepted as significance limit.*

To determine the variables that can predict the development of GDM and the odds ratio, binominal logistic regression analysis was performed with femur adipose tissue and humerus adipose tissue thicknesses, which were found significantly different in previous studies. Groups without GDM were taken as the reference category. According to this analysis, femoral adipose tissue thickness was determined as predictive data for the development of GDM. Accordingly, every 1 mm increase in the thickness of the femoral adipose tissue can increase the probability of GDM by 1.7 times (p=0.011) (Table-5).

Table-2. Correlations between patient characteristics and fetal adipose tissue components

n=300	Adipose tissue thickness of the anterior abdominal wall (mm)		Adipose tissue thickness of the femur (mm)		Adipose tissue thickness of the humerus (mm)		Adipose tissue thickness of the scapula (mm)		Total adipose tissue thickness (mm)	
	r	p	r	p	r	p	r	p	r	p
Age (years)	-0.04	0.47*	-0.08	0.17*	-0.09	0.12*	-0.01	0.87*	-0.06	0.29*
Body mass index (kg/m^2)	0.11	0.063#	0.08	0.15#	0.11	0.052#	0.13	0.024*	0.14	0.013*
Gestational Diabetes	0.05	0.42*	0.19	0.001*	0.13	0.023*	0.05	0.42*	0.05	0.35*

*mm: millimeter, r: correlation coefficient, kg/m^2: kilogram/square meter, Spearmen test: * and Pearson: # (p< 0.05 considered significant)*

Table 4. Evaluation of parameters between the control group, impaired glucose tolerance group, and gestational diabetes group

Parameters	Healthy group (n=170)	Impaired glucose tolerance group (n=70)	Gestational diabetes group (n=60)	P	P* 1&2	P* 1&3	P* 2&3
	X±SD/Median (min-max)						
Age (years)	27(18-43)	28(18-43)	27(18-45)	0.93#	0.82	<0.82	0.71
Body mass index (kg/m^2)	27.8±3.5	28.3±4.2	28.05±4	0.61	0.59	0.90	0.91
Anterior abdominal wall adipose tissue thickness (mm)	4.9±0.7	4.9±0.9	5.1±1	0.55	0.99	0.70	0.89
Femur adipose tissue thickness (mm)	3.7±0.6	4±0.4	4±0.5	0.005	0.88	0.01	0.16
Humeral adipose tissue thickness (mm)	3.7±0.6	3.7±0.6	3.5±0.6	0.12	0.99	0.07	0.42
Scapula adipose tissue thickness (mm)	4.2±2.7	4±0.8	4.1±0.9	0.65#	0.68	0.35	0.73
Total adipose tissue thickness (mm)	17±3.2	16.8±2.2	16.5±2.3	0.51#	0.46	0.31	0.59

mm: millimeter; kg/m^2: kilogram/square meter p: One-way ANOVA (mean±SD); p#: Kruskal Wallis (median(min-max)); p: Post-Hoc Tukey and Tamhane's T2*

ROC analysis was performed in terms of femoral adipose tissue thickness measurement. Accordingly, the area under the process characteristic curve was calculated as 0.642 and was statistically significant (p=0.001).

Table-5. Binary logistic regression analysis results in terms of humerus and femur adipose tissue measurements between groups with and without Gestational Diabetes

Parameters	Analyses			
	Wald	OR	CI (%95)	p
Femur adipose tissue thickness (mm)	6.3	1.77	1.03-2.77	0.011
Humeral adipose tissue thickness (mm)	0.7	1.23	0.76-1.98	0.39

CI (95%); confidence interval; OR: odds ratio. Wald: test statistic value. Binominal logistic regression was used because the dependent variable consisted of 2 groups. The control group was taken as the reference category. Hosmer and Lemeshow test showed p>0.281 and the models fit well with the data.

If the femoral adipose tissue thickness is over 4.1 mm, the probability of developing GDM can be seen with a sensitivity of 63.8% and a specificity of 65% (Table-6) (Figure-2).

Discussion

The first aim of our study was to observe an auxiliary screening method for the prediction or follow-up of GDM based on previous literature reviews of fetal adipose mass and contribute to the literature in this respect.

Figure 2. ROC analysis table for the prediction of gestational diabetes of the femoral adipose tissue threshold value

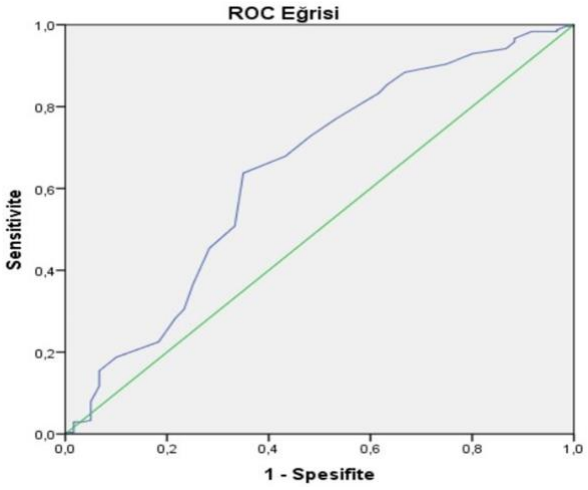


Table-6. ROC analysis table for the prediction of gestational diabetes of the femoral adipose tissue threshold value

Parameters	AUC (%95)	Cut off	P	Sensitivity	Specificity
Femur adipose tissue thickness (mm)	0.642 (0.559 - 0.726)	4.1	0.001	63.8	65

AUC: Area under curve

We analyzed the results of 300 pregnant women who applied to the pregnant outpatient clinic between April 2020 and July 2020 in our clinic and met the conditions of our study. A total of 60 patients with GDM, 70 with impaired glucose tolerance, and 170 patients with average GCT results of 50 g were included.

