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ORIGINAL ARTICLE

Gestational diabetes mellitus: different management strategies should be adopted for different subsets of patients diagnosed by oral glucose tolerance test

Maria Joana Santos[1,2] · Vera Fernandes[1] · The Portuguese Pregnancy and Diabetes Study Group[3]

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Abstract

Purpose To compare women diagnosed with gestational diabetes mellitus (GDM) according to the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) diagnostic criteria based on the number of OGTT diagnostic criteria, which OGTT parameters are altered and the glycemic deviation from proposed diagnostic cutoffs.

Methods Cross-sectional, multicentric study of women diagnosed with GDM between 24–28 weeks of pregnancy according to the IADPSG criteria, in Portugal, between 2012–2014. Primary outcomes: large for gestational age (LGA) and maternal glucose metabolism status after delivery. Secondary outcome: small for gestational age (SGA).

Results Three-thousand three-hundred fourteen patients were included; 67% had 1 OGTT altered value; 3.6% had LGA and 13% had SGA newborns; 7% had prediabetes/diabetes after delivery. Three diagnostic criteria in OGTT (OR 3.02; $p < 0.001$), a diagnostic value at 0 min (OR 2.09; $p = 0.002$) and 60 min (OR 1.70; $p = 0.022$) and glucose deviation at 0 min (OR 1.02; $p = 0.014$) were predictors of LGA. Having 2 (OR 1.94; $p < 0.001$) or 3 (OR 3.93; $p < 0.001$) diagnostic criteria in OGTT, a diagnostic value at 0 min (OR 1.76; $p = 0.002$), at 60 min (OR 1.57; $p = 0.007$) and at 120 min (OR 3.11; $p < 0.001$), the glucose deviation at 0 (OR 1.02; $p = 0.017$) and 120 min (OR 1.02; $p < 0.001$) were predictors of prediabetes/diabetes after delivery. Insufficient weight gain in pregnancy (OR 1.49; $p < 0.001$) and lower maternal BMI (OR 0.97; $p = 0.024$) were associated with SGA.

Conclusion IADPSG diagnostic criteria include a heterogeneous group of women, for whom different management strategies should be adopted to obtain ideal pregnancy outcomes.

Keywords Diabetes, Gestational · Fetal macrosomia · Infant, small for gestational age · Body mass index

Introduction

Gestational diabetes mellitus (GDM) has been a subject of controversy, regarding its definition, diagnostic criteria, treatment goals, and clinical implications.

According to the American Diabetes Association (ADA), GDM is defined as "diabetes that is first diagnosed in the second or third trimester of pregnancy that is not clearly either preexisting type 1 or type 2 diabetes" [1].

In 2008, the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study was the first large-scale multinational study to show that maternal hyperglycemia between 24–28 weeks was linearly and positively correlated with large for gestational age (LGA) infants, caesarian rate, cord-blood serum C-peptide level, and neonatal hypoglycemia. No glycemic threshold for a greater risk was identified for most outcomes [2].

Based on the findings of the HAPO study, the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) proposed, in 2011, a major change in the diagnostic criteria of GDM: a one-step diagnostic approach based on a 2 h 75-g oral glucose tolerance test (OGTT)

✉ Maria Joana Santos
mjoanasantos@hotmail.com

[1] Endocrinology Department, Hospital de Braga, Sete Fontes–São Victor, 4710-243 Braga, Portugal

[2] Harvard Medical School's Portugal Clinical Scholars Research Training Program, Lisboa, Portugal

[3] The Portuguese Society of Diabetology, R. do Salitre, 149-3°Esq, 1250-198 Lisboa, Portugal

between 24–28 weeks of gestation in all women not previously known to have diabetes or GDM [3]. Based on the average fasting, 1 h, and 2 h plasma glucose values obtained in the HAPO study population and on an odds ratio (OR) of 1.75 for the studied adverse outcomes, the IADPSG proposed new diagnostic criteria thresholds for the diagnosis of GDM. The diagnosis is made based on, at least, one altered parameter [3]. This was an attempt to uniformize diagnostic standards, as different diagnostic procedures and thresholds were used previously worldwide. However, these new guidelines imply that the individual glucose OGTT values are independent predictors of adverse outcomes and the that relative importance of each value is similar.

