

THE UTILITY OF GLYCATED HEMOGLOBIN, DETERMINED IN THE SECOND TRIMESTER OF PREGNANCY, IN DIAGNOSING GESTATIONAL DIABETES

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Abstract

Background and Aims: Gestational diabetes (GD) identifies a pregnancy with high obstetrical risk due to the possible complications that may appear and which are associated with significant perinatal mortality and morbidity. The role of HbA1c in diagnosing GD is still debatable. Our aim was to evaluate the clinical utility of HbA1c assessed in the second trimester of pregnancy (before performing the oral glucose tolerance test - OGTT) in establishing the macrosomia risk, and also for diagnosing GD.

Material and methods: This was an observational study on a group of 165 pregnant women followed from the first trimester of pregnancy in whom we measured HbA1c in the second trimester, before running an OGTT with 100 grams of glucose and who delivered at term (37 – 41 weeks of pregnancy). Finally, HbA1c and OGTT were performed only in 132 women, these being the subjects of our study. **Results:** The average value of HbA1c was $4.85 \pm 1.23\%$. HbA1c was higher in the group having gestational diabetes ($6.58 \pm 0.74\%$) in comparison to the group not having GD ($4.52 \pm 0.80\%$). The Receiver Operating Characteristic (ROC) curve for HbA1c determined in the second trimester, for diagnosis of GD, has an area under the curve (AUC) of 0.939. **Conclusions:** HbA1c value could be considered as a sensitive and specific predictive factor in appreciating the macrosomia risk and could be set as an extra criterion in GD diagnosis.

key words: gestational diabetes, glycated hemoglobin, macrosomia.

Background and Aims

It is known that increased values of HbA1c, in the case of pregnant women with pregestational diabetes are correlated with the appearance of congenital malformations and spontaneous abortions. Still, the role of HbA1c in diagnosing and monitoring gestational diabetes (GD) is debatable [1].

The aim of this study was to evaluate the clinic utility of HbA1c, determined in the second trimester of pregnancy (before performing the oral glucose tolerance test - OGTT with 100 grams of glucose), in evaluating macrosomia risk and also for diagnosing GD.

Materials and methods

We have run an observational prospective cohort study on a group of 165 pregnant women

monitored from the first trimester of pregnancy (up to 16 weeks of pregnancy), who have delivered at term (37 – 41 weeks of pregnancy), in whom in the second trimester we have determined HbA1c before performing the OGTT. From the total number of 165 pregnant women included initially, HbA1c and OGTT were finally performed in only 132 women, these being the subjects of our study.

The future mothers were taken into evidence in the first half of their pregnancy (up to 16 weeks of gestation) and finally gave birth on due date in Oradea Clinic Hospital for Obstetrics and Gynaecology between January 2009 and June 2011. For each woman we registered: age, residence background (urban/rural), height and weight, information used for calculating body mass index (BMI), gestational age when registered, personal physiological and pathological along with obstetric history, blood pressure, medicine use and substance abuse. The personal file also included data regarding the presence of risk factors for GD including family history of diabetes, obesity, parity, history of gestational diabetes or previous macrosomic fetus deliveries.

Inclusion criteria were: age 18 and over, spontaneous pregnancies (obtained without ovarian stimulation and / or after assisted human reproductive technologies), the absence of pathology associated to pregnancy, no chronic treatment with medications, presence of risk factors for gestational diabetes.

HbA1c was measured from maternal venous blood samples in the second trimester, at 24 – 28 weeks of gestation (with a variation of ± 2 weeks). The method of determination was the immunoturbidimetric (standardized by DCCT: Diabetes Control and Complications Trial and certificate by NGSP: National Glycohemoglobin Standardization Program), and total hemoglobin has been determined from hemolysate by colorimetric method with alkaline hematin [2].

We separated the pregnant women in two groups: group I without GD and the second group diagnosed with GD. The diagnosis of GD in the second trimester of pregnancy was set using Carpenter's and Coustan's criteria for OGTT's using 100 g glucose [2]. Although IADPSG recommend since 2009 the 75 g glucose test with 3 measurements, we opted for the 100 g test with 4 measurements since we begun the study with it.

For each pregnant woman the pregnancy evolution was monitored by periodic obstetrical examinations, which included 2D scanning and Doppler ultrasound. The first ultrasound examination was done, in the case of all future mothers, when taken into evidence, in the first trimester of pregnancy in order to determine gestation age.

