

## ORIGINAL ARTICLE

# Predictors of postpartum diabetes mellitus in patients with gestational diabetes<sup>☆</sup>



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## KEYWORDS

Gestational diabetes;  
Risk factor;  
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Oral glucose  
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## Abstract

**Introduction:** Gestational diabetes (GD) is related to development of diabetes mellitus (DM) after delivery. The predictive factors in this association are not yet well defined. Objective: to study the predictive factors of dysglucosis in the postpartum period in a sample of patients with GD.

**Material and methods:** A total of 1765 women with DG were studied. Variables analyzed: anthropometric data and maternal history. Glycemia in OGTT with 100 g (basal: 1, 2 and 3 h) and HbA<sub>1c</sub>. Use of insulin in pregnancy. The OGTT with 75 g and HbA<sub>1c</sub> at 3 months after delivery.

**Results:** Postpartum DM prevalence 2.1%. Among these patients, there was a higher percentage of patients with a history of GD (25.9 vs. 12.9%;  $p < 0.05$ ), pre-pregnancy obesity (20.8 vs. 14.9%;  $p < 0.05$ ) and insulin use during pregnancy (79.2 vs. 20%;  $p < 0.01$ ). In the OGTT with 100 g, the number of pathological points was higher ( $3.18 \pm 0.69$  in DM vs.  $2.3 \pm 0.28$  normal,  $2.6 \pm 0.47$  IFG,  $2.5 \pm 0.32$  IGT;  $p < 0.001$ ). In the OGTT 100 g, the blood glucose level above which the diagnosis of postpartum DM is most likely is 189 mg/dl in the 2 h determination (S: 86.2%, E: 72%). A level of HbA<sub>1c</sub>  $\geq 5.9\%$  during pregnancy has a specificity of 95.9% for the diagnosis of postpartum DM in our sample.

**Conclusion:** We show factors associated with the diagnosis of postpartum DM, among which are quantitative determinations such as glycemia at 2 h of the OGTT with 100 g and HbA<sub>1c</sub> during pregnancy in patients with DG.

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**PALABRAS CLAVE**

Diabetes gestacional;  
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Posparto;  
Sobrecarga oral de  
glucosa

**Factores predictores de diabetes mellitus posparto en pacientes con diabetes gestacional****Resumen**

**Introducción:** La diabetes gestacional (DG) está relacionada con el desarrollo de la diabetes mellitus (DM) tras el parto. Los predictores en esta asociación aún no están bien definidos. El objetivo de nuestro trabajo es estudiar los factores predictores de disglucosia en el posparto en una muestra de pacientes con DG.

**Material y métodos:** Un total de 1.765 mujeres con DG fueron estudiadas. Variables analizadas: datos antropométricos y antecedentes maternos. Glucemia en sobrecarga de glucosa (SOG) con 100 g (basal: 1, 2 y 3 h) y HbA<sub>1c</sub>. Uso de insulina en la gestación. La SOG con 75 g y HbA<sub>1c</sub> a los 3 meses tras el parto.

**Resultados:** Prevalencia DM posparto: 2,1%. Entre estas pacientes hubo mayor porcentaje de pacientes con antecedentes de DG (25,9 vs. 12,9%;  $p < 0,05$ ), obesidad pregestacional (20,8 vs. 14,9%;  $p < 0,05$ ) y uso de insulina durante el embarazo (79,2 vs. 20%;  $p < 0,01$ ). En la SOG con 100 g, el número de puntos patológicos fue mayor ( $3,18 \pm 0,69$  en DM vs.  $2,3 \pm 0,28$  normal,  $2,6 \pm 0,47$  GBA,  $2,5 \pm 0,32$  IHC;  $p < 0,001$ ). En la SOG con 100 g, el nivel de glucemia por encima del cual es más probable el diagnóstico de DM posparto es 189 mg/dl en la determinación a las 2 h (S: 86,2%; E: 72%). Un nivel de HbA<sub>1c</sub>  $\geq 5,9\%$  durante la gestación tiene una especificidad del 95,9% para el diagnóstico de DM posparto en nuestra muestra.

**Conclusión:** Evidenciamos factores asociados al diagnóstico de DM posparto entre los que se encuentran determinaciones cuantitativas como la glucemia a las 2 h de la SOG con 100 g y la HbA<sub>1c</sub> durante la gestación en pacientes con DG.