This change was not universally adopted and has been a topic of extensive debate, with some advocating that it led to a significant increased incidence of GDM, with consequent burden on the health care systems and medicalization of previously considered healthy pregnancies, with potential implications on women's quality of life [1]. On the other hand, the pathophysiologic basis of impaired fasting glucose and impaired glucose tolerance in OGTT are different. While the former seems to be related to insulin resistance, the latter is due to decreased beta-cell function, either in early- and late-phases of insulin secretion [4].

In Portugal, the new IADPSG diagnostic criteria were nationally adopted in 2011.

However, there is lack of evidence from randomized controlled trials comparing the old vs. new diagnostic criteria for GDM and showing the benefits of treating modestly elevated glycemic values in the mother's future risk of diabetes and the fetus metabolic benefits in its future life [1]. Moreover, there are no data showing the best treatment approach for these newly diagnosed women, namely the ideal intensity of treatment and monitoring during pregnancy [1]. In fact, the IADPSG diagnostic criteria classify equally a potentially heterogenous group of women, who are monitored and treated the same way, with the same treatment targets during pregnancy.

We hypothesized that women diagnosed according to these criteria in the second trimester of pregnancy using 2 h 75-g OGTT constitute an heterogenous group and may warrant different treatment strategies and targets.

In this study, our aim is to compare different subsets of women diagnosed with GDM according to the IADPSG 1-step approach, based on the number of OGTT diagnostic criteria, which OGTT parameter is/are altered and the glycemic deviation from proposed diagnostic cutoffs. Our primary outcomes are the occurrence of LGA newborn and the reclassification status of maternal glucose metabolism after birth as prediabetes or diabetes. Our secondary outcome is the occurrence of small for gestational age (SGA) newborn.

Methods

This is a cross-sectional, multicentric, nation-wide study of women diagnosed with GDM and followed at the medical centers of the Portuguese Group for the Study of Diabetes and Pregnancy, between 1st January 2012 and 31st December 2014. The centers included are representative of Portugal's mainland. Each center sent their data, obtained from the patients' medical records, to the coordinator of the study group. The merged data were blinded for both patient and hospital identification.

We included women diagnosed with GDM between 24–28 weeks of pregnancy according to the IADPSG criteria [3]. We excluded multiple pregnancies, women with pregestational diabetes, women diagnosed with GDM before or after 24–28 weeks, women who gave birth to newborns before 28 weeks, and cases with lack of information about any of the three parameters of 2 h 75-g OGTT.

We studied the following variables: maternal characteristics (age, diabetes mellitus in first degree relatives, previous GDM, previous macrosomia, pre-pregnancy body mass index (BMI)); factors related to the present pregnancy (OGTT parameters, weight gain, need for hypoglycaemic therapy); factors related to the newborn (sex, gestational age (GA) and birthweight); reclassification of maternal glucose metabolism 6 to 12 weeks after delivery, according to ADA criteria [1]. Women were treated with hypoglycemic drugs to achieve the following therapeutic goals: glucose before meals < 90 mg/dl; glucose 1 h after meals: < 120 mg/dl, according to national standards.

According to the pre-pregnancy BMI, we divided women in four groups: "Underweight" (BMI ≤ 18.4 Kg/m^2), "Normal weight" (BMI 18.5–24.9 Kg/m^2); "Overweight" (BMI 25.0–29.9 Kg/m^2) and "Obese" (BMI ≥ 30.0 Kg/m^2). We classified weight gain in pregnancy according to the Institute of Medicine's recommendations as "insufficient", "adequate" or "excessive" for BMI category [5].