Statistic analysis

Quantitative data were expressed as average \pm standard deviation. The statistic comparison of the data was done using the Student t test to compare the average values of the different group characteristics and Pearson correlation test to compare two characteristics of a group. The p value was considered significant at $\alpha = 0.05$. The diagnostic precision of HbA1c during the second trimester of pregnancy for fetal birth weight prediction was investigated with the help of the area under the *Receiver Operating Characteristic* - ROC curve (AUC). The confidence interval (95% CI), diagnostic level, sensitivity and specificity were determined. For statistical analysis we used the SPSS 19 software

Results

The social-demographic and anthropometric (BMI) maternal parameters as well as the risk factors for gestational diabetes, are given in [Table 1](#).

Table 1. Social-demographic and anthropometric parameters of the study group.

	WHOLE GROUP N=132	GROUP II without GD N=106	GROUP I with GD N=26	p
Age (years)	28.29±4.67 Min: 20 Max: 43	27.56±4.45 Min: 20 Max: 43	31.31±4.47 Min: 24 Max: 41	0.0002
Background	R: 56 (42.42%) U: 76 (57.58%)	R: 46 (43.39%) U: 60 (56.61%)	R: 10 (28.46%) U: 16 (61.54%)	-
BMI (kg/m ²)	25.74±3.92 Min: 18.6 Max: 38.6	25.23±3.64 Min: 18.6 Max: 36	27.84±4.45 Min: 21.1 Max: 38.6	0.0022
Parity	1.53±1.12 Min: 1 Max: 6	1.45±0.90 Min: 1 Max: 6	1.81±1.57 Min: 1 Max: 6	0.1314

R – Rural; U – Urban

Table 2. Frequency of GD risk factors in the two study groups.

RISK FACTORS	Without GD		With GD		p
	Nr.	%	Nr.	%	
Diabetes in family history	6	5.3	2	11.1	0.065
Obesity	19	16.7	7	38.9	<0.001
Age > 30 years	32	28.1	8	44.4	0.001
Previous macrosomic births	3	2.6	3	16.7	<0.001
Parity > 4	3	2.6	2	11.1	<0.001

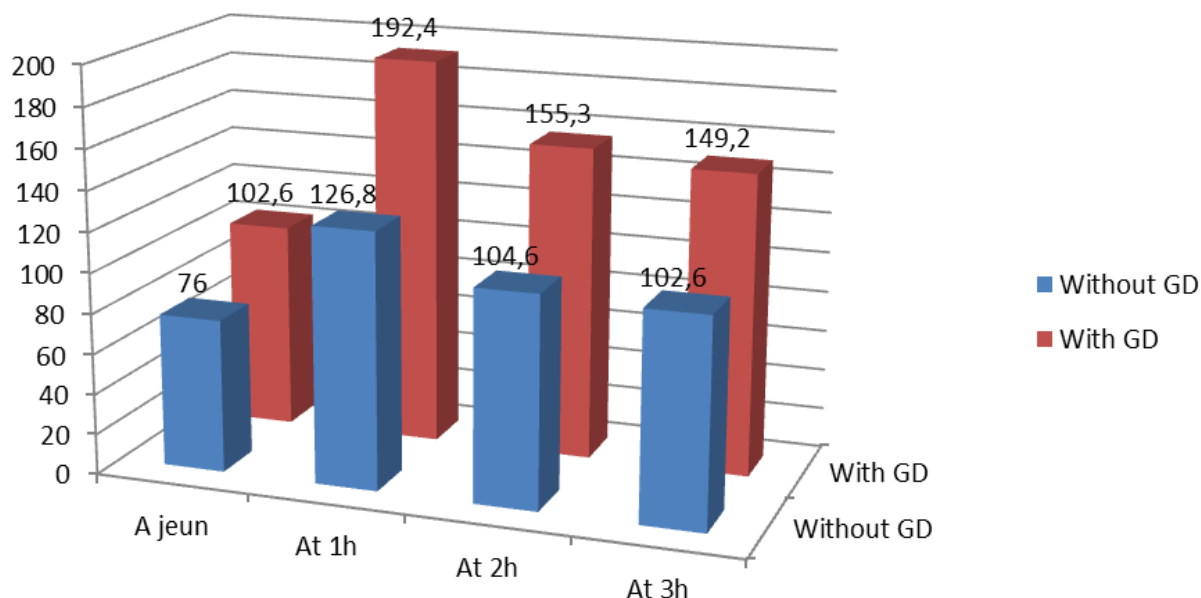


Figure 1. Average values of blood glucose during the second trimester OGTT.