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**Introduction**

Gestational diabetes (GD) is defined as carbohydrate intolerance of variable intensity diagnosed for the first time during pregnancy, regardless of the treatment used to control it or its postpartum course.<sup>1</sup>

The prevalence of GD in Spain ranges from 4.5% to 11.6% of all pregnancies, depending on the study and the criteria used to diagnose the condition.<sup>2</sup>

Gestational diabetes is related to metabolic syndrome, high blood pressure, dyslipidemia and obesity in the future, and the literature indicates that over 50% of all affected patients develop type 2 diabetes mellitus (DM) in the course of follow-up.<sup>3</sup> The current clinical practice guidelines<sup>4</sup> therefore recommend early patient reassessment after delivery. However, in routine practice it is difficult to ensure patient compliance once pregnancy has ended.<sup>5</sup>

There is evidence that the incidence of DM can be reduced by the adoption of healthy lifestyle habits. Despite this, some studies have found that less than half of all patients with GD undergo postpartum reassessment.<sup>6</sup>

The reporting of factors implicated in the development of DM may help increase the number of patients adhering to prevention programs.

However, the lack of data for individual risk estimation means that the healthcare professionals involved in the care of women with GD fail to optimize patient counseling in this regard.<sup>7</sup>

We therefore conducted a study with the primary aim of analyzing the factors related to postpartum diabetes in a sample of patients with GD.

**Material and methods**

A retrospective observational study was made, using information collected from the specialist GD unit of Hospital Universitario de Getafe (Madrid, Spain). We selected a total of 1765 single pregnancy women diagnosed with GD according to the criteria of the National Diabetes Data Group (NDDG) between 1993 and 2013. The study was carried out with the approval of the hospital Ethics Committee.

We evaluated the women with no history of diabetes between 24 and 28 weeks of pregnancy based on the O'Sullivan test after a 12-h fasting period. If any known risk factor for GD was detected (age > 35 years, a body mass index [BMI]  $\geq 30$  kg/m<sup>2</sup>, previous GD or a family history of DM), the screening test was performed in the first trimester of pregnancy. When the plasma glucose levels recorded 1 h after an oral glucose tolerance test (OGTT) with 50 g were  $\geq 140$  mg/dl, the OGTT was repeated with 100 g, and the fasting plasma glucose levels were measured 1, 2 and 3 h after intake, with the recording of glycosylated hemoglobin (HbA<sub>1c</sub>) (DCCT). Gestational diabetes was diagnosed according to the NDDG criteria: two or more plasma glucose values above the following limits: 105 mg/dl basal: 190 mg/dl in 1 h, 165 mg/dl in 2 h and 145 mg/dl in 3 h.

If GD was diagnosed, we prescribed dietary measures (50% carbohydrate, 20% protein and 30% fat) with a calorie supply of 35 kcal/kg in low-weight patients, 30 kcal/kg in patients with normal weight, 25 kcal/kg in overweight women and 15 kcal/kg in obese patients. In addition, recommendations for moderate and regular physical activity (brisk walking for at least 1 h a day) were made. Insulin

therapy was started if optimal glycemia targets were consistently not met (fasting capillary blood glucose > 95 mg/dl or 1 h postprandial > 140 mg/dl).

Three months after delivery, an OGTT was performed with 75 g and HbA<sub>1c</sub> (DCCT) was measured in order to reassess postpartum altered glucose. Normal fasting glycemia was defined as <100 mg/dl and 2 h <140 mg/dl; impaired fasting glucose (IFG) was defined as fasting glycemia between 100 and 125 mg/dl; carbohydrate intolerance (CHI) was defined as blood glucose after 2 h between 140 and 199 mg/dl; and DM was defined as fasting glycemia  $\geq$  126 mg/dl and/or 2 h  $\geq$  200 mg/dl.

The exclusion criteria were multiple pregnancies, delivery <20 weeks and incomplete follow-up to delivery.

The following data were analyzed.

## Clinical data

Maternal age, maternal origin and maternal pregestational body weight (kg) and the BMI (kg/m<sup>2</sup>), obesity being defined as a BMI  $\geq$  30 kg/m<sup>2</sup>, together with weight gain during pregnancy, a history of DM in first-degree relatives, and a history of GD in the patient.