We also classified newborns as "Small for Gestational Age (SGA)" if weight for gestational age below 10th percentile; "Adequate for Gestational Age (AGA)" if weight for gestational age between 10th–90th percentile and "Large for Gestational Age (LGA)" if weight for gestational age above 90th percentile, according to Fenton Growth Charts [6].

For statistical analysis, we used STATA IC 14® software. In the descriptive analysis, for quantitative variables, we used central tendency measures and dispersion measures and for qualitative variables we used absolute numbers and percentages. We looked for associations between outcomes and qualitative covariates using the Chi-square test and for differences in the distribution of quantitative variables using Anova and Kruskall–wallis tests.

For the studied outcomes, we created three multiple logistic regression models based on different ways of analyzing glucose values at 0, 60, and 120 min in OGTT: model 1 (number of diagnostic criteria); model 2 (which OGTT parameters were altered); model 3 (glycemic difference from the proposed diagnostic cutoffs). In logistic model building, we adjusted for potential confounders using a stepwise regression with a backward elimination approach. We constructed receiver operating characteristic (ROC) curves and calculated areas under the curves (AUCs) to compare the different models of logistic regression for each outcome.

A 2-sided p-value ≤ 0.05 was considered statistically significant. In logistic regression, for the two primary outcomes, we adopted a conservative approach and used a Bonferroni correction, considering a significant value if $p <$ 0.025. A complete-case analysis was used to deal with missing data.

This research was conducted according to the Declaration of Helsinki.

Results

In the study period, 8911 women with GDM were followed at the medical centers participating in the study. After applying the inclusion and exclusion criteria, 3314 women were included in the study. The number of participants with missing data for each variable of interest was as follows: maternal age ($n = 6$), DM in first degree relatives ($n = 116$), previous GDM ($n = 82$), previous macrosomia ($n = 94$), pre-pregnancy BMI ($n = 150$), weight gain ($n = 379$), need for insulin ($n = 36$) or oral antidiabetic agents ($n = 2311$), fetal sex ($n = 162$), week of delivery ($n = 108$), birthweight ($n = 101$), reclassification of maternal glucose metabolism after delivery ($n = 943$). There were no missing values in all categories related to OGTT results.

The patients' mean age was 33.4 ± 5.3 years. More than 50% were overweight or obese and 25% had an excessive weight gain during pregnancy. Most women were diagnosed with GDM based on only one diagnostic criteria in OGTT; 27% had a diagnostic value at 0 min and >50% had diagnostic values at 60 and 120 min. The glucose value deviation from the proposed diagnostic cutoffs varied greatly in this population. After GDM diagnosis, >40% of the women required insulin treatment to achieve the desired therapeutic goals. Only 113 newborns (3.5%) were LGA; however, a greater proportion (13.2%) were SGA. After delivery, 7% of the women were classified as having prediabetes/diabetes (Table 1).

Mothers of LGA infants had higher glucose values at 0 and 60 min in OGTT, a higher percentage of diagnosis based on three OGTT criteria, higher initial BMI, greater prevalence of previous GDM, previous macrosomia, need for insulin treatment and an increased prevalence of excessive weight gain during pregnancy than mothers of non LGA infants. Mothers of SGA infants had a significantly lower BMI and a greater frequency of insufficient weight gain in pregnancy; 38% of these women were treated with insulin. Most of these women had only one diagnostic value in OGTT (Table 2).

The diagnosis of prediabetes/diabetes after delivery was positively associated with maternal age, family history of diabetes, excessive weight gain in pregnancy, insulin treatment, the number of diagnostic criteria and higher glucose values in OGTT at 0, 60, and 120 min (Table 3).

Table 4 shows the OR for LGA and SGA and for prediabetes/diabetes diagnosis after pregnancy in the three different logistic regression models previously described. Having three diagnostic criteria in OGTT, a diagnostic value at 0 and 60 min and the absolute glucose difference at 0 min from proposed cutoff were significant predictors of LGA. Previous macrosomia, maternal BMI, and excessive weight gain in pregnancy were also associated with LGA (Table 4).