In the group with GD, 44.4% of the women were older than 30 years old, 1.6 more than in the group without DG, the average age being significantly higher in the group with GD (31.31 years over 27.56 years) (p=0.0002).

We are detailing in [Table 2](#) the analysis of the risk factors for GD identified in the two study groups.

Most of the pregnant women without GD had a normal weight (54.4%), while in the group diagnosed with GD only 44.4% had normal weight. Obesity prevalence is two times higher in the group having GD (38.9% versus 16.7%; $p < 0.001$).

The majority of subjects were at their first pregnancy in both groups, multiparity representing 29.8% in the group without GD and 33.3% in the group suffering of GD ($p = 0.458$).

At least one of the risk factors identified as important in developing GD was present in the case of 36.8% of the pregnant women without GD, and in the case of 66.7% diagnosed with GD. In the case of the patients with only one risk factor, the most frequent was the age, over 30, (20 cases in the group without DG – 17.5%,

versus 3 cases in the group with DG – 16.7%; $p = 0.830$).

The prevalence of subjects with at least two associated risk factors was 2.8 higher in the group with GD (38.9% versus 14.0%; $p < 0.001$). The most frequent association of two risk factors was obesity along with the age over 30 years old (7 cases in the group without GD - 6.1%, versus 2 cases in those diagnosed with GD – 11.1%; $p = 0.112$).

We are giving in [Figure 1](#) the mean values of blood glucose during the diagnostic second trimester OGTT for the two study groups.

In the group without GD, 4 of the subjects registered values of $HbA1c \geq 6.5$ (3.8%), significantly lower ($p < 0.001$) compared to women diagnosed with GD (57.7%). We are showing in [Figure 2](#) the distribution of HbA1c as median and range of quartiles.

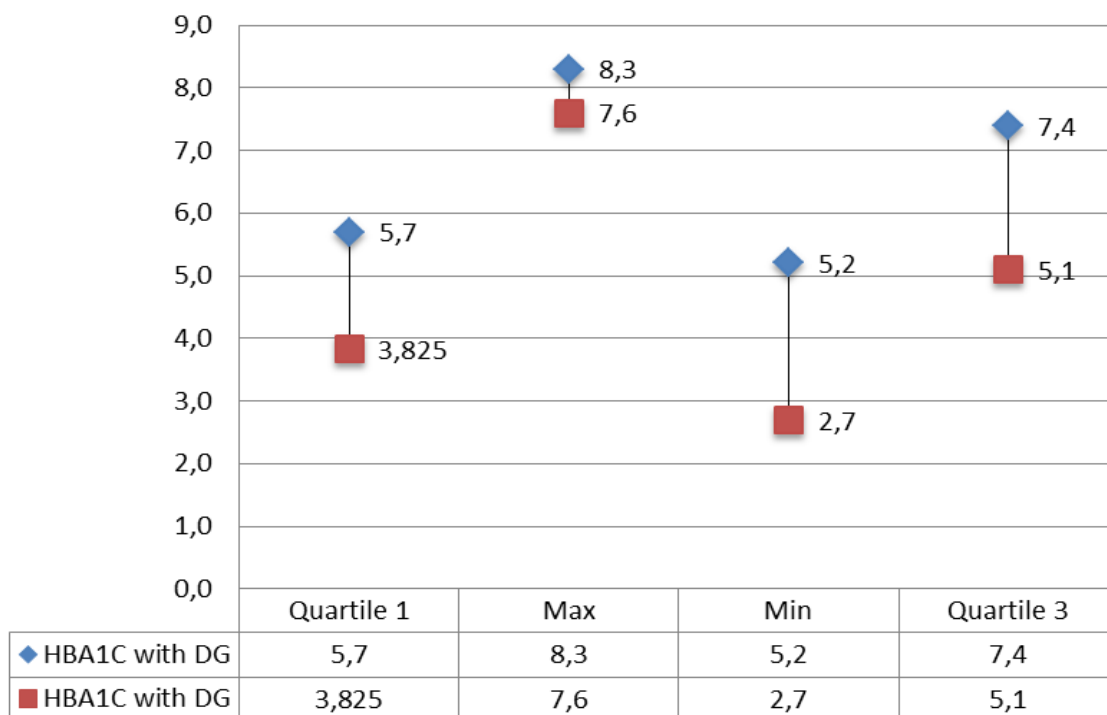


Figure 2. The distribution of HbA1c as median and range of quartiles.