The adipose tissue thickness of the anterior abdominal wall was 4.9±0.7 mm in healthy pregnancies we measured at 28 weeks and 5.1±1 mm in the anterior abdominal wall adipose tissue thickness in pregnant women with GDM. This measurement did not make a statistical difference in patients with diabetes. Likewise, scapula adipose tissue thickness and total adipose tissue components were not different from healthy pregnant women. However, femoral adipose tissue thickness measurements were significantly increased in the diabetes group compared to healthy pregnant women (Table-1).

Gestational Diabetes Mellitus is a carbohydrate intolerance condition that develops during pregnancy. Its prevalence depends on multifactorial factors. While some women can maintain euglycemic control with diet alone, 30% of pregnant women need drug treatment. With the diagnosis and control of GDM, severe reductions in the results of preeclampsia, macrosomia, and shoulder dystocia are observed.(14)

In normal pregnancies, subcutaneous adipose tissue is stored in the third trimester and constitutes 4-5% of the total body weight in the 28th week. Even when the diabetic patient can maintain tight glucose control, fetal adipose tissue distribution may differ from normal pregnancies.

In a study conducted in 2014, fetal anterior abdominal wall adipose tissue thickness was higher in patients with impaired 50 g GCT test.(15) According to another study, the thickness of the forearm, leg, subscapular, and anterior abdominal wall adipose tissue was higher in women with GDM than in healthy pregnant women.(16) Bernstein et al.(17) and Whitelaw A.(18) explained that subcutaneous adiposity seems a substantial index of maternal glucose control. Akselim B. et al.(13) found that the total fetal adipose tissue complex had role during delivery in terms of labor dystocia and operative delivery. Higgins MF. et al.(19) declared that measuring fetal anterior abdominal wall thickness in diabetic pregnancy may have a role in predicting macrosomia.

Femoral adipose tissue thickness was significantly different between healthy pregnant women, women with impaired glucose tolerance, and women with GDM diagnosis (3.7±0.5 mm, 4±0.4 mm, 4±0.6 mm, respectively) (p=0.005). When we compared the groups among themselves, the thickness of the femoral adipose tissue again differed between healthy pregnant women and pregnant women with GDM.

In these intergroup comparisons, we also performed binary logistic regression analysis to determine the diagnostic value of the femur adipose tissue measurements, which differ in GDM patients, and evaluate the effect level on the disease. Accordingly, as the femoral adipose tissue thickness increases by 1 mm, the probability of GDM may increase 1.7 times.

We aimed to determine a threshold value for the thickness of the femoral adipose tissue in the control group. In ROC analysis, when the femoral adipose tissue thickness exceeds 4.1 mm, the probability of GDM increases with a sensitivity and specificity of 63 and 65%.

According to the findings of our study, femoral adipose tissue thickness would be a significant predictor in the prediction of GDM, and it can be an additional helpful screening method in the GDM patient population for close follow-up and reducing diabetes-related morbidity. Although in some of the literature studies, the anterior abdominal wall adipose tissue thickness was more significant in the prediction of GDM (16,20,21), this situation was not observed in our study. One reason for this may be that the number of patients we evaluated was relatively small. The evaluation was made on the population living in the same geographical area.

While the relationship between fetal adipose tissue composite measured by ultrasound and GDM was evaluated in our study, the effect of increased fetal adiposity on delivery type, fetal weight, and postnatal fetal-maternal outcomes could not be evaluated. In some studies, in the literature, it has been shown that babies with increased adipose tissue are more likely to suffer from macrosomia and intrapartum complications.(22,23) These studies and our study show that fetal adiposity may be an additional evaluation of routine biometric parameters in the future.

One of the limitations of our work was to access patients with GDM because of a small number of patients. However, our study population could have been more homogeneous and complicated. Another weakness was we did not associate sonographic findings with postpartum neonatal adiposity findings. It also predicted rarer and possible complications of adipose tissue such as shoulder dystocia and Erb palsy. Some babies with high adiposity may be at risk of plexus injury and permanent paralysis due to shoulder dystocia; however, it would require much larger cohort studies given their relatively rare occurrence. For this, there is a need for prospective and longer-term studies with a more significant number of diabetic patients. The other strength was that measurement of fetal adipose tissue components is not a part of routine biometric measurements. Our study could not analyze the relationship between adipose tissue components and biometric parameters in detail. Perhaps these adipose tissue components affect gestational diabetes via affecting biometric parameters . More long-term studies are needed for this analysis.

In conclusion, we aimed to predict the diagnosis of GDM by measuring the thickness of the femur, humerus, abdomen, and scapula of pregnant women at 24-28 weeks. Furthermore, maybe a proper additional screening method to reduce morbidity due to GDM.

Disclosure

Authors have no potential conflicts of interest to disclose.

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