Having 2 or 3 GDM diagnostic criteria, a diagnostic value at 0, 60, or 120 min and the glucose difference from proposed cutoffs at 0 and 120 min were predictors of reclassification status after birth. A family history of diabetes was also associated with this outcome (Table 4).

Insufficient weight gain in pregnancy (OR 1.49; CI 95% 1.19–1.86, $p < 0.001$) and lower maternal BMI (OR 0.97; CI 95% 0.95–0.997, $p = 0.024$) were significant predictors of SGA in multiple logistic regression. Need for insulin treatment was not (OR 0.82; CI 95% 0.65–1.02, $p = 0.08$). When the analysis was adjusted for the OGTT values as described in Table 4, only a diagnostic value at 0 min and the glycemic difference at 0 min were significant predictors of SGA (Table 4).

Discussion

GDM affects a significant proportion of women, following the increasing global prevalence of overweight and obesity in women of reproductive age. Although it has been demonstrated that even slightly elevated glycemic levels are associated with adverse outcomes in pregnancy, the relationship between different OGTT characteristics, namely the number of diagnostic criteria and which values are elevated, as well as the appropriate management strategies for different patients remain controversial.

Aiming to contribute to further clarify this question, we compared women diagnosed with GDM between 24–28 weeks of pregnancy through 75-g OGTT according to the number of diagnostic criteria, which criteria were

Table 1 Characterization of the total population and according to each diagnostic criterion

	Total population $N = 3314$	OGTT 0′ diagnostic $N = 896$ (27.0%)	OGTT 60′ diagnostic $N = 1814$ (54.7%)	OGTT 120′ diagnostic $N = 1910$ (57.6%)
Maternal initial characteristics				
Maternal age (years)[a]	33.4 ± 5.3 (15–52)	33.1 ± 5.7 (15–52)	33.7 ± 5.3 (17–48)	33.7 ± 5.1 (15–52)
DM family history	1497 (46.8%)	401 (46.4%)	863 (49.2%)	895 (48.5%)
Previous GDM	378 (11.7%)	105 (12.0%)	260 (14.7%)	220 (11.8%)
Previous macrosomia	130 (4.0%)	50 (5.8%)	68 (3.8%)	61 (3.3%)
Maternal BMI (Kg/m^2)[b]	25.3 (22.6–29.5) (14.7–51.4)	27.4 (23.9–32.5) (17.0–48.7)	25.7 (22.9–30.0) (14.7–51.4)	25.0 (22.5–28.8) (16.2–48.7)
Maternal BMI categories (Kg/m^2)				
≤18.4	58 (1.8%)	13 (1.5%)	24 (1.4%)	31 (1.7%)
18.5–24.9	1424 (45.0%)	273 (32.0%)	744 (42.9%)	866 (47.4%)
25.0–29.9	952 (30.1%)	260 (30.5%)	530 (30.6%)	560 (30.6%)
≥30.0	730 (23.1%)	307 (36.0%)	436 (25.1%)	372 (20.3%)
OGTT values (mg/dl)				
Glucose value at 0′[b]	82 (75–92) (45–200)	95 (93–100) (92–200)	82 (76–89) (46–200)	80 (74–87) (45–200)
Glucose value at 60′[b]	181 (159–193) (54–338)	168 (138–194) (54–338)	191 (185–202) (180–338)	176 (158–194) (65–338)
Glucose value at 120′[b]	155 (132–168) (46–317)	134 (111–161) (49–317)	151 (131–170) (46–317)	165 (158–176) (153–317)
Number of diagnostic criteria				
1	2220 (67.0%)	461 (51.5%)	799 (44.1%)	960 (50.3%)
2	882 (26.6%)	223 (24.9%)	803 (44.3%)	738 (38.6%)
3	212 (6.4%)	212 (23.7%)	212 (11.7%)	212 (11.1%)
Glycemic difference at 0′[b]	−10 (−17; 0) (−47; 108)	3 (1–8) (0–108)	−10 (−16; −3) (−46; 108)	−12 (−18; −5) (−47; 108)
Glycemic difference at 60′[b]	1 (−21; 13) (−126; 158)	−12 (−42; 14) (−126; 158)	11 (5–22) (0–158)	−4 (−22; 14) (−115; 158)
Glycemic difference at 120′[b]	2 (−21; 15) (−107; 164)	−19 (−42; 8) (−104; 164)	−2 (−22; 17) (−107; 164)	12 (5–23) (0–164)
Total glycemic difference[a]	−16.1 ± 49.9 (−198; 420)	−21.2 ± 77.2 (−198; 420)	5.4 ± 48.1 (−127; 420)	2.0 ± 48.6 (−158; 420)
Factors related to present pregnancy				
Maternal weight gain (Kg)[a]	9.96 ± 5.43 (−7; 36)	10.2 ± 6.1 (−7; 36)	10.0 ± 5.4 (−6.4; 32)	9.7 ± 5.3 (−6; 32)
Maternal weight gain				
Insufficient	1202 (41.6%)	256 (33.0%)	626 (39.6%)	764 (45.6%)
Adequate	966 (33.4%)	263 (33.8%)	552 (35.0%)	543 (32.4%)
Excessive	724 (25.0%)	258 (33.2%)	402 (25.4%)	369 (22.0%)
Insulin	1432 (43.7%)	488 (54.8%)	842 (47.0%)	834 (44.2%)
Oral agents	44 (4.4%)	22 (7.9%)	20 (3.8%)	21 (3.6%)
Factors related to birth/neonatal period				
Delivery week[b]	39 (38–39) (28–42)	39 (38–39) (28–41)	39 (38–39) (28–41)	39 (38–39) (28–42)
Birthweight (g)[a]	3128.7 ± 486.3 (840–4975)	3196.7 ± 480.6 (1350–4850)	3128.9 ± 506.6 (840–4850)	3108.4 ± 487.7 (840–4975)
Fetal sex				