## Laboratory test data

Plasma glucose in GD diagnostic testing after an OGTT with 100 g (basal: 1, 2 and 3 h). The number of points with pathological blood glucose values among the four measurements (2, 3 or 4 pathological points in the OGTT). The glycemic response to reassessment testing three months after delivery using an OGTT with 75 g. Glycosylated hemoglobin at the time of the diagnosis of GD and three months after delivery. Insulin use during pregnancy in order to secure good blood glucose control.

## Statistical analysis

Qualitative variables were reported as frequency distributions, and quantitative variables as the mean and standard deviation (SD) (data exhibiting a normal distribution).

The behavior of the quantitative parameters was analyzed for each of the independent variables based on the Student t-test (for comparisons of a variable with two categories) or analysis of variance (ANOVA).

Diagnostic performance curves (receiver operating curves [ROCs]) were used for the parameters of the OGTT with 100 g in order to detect the points discriminating the presence of postpartum DM, with the calculation of sensitivity and specificity.

Linear regression models were fitted to assess factors associated with the development of postpartum DM.

Statistical significance was considered for  $p < 0.05$ . The SPSS<sup>®</sup> version 15.0 statistical package for MS Windows<sup>®</sup> was used throughout.

## Results

A total of 1765 patients were included in the study, with an age of  $32.5 \pm 4.3$  years (mean  $\pm$  SD). Of these patients,

**Table 1** Maternal characteristics of the study sample: personal history, family history, anthropometric measurements and percentage of patients treated with insulin.

Mean age (years)	32.5 $\pm$ 4.3
Family history of DM (%) (n = 1070)	60.6
History of GD (%) (n = 231)	13.1
Mean pregestational weight (kg)	68.4 $\pm$ 14.7
Mean height (m)	1.59 $\pm$ 0.06
Pregestational BMI (kg/m <sup>2</sup> )	26.9 $\pm$ 5.4
Obesity (%) (n = 381)	21.6
GD diagnosis week	29.2 $\pm$ 5.9
Insulin (%) (n = 354)	20.1
Weight at start of third trimester (kg)	75.6 $\pm$ 14.1
Total weight gain (kg)	8.2 $\pm$ 5.3

GD: gestational diabetes; DM: diabetes mellitus; BMI: body mass index.

14.2% (n = 251) were foreigners. The pregestational BMI was  $26.9 \pm 5.4$  kg/m<sup>2</sup>, and 21.6% of the patients had pregestational obesity. A total of 60.6% of the sample had a history of first-degree relatives with DM, and 13.1% had experienced at least one episode of GD in previous pregnancies.

The diagnosis of GD leading to the start of treatment (based on dietary and physical activity recommendations) was established at  $29.2 \pm 5.9$  weeks of pregnancy on average. During pregnancy, insulin therapy was required by 20.1% of the patients to improve blood glucose control (Table 1).

With regard to the neonatal and delivery characteristics, 10.1% of the infants presented macrosomia (n = 171). In turn, 27.1% of the deliveries were by cesarean section (n = 474), and the mean gestational age at delivery was  $38.8 \pm 2.1$  weeks.

At an average of 3.5 months ( $\pm 0.4$ ) after delivery, the OGTT was performed with 75 g of glucose to determine whether any postpartum glucose alterations persisted. This reassessment found that 77.8% of the women had a normal OGTT, 9.5% presented IFG, 10.8% had CHI, and 2.1% were diagnosed with DM after pregnancy. A total of 524 patients (29.7%) were lost over postpartum follow-up. Thus, a total of 1241 patients (70.3%) were followed-up on until reassessment after delivery. Analysis of the baseline characteristics of the patients lost to follow-up revealed no statistically significant differences versus the other patients.

In the analysis of predictors of DM after delivery, we took into consideration the clinical and laboratory test parameters, focusing mainly on blood glucose levels in the OGTT with 100 g and HbA<sub>1c</sub> during pregnancy (DCCT).

## Clinical data

The study of the clinical parameters showed differences according to a history of GD in previous pregnancies. In this regard, 25% of the patients who finally had postpartum DM presented a history of GD in previous pregnancies, versus only 12.9% of the patients who did not have DM after delivery ( $p < 0.05$ ).

In the patients of other origin (i.e., not Spanish), the probability of postpartum DM was higher than among the Spanish patients (6.8% versus 1.3%;  $p < 0.01$ ).