HbA1c values $\geq 6.5\%$ in the second trimester of pregnancy was recorded in 19 cases (14.40%).

The prevalence of gestational diabetes was 68.42% in patients with $HbA1c \geq 6.5\%$, while in

patients with HbA1c levels below 6.5%, the prevalence of gestational diabetes was 4.42%, which suggested that the HbA1c could be a diagnostic test for gestational diabetes.

Using HbA1c value as predictive factor in the diagnosis of GD, the area under the curve was 0.939 (95% CI = .907 to .971) as shown in [Figure 3](#).

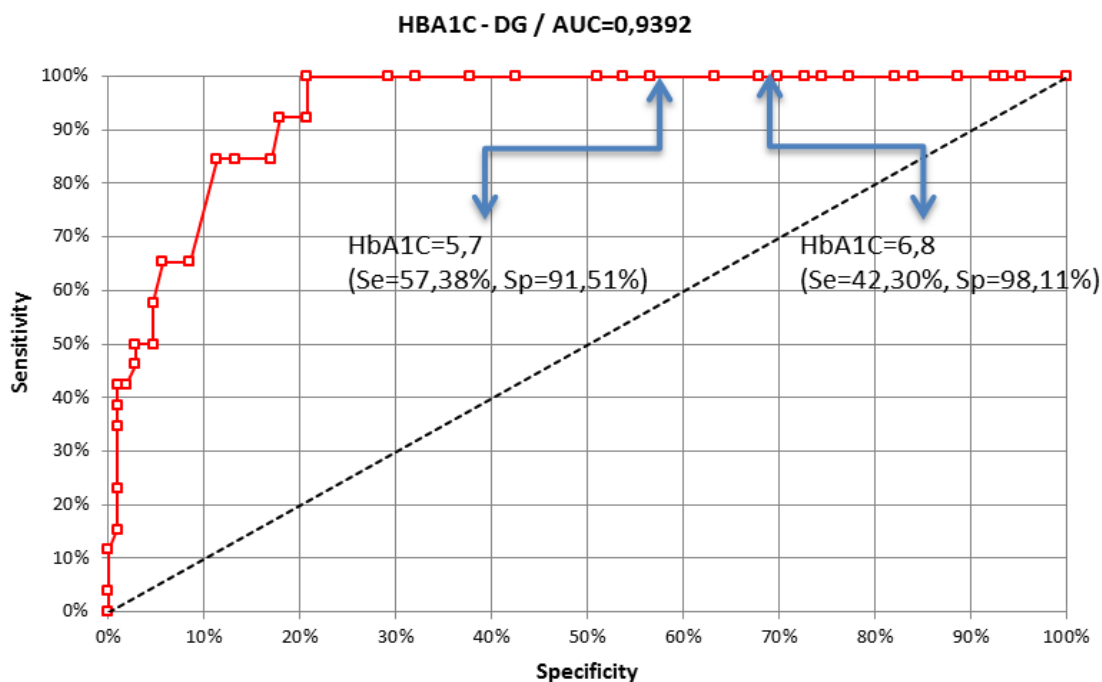


Figure 3. ROC curve for assessing diagnosis of GD using the 6.5% HbA1c value.