Table 1 (continued)

	Total population $N = 3314$	OGTT 0′ diagnostic $N = 896$ (27.0%)	OGTT 60′ diagnostic $N = 1814$ (54.7%)	OGTT 120′ diagnostic $N = 1910$ (57.6%)
Male	1640 (52.0%)	441 (51.6%)	906 (52.8%)	925 (50.9%)
Female	1512 (48.0%)	413 (48.4%)	809 (47.2%)	892 (49.1%)
Fetal weight categories				
AGA	2650 (83.3%)	740 (85.9%)	1427 (82.0%)	1515 (82.6%)
SGA	419 (13.2%)	68 (7.9%)	237 (13.6%)	260 (14.2%)
LGA	113 (3.5%)	54 (6.3%)	77 (4.4%)	59 (3.2%)
Reclassification of maternal glucose metabolism				
Normal	2195 (92.6%)	554 (91.3%)	1208 (91.8%)	1263 (90.3%)
Prediabetes	162 (6.8%)	48 (7.9%)	99 (7.5%)	123 (8.8%)
Diabetes	14 (0.6%)	5 (0.8%)	9 (0.7%)	13 (0.9%)

AGA adequate for gestational age, *BMI* body mass index, *DM* diabetes mellitus, *GDM* gestational diabetes mellitus, *LGA* large for gestational age, *OGTT* oral glucose tolerance test, *SGA* small for gestational age

[a]Mean ± SD (minimum-maximum)

[b]Median (P25–P75) (minimum-maximum)

altered and the magnitude of the deviation from proposed cutoffs.

In this cohort, the diagnosis of GDM was mostly made based on a single altered OGTT value, namely after 60 or 120 min. Black et al. [7], in a study of 1691 women with untreated GDM diagnosed by IADPSG criteria, have reported that most women were also diagnosed based on one single altered OGTT value, but in that cohort the fasting value was the most frequently elevated.