**Table 2** Percentage of patients with pathological blood glucose levels at the different OGTT 100 g measurement points according to the postpartum reassessment groups (normal, IFG, CHI and DM).

	Postpartum reassessment			
	Normal% (n=965)	IFG% (n=118)	CHI% (n=134)	DM% (n=261)
Basal	9.6 (n=93)	38.5 (n=45)	20.5 (n=27)	14.5 (n=38)
1 h	81.3 (n=785)	90 (n=106)	88.4 (n=118)	88.2 (n=230)
2 h	92.1 (n=889)	80.8 (n=95)	96.4 (n=129)	100 (n=261)
3 h	39.9 (n=385)	38.6 (n=46)	49.5 (n=66.3)	71.4 (n=186)

DM: diabetes mellitus; IFG: impaired fasting glucose; CHI: carbohydrate intolerance; OGTT: oral glucose tolerance test.

Differences were also found in relation to pregestational obesity, with the percentage of DM in obese patients being 20.8% versus 14.9% in the non-obese women ( $p < 0.05$ ).

Statistically significant differences were observed in relation to insulin use: of the patients who finally had DM after delivery, 79.2% required insulin treatment to improve their blood glucose control, while only 20% of the women with no DM at reassessment required insulin treatment ( $p < 0.01$ ).

There were no significant differences in the postpartum reassessment results after the family history of DM was taken into consideration (59.2% versus 61.3% of the patients with postpartum DM) ( $p > 0.05$ ).

Likewise, no differences were found in maternal weight gain during pregnancy, with the patients with no DM after delivery presenting a weight gain of  $8.1 \pm 4.3$  kg versus  $8.3 \pm 5.9$  kg in those with postpartum DM ( $p > 0.05$ ).

### Laboratory test data

On analyzing the laboratory test data, we focused on the OGTT glycemia measurements with 100 g of glucose and the HbA<sub>1c</sub> levels during pregnancy.

#### Oral glucose tolerance test with 100 g

The mean glycemia values recorded in the diagnostic OGTT with 100 g were as follows: mean basal blood glucose:  $91.6 \pm 16.0$  mg/dl; after 1 h:  $210.2 \pm 27.7$  mg/dl; after 2 h:  $187.4 \pm 27.7$  mg/dl; and after 3 h:  $138.4 \pm 37.0$  mg/dl.

In the above-mentioned OGTT with 100 g of glucose, 15.5% of the global patients presented pathological glycemia at baseline, 82.6% showed impaired glycemia in the measurement obtained after 1 h, 91.6% in the measurement after 2 h, and 42.5% in the measurement after 3 h.

The percentage of patients with pathological findings at the different points of the OGTT with 100 g of glucose according to postpartum reassessment is given in Table 2.

Independently of postpartum reassessment, the blood glucose values most often found to be altered in the OGTT with 100 g of glucose were those corresponding to one and 2 h after glucose intake in all the groups ( $p < 0.01$ ). Statistically significant differences were observed on comparing the values 1 and 2 h after glucose intake versus baseline and the 3 h point ( $p < 0.01$ ). By contrast, no significant differences were recorded between the measurements after 1 and 2 h ( $p > 0.05$ ) or at baseline versus the measurement after 3 h ( $p > 0.05$ ) (Table 2).

In relation to the percentage of patients presenting alterations of the different points of the OGTT with 100 g of

glucose, the postpartum reassessment showed the group with IFG to include a larger proportion of women with pathological glucose values at baseline ( $p < 0.001$ ) (Table 2).

No statistically significant differences were found for the remaining measurement points.

Since the diagnosis of GD according to the NDDG is based on the recording of two or more pathological points in the OGTT with 100 g, we studied the percentage of patients with 2, 3 or 4 pathological points (baseline: 1, 2 or 3 h).

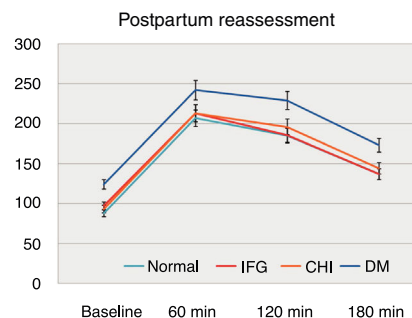
We found that 76% of the patients had two pathological points, 25.6% three points, and 2.4% four pathological points.