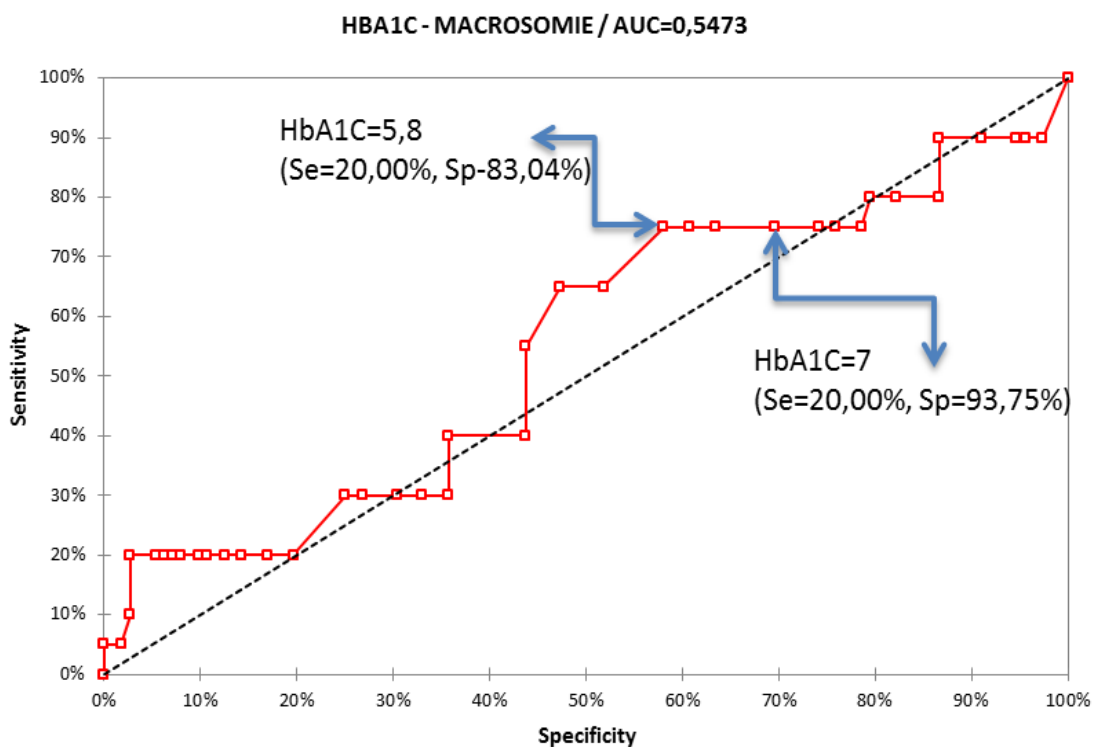


Figure 4. ROC curve for assessing macrosomia risk using the 6.5% HbA1c value.

Specificity (Sp), sensitivity (Sn), positive predictive value (PPV), negative predictive value (NPV) and the cut-off values of HbA1c determined before running OGTT for diagnosing GD are given in [Table 3](#).

Table 3. Specificity, sensitivity, PPV, NPV and cut-off values for the ROC curves for diagnosing of GD.

CUT- OFF VALUE	PPV	NPV	Sensitivity (CI 95%)	Specificity (CI 95%)
>5,1%	54.17	10.00	100.00% (84.41-100.00)	79.25% (70,46-85.90)
>6,5%	80.00	88.03	46.15% (28.81-64.52)	97.17% (91.56-99.35)

Table 4. Fetal birth weight and birth type.

	WHOLE GROUP N=132	GROUP II without GD N=106	GROUP I with GD N=26	p
New borns' birth weight	3502.27±492.92 g Min:2500 g Max:4800 g	3489.62±460.21 g Min:2500 g Max:4600 g	3553.84±604,61 g Min:2500 g Max:4800 g	0.553
Type of birth	Natural: 91 68.94% C-Section: 41 31.06%	Natural: 77 (72.64%) C-Section: 29 (27.36%)	Natural: 14 (53.85%) C-Section: 12 (46.15%)	-

C-Section: Caesarean Section.

Table 5. Distribution of newborns according to birth weight.

	with GD	without GD
AGA	16 61.53%	90 84.91%
SGA	4 23.08%	2 1.88%
Macrosomia	6 15.39%	14 13.21%

AGA- adequate for gestational age, SGA- small for gestational age.

Using the value of HbA1c > 6.5% for the prediction of the macrosomia risk, the area under the ROC curve (AUC) was of 0.547 (CI 95%= 0.402- 0.692) as shown in [Figure 4](#).

New borns' birth weight and the method of giving birth are presented in [Table 4](#).

In the group with GD, C-section was performed in 46.15% of the cases, while in the group without GD, this was done only in 27.36%.

When it comes to grouping the mothers according to new born weight, there are no significant differences between the groups (p=0.553).