In our study, in all three parameters, the median glycemic difference above the proposed cutoff was low and showed a narrow interquartile range. Therefore, only a minority of these women showed a marked hyperglycemic value. This may be relevant since the inter- and intra-assay variability is not considered when the diagnosis is made in a 1-step diagnostic approach. It can be questioned if, in women with only one slightly elevated glycemic value, repeating the diagnostic test would confirm the diagnosis.

Despite this, more than 40% of women received insulin treatment, which may have been due to the strict glycemic targets adopted at that time in Portugal (glucose before meals < 90 mg/dl; 1 h after meal: < 120 mg/dl).

We found a positive association between the number of diagnostic criteria in OGTT and LGA, but only the presence of three diagnostic criteria was predictor of this outcome. A Chinese study, including 2927 women with GDM according to the same criteria, found similar results, with the strongest association in patients with three abnormal values [8].

In our study, higher glucose levels at 0 and 60 min were associated with LGA, with a strongest association for the fasting value. In the HAPO study, none of the three OGTT values was superior in predicting fetal adiposity [9]. However, others have shown the association of fasting hyperglycemia and LGA. Black et al. reported that a diagnostic value at 0 and 60 min in OGTT was associated with increased risk for LGA, with greater risk for abnormal fasting glucose (either isolated or associated with impaired tolerance test (IGT)), compared to patients with only IGT [7]. Feng et al. [8] also found that fasting hyperglycemia had the strongest association with LGA (OR 1.7; CI 1.29–2.25), with increasing risk of LGA as fasting glucose levels increased. Others have reported similar findings [10, 11]. Maternal BMI and excessive weight gain in pregnancy were predictors of LGA in all logistic regression models, independently of glycemic values, as previously reported [12–14].

In this GDM population, we found a relatively low prevalence of LGA infants and a surprisingly higher percentage of SGA infants, namely in mothers with lower pre-pregnancy BMI and with insufficient weight gain in pregnancy. Although this may reflect the achievement of a therapeutic goal (low LGA prevalence), it could also be questioned if it reflects over diagnosis of GDM and/or overtreatment of these women, due to the strict glycemic targets adopted, at expenses of a high prevalence of insulin treatment and of insufficient weight gain. It should be noticed that either too much or too little weight gain in pregnancy can adversely impact the health of children, as very low weight gain in pregnancy is associated with SGA neonates which, in turn, is a risk factor for preterm delivery, hypertension, cardiovascular disease, and diabetes in future