With regard to the number of pathological points according to the situation at postpartum reassessment, differences were found between patients who finally had DM after delivery ( $3.18 \pm 0.69$ ) versus those without ( $2.5 \pm 0.45$ ) ( $p < 0.001$ ). The fact of yielding pathological glycemia values at all four points of the OGTT was related to postpartum DM: 12% of these patients presented postpartum DM versus only 1.1% of those with two or three pathological points ( $p < 0.01$ ).

On considering the glycemia values in the OGTT with 100 g of glucose according to postpartum reassessment, we found that the women with postpartum DM had significantly higher values at baseline and after 1, 2 and 3 h versus the other groups ( $p < 0.01$ ) (Fig. 1).

We found no statistically significant differences on comparing the values of the OGTT with 100 g of glucose among the groups with normal values at reassessment, IFG or CHI at postpartum (Fig. 1).

Taking the above into account, we analyzed the data based on the ROC curves for each of the points of the OGTT



**Figure 1** Blood glucose values at the different measurement points in the OGTT with 100 g of glucose according to postpartum reassessment (normal, IFG, CHI or DM).

**Table 3** Sensitivity, specificity and ROC curve corresponding to blood glucose at each OGTT 100 g measurement point in patients with postpartum DM.

OGTT 100 g	Glycemia (mg/dl)	Sensitivity (%)	Specificity (%)	Area ROC curve	95%CI
Basal	97	72.3	74.1	0.76	0.65–0.89
1 h	222	73.4	74.5	0.72	0.52–0.84
2 h	189	86.2	72.0	0.85	0.72–0.92
3 h	150	72.9	60.2	0.72	0.52–0.85

DM: diabetes mellitus; 95%CI: 95% confidence interval; OGTT: oral glucose tolerance test.

with 100 g of glucose, and found the most representative point in relation to postpartum DM to be the measurement obtained 2 h after glucose intake ( $p < 0.01$ ; with AUC: 0.85). Within this setting, the most sensitive and specific glycemia value for predicting postpartum DM was seen to be 189 mg/dl (sensitivity: 86.2%; specificity: 72%) (Table 3).

### HbA<sub>1c</sub>

The mean HbA<sub>1c</sub> concentration at the time of the diagnosis of GD was  $5.3\% \pm 0.4$ , versus  $5.2\% \pm 0.6$  at postpartum reassessment.

On examining the HbA<sub>1c</sub> levels during pregnancy and after delivery in relation to postpartum reassessment, we observed significant differences in HbA<sub>1c</sub> on comparing the patients with DM after delivery versus the other groups (Table 4).

In relation to the above, we explored the possible existence of an association between HbA<sub>1c</sub> measured during pregnancy and the development of postpartum DM. We found an HbA<sub>1c</sub> concentration of 5.9% or higher to be very specific in predicting postpartum DM (specificity: 95.9%; sensitivity: 69%; area under the ROC curve: 0.77) ( $p = 0.01$ ).

The multivariate analysis adjusted for age, the maternal BMI, maternal origin and fasting glucose showed a statistically significant relationship between blood glucose measured 2 h after the OGTT and a diagnosis of DM after delivery ( $p = 0.02$ ), and between HbA<sub>1c</sub> determined at the diagnosis of pregnancy and postpartum DM ( $p = 0.03$ ).

## Discussion

The risk of DM in patients with a history of GD is clearly high, with over 50% of such patients developing DM over the years.<sup>8,9</sup>

The incidence reported in the literature is highly variable, ranging from 3% at early postpartum assessment (3–6 months)<sup>10</sup> to 50–70% at 15–25 years postpartum.<sup>3</sup>

For this reason, the clinical guidelines recommend assessment following delivery at intervals of approximately 4–12 weeks using the OGTT with 75 g of glucose.<sup>4</sup> However, in this phase a considerable percentage of patients are lost

to follow-up, and the test is not performed. Studies of GD analyzing data based on postpartum reassessment usually assume a loss to follow-up of over 50%.<sup>10,11</sup> In our study, we were able to follow-up on over 70% of the women in postpartum reassessment, so giving an added value to the results obtained.

The early identification of patients with a greater probability of postpartum DM is very important. In this regard, and based on objective data, we should insist on the need for a reassessment of blood glucose alterations after delivery, with the OGTT being given early when required.