The risk of a small for gestational age baby is 2 times higher in the case of pregnant women having GD as shown in [Table 5](#).

Discussions

The age over 30 years is one of the high risk factors involved in developing GD. This fact is proven in this study by the fact that, in the group with GD, there were 1.6 more pregnant women aged over 30 years compared to the other group. Even more, in the group with GD, 16.7 % of the subjects were over 35 years, this is 4.8 times more than in the group without GD, the average age being significantly higher in the group with GD (31.31 years old versus 27.56 years old, p=0,0002).

Obesity is another important risk factor in developing GD. This fact is shown in the present study, in which GD prevalence was more than twice higher in the group having GD (38.9%), in comparison to the other group (16.7%).

Regarding the order of risk factors for GD identified in our study, this was: Age over 30 years (44.4% of the cases); Obesity (38.9% of the cases); Previous macrosomic births (16.7% of the cases); and the presence of family history of diabetes, respectively *multiparity* (11.1% cases each). The results of this study regarding the presence of GD risk factors in women who developed GD are in line with those of previous studies in this field. [3]

The risk of gestational diabetes in the present study was 2.1 higher in the presence of only one risk factor. Even more, the association of 2 or 3 risk factors increases the risk of GD to 3.5 (RR=3,467), respectively 4.9 (RR=4,875).

The main fetal consequence of GD is macrosomia and represents the main cause of maternal and fetal morbidity and perinatal mortality. Later in life, the macrosomic newborns show a great risk of developing obesity during childhood, adolescence or adulthood, and thus a higher risk for developing cardiovascular and metabolic complications. [4] Fetal growth is the result of a complex interaction of different genetic and environmental factors, and the evaluation of a pregnancy predisposed to fetal macrosomia is difficult. Therefore, the prevention of fetal macrosomia is totally dependent on the correct identification of risk factors like: mother's weight, excessive weight gain during pregnancy and glycemic control. These are risk factors for fetal macrosomia and their control can bring benefits not only to the mother's health, but also to the baby's health [5].

Other factors that could play a role in complications' appearance during a pregnancy complicated with diabetes are great fluctuations of maternal glycemia and do not depend on the average value of glycemia [6]. Derr and his collaborators also say that the level of HbA1c is not influenced by the glycaemic instability [7].

The evaluation of gestational diabetes risk must be done from the first prenatal visit by determining glycemia. During pregnancy the normal values are considered to be of 60- 92 mg/dl [8].

Since HbA1c values higher than 6.5% are considered by the American Diabetes Association (ADA) a diagnostic criterion for diabetes [9], we analyzed for this cut-off the PPV and NPV of HbA1c for diagnosis of GD and for macrosomia risk evaluation. Thus regarding diagnosis of GD, for HbA1c values $\geq 6.5\%$, PPV is (80.00%), and specificity is higher than sensitivity (97.17% vs. 46.15%). For HbA1c values $>4\%$ sensitivity is higher than specificity, and PPV is 26.00%. In this study, the value of HbA1c could be considered a sensitive and specific predictive factor in appreciating macrosomia risk, aspect which could be in accordance with other studies run in the field [10].

The evaluation of fetal growth and development in the second and third trimester of pregnancy, by estimating fetal weight with the help of ultrasound, is necessary for setting an adequate birth management.

In other studies [11,12], GD increased the percentage of C-section births significantly. In the present study, the risk of giving birth by C-section was 1.7 higher in the group having GD than in the other group. Though early identification of GD lowers the risk of fetal macrosomia, it doesn't prevent C-section which is frequent in these cases due to the presence of associated pathologies [13,14].

The most important fetal consequence of GD, represented by macrosomia, was statistically correlated with GD. In this study, the risk of giving birth to a macrosomic baby was 1.16 times higher in the case of the mothers having GD (RR=1.16). From this point of view, our study is in agreement with other studies run in many other countries [15-17].

This study has several limitations: the limited number of cases, especially the small number of cases with a low social standard, thus the group not being representative for the population of pregnant women in our country.

Conclusions

After running the present study, we can say that HbA1c value could be considered a sensitive and specific predictive factor in

appreciating the macrosomia risk and could be set as an extra criterion when diagnosing GD. Still, more profound studies regarding the role of HbA1c in monitoring fetal growth and development are necessary, especially in the case of HbA1c determined in the second trimester of pregnancy.

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