A comprehensive review of the risk factors for DM in patients with GD shows clinical data such as pregestational overweight or obesity to be the most commonly analyzed factors,<sup>12–14</sup> along with insulin use during pregnancy<sup>3,15</sup> or a history of GD in previous pregnancies.<sup>16,17</sup>

A meta-analysis conducted in 2016 by Rayanagoudar et al.<sup>18</sup> showed that women requiring insulin to improve the control of GD are at a greater risk of developing future DM, with a relative risk (RR) of 3.66 as compared to those not requiring insulin. In obese patients the RR was 3.18. There is strong evidence of an association between these factors and DM in women with a history of GD,<sup>19–21</sup> which is consistent with the data obtained in our study.

In studies examining laboratory test data as predictors of DM after delivery, the most widely analyzed parameter is fasting blood glucose, which appears to be related to the development of future DM.<sup>10,22–24</sup>

However, fewer studies have analyzed the remaining measurement points in the OGTT with 100 g of glucose. The meta-analysis conducted by Rayanagoudar et al.<sup>18</sup> suggests that the blood glucose levels at baseline and recorded at 1, 2 and 3 h in the OGTT with 100 g may be related to the occurrence of postpartum DM (RR: 3.5, 3.05, 3.46 and 3.2, respectively), though the supporting studies are very few and the level of evidence is therefore very low.<sup>25</sup>

A number of studies have been carried out in the Spanish population, such as that published by Albareda et al.<sup>26</sup> These authors identified the pregestational BMI, glycemia > 210 mg/dl at 2 h and the presence of four pathological points in the OGTT as predictors of diabetes. Mention should also be made of a recent study carried out by Monroy

**Table 4** Relationship between HbA<sub>1c</sub> concentration during pregnancy and postpartum reassessment.

Postpartum reassessment	Normal	IFG	CHI	DM	p-value
HbA <sub>1c</sub> pregnancy	$4.9 \pm 0.56$	$5.2 \pm 0.7$	$5.1 \pm 0.7$	$6.2 \pm 1.6$	< 0.01

DM: diabetes mellitus; IFG: impaired fasting glucose; CHI: carbohydrate intolerance.



et al.<sup>27</sup> in which an association was recorded between glycemia at each OGTT measurement point and the risk of postpartum glycemia disorders (RR between 1.0 and 1.4).

In our study we focused on the data which could be afforded by the OGTT with 100 g of glucose. We found a large proportion of the patients to be diagnosed with GD on the basis of only two altered points on the curve (76% of the women versus 25.6% with 3 altered points and 2.4% with 4 altered points). The most frequently altered measurements were those obtained one and 2 h after glucose intake; these were therefore the two most relevant points in diagnosing GD.

In patients with postpartum DM, the blood glucose levels in the above-mentioned OGTT were higher. We thus sought to determine the most significant measurement point and the glycemia threshold above which a diagnosis of DM proves more likely in postpartum reassessment. We found glycemia  $\geq 189$  mg/dl recorded after 2 h in the OGTT with 100 g of glucose to be related to a greater probability of postpartum DM. The multivariate analysis adjusted for factors related to postpartum diabetes confirmed its association independently.

With regard to HbA<sub>1c</sub> determined during pregnancy, the literature describes an association with postpartum DM (RR: 2.56), but the evidence is weak.<sup>18</sup> In our study we found that patients who were finally diagnosed with DM in the postpartum period had higher HbA<sub>1c</sub> concentrations during pregnancy than the other women. Our analysis found an HbA<sub>1c</sub> concentration of 5.9% or more at the diagnosis of GD to be very specific (95.9%) in predicting postpartum DM.

We consider our findings to be very important, since they may allow us to identify those women at an increased risk of developing DM after delivery, based on objective information drawn from the OGTT with 100 g and HbA<sub>1c</sub> measurements during pregnancy. This may allow us to provide more firm recommendations for those patients at increased risk. On the one hand, adherence to testing in postpartum reassessment is indicated, and on the other hand adherence to the provided recommendations is needed in order to lessen the risk of future DM as far as possible.

It may therefore be concluded that in our sample of patients with GD, certain laboratory test parameters such as blood glucose at 2 h in the OGTT with 100 g or HbA<sub>1c</sub> measurements performed during pregnancy are related to the diagnosis of postpartum DM.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

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