Table 2 Comparison of the three subgroups of fetal weight categories

	Fetal weight categories			
	SGA $N = 419$ (13.2%)	AGA $N = 2650$ (83.3%)	LGA $N = 113$ (3.5%)	*p*-value
OGTT values (mg/dl)				
Glucose value at 0′[a]	79 (73–86)	83 (75–92)	90 (83–95)	<0.001
Glucose value at 60′[a]	182 (163–192)	181 (158–193)	186 (166–199)	0.041
Glucose value at 120′[a]	156 (137–168)	155 (131–167)	154 (126–167)	0.122
Diagnostic value at 0′	68 (16.2%)	740 (27.9%)	54 (47.8%)	<0.001
Diagnostic value at 60′	237 (56.6%)	1427 (53.9%)	77 (68.1%)	0.008
Diagnostic value at 120′	260 (62.1%)	1515 (57.2%)	59 (52.2%)	0.084
Number of diagnostic criteria				
1	288 (68.7%)	1786 (67.4%)	60 (53.1%)	<0.001
2	116 (27.7%)	696 (26.3%)	29 (25.7%)	
3	15 (3.6%)	168 (6.3%)	24 (21.2%)	
Glycemic difference at 0′[a]	−13 (−19; −6)	−9 (−17; 0)	−2 (−9; 3)	<0.001
Glycemic difference at 60′[a]	2 (−17; 12)	1 (−22; 13)	6 (−14; 19)	0.041
Glycemic difference at 120′[a]	3 (−16; 15)	2 (−22; 14)	1 (−27; 14)	0.122
Total glycemic difference[b]	−15.4 ± 41.9	−16.8 ± 50.6	−5.3 ± 66.6	0.058
Maternal initial characteristics				
Maternal age (years)[b]	33.2 ± 5.5	33.4 ± 5.3	34.1 ± 5.6	0.289
DM family history	187 (46.4%)	1193 (46.6%)	59 (53.2%)	0.393
Previous GDM	32 (7.9%)	306 (11.8%)	23 (20.7%)	0.001
Previous macrosomia	2 (0.5%)	98 (3.8%)	23 (20.9%)	<0.001
Maternal BMI (Kg/m^2)[a]	24.4 (21.8–28.4)	25.4 (22.6–29.4)	29.0 (24.7–34.8)	<0.001
Factors related to present pregnancy				
Maternal excessive weight gain	61 (16.2%)	592 (25.3%)	56 (57.1%)	<0.001
Maternal insufficient weight gain	192 (50.9%)	961 (41.0%)	16 (16.3%)	<0.001
Insulin	158 (38.0%)	1169 (44.2%)	63 (55.8%)	0.002
Oral agents	4 (3.1%)	34 (4.2%)	2 (6.1%)	0.718

AGA adequate for gestational age, *BMI* body mass index, *DM* diabetes mellitus, *GDM* gestational diabetes mellitus, *LGA* large for gestational age; *OGTT* oral glucose tolerance test, *SGA* small for gestational age

[a]Median (P25–P75) (minimum-maximum)

[b]Mean ± SD

life [8, 15]. This may support the idea that women with GD diagnosed with IADPSG criteria may not all need the same intensive treatment approach. In fact, others have found that about 1/3 of women with GDM according to IADPSG criteria have rates of fetal macrosomia only slightly above women with no GDM [16].

It has long been recognized that women with GDM have an increased risk for type 2 diabetes mellitus. Maternal BMI, GDM severity, and low C-peptide levels have been associated with this outcome [15]. In our study, women with post-delivery diagnosis of prediabetes/diabetes had a higher age, greater prevalence of diabetes family history and of excessive weight gain in pregnancy than women with normal glucose status at reclassification. In multiple logistic regression, however, only diabetes family history remained a significant predictor of this outcome.

Although only a minority of patients were diagnosed as having prediabetes/diabetes after delivery, women with a greater glycemic dysfunction (diagnosed either based on the number of diagnostic criteria in OGTT, which diagnostic criteria were elevated and the magnitude of the glycemic deviation) had an increased risk for diabetes in the near future. The association with the number of abnormal values in OGTT has previously been shown in women diagnosed with GDM through the 100-g diagnostic OGTT [17]. However, it must be noted that, in a GDM women population according to these diagnostic criteria, more than 90% had normal OGTT after delivery. More than 40% of these

Table 3 Comparison of the two subgroups of glucose metabolism reclassification after delivery

	Reclassification after delivery		
	Normal $N = 2195$ (92.6%)	Prediabetes/diabetes $N = 176$ (7.4%)	p-value
OGTT values (mg/dl)			
Glucose value at 0′[a]	82 (75–92)	84 (77–93)	0.005
Glucose value at 60′[a]	181 (159–192)	186.5 (168–206.5)	<0.001
Glucose value at 120′[a]	155 (132–167)	166.5 (154.5–183)	<0.001
Diagnostic value at 0′	554 (25.2%)	53 (30.1%)	0.154
Diagnostic value at 60′	1208 (55.0%)	108 (61.4%)	0.104
Diagnostic value at 120′	1263 (57.5%)	136 (77.3%)	<0.001
Number diagnostic criteria			
1	1483 (67.6%)	83 (47.2%)	<0.001
2	594 (27.1%)	65 (36.9%)	
3	118 (5.4%)	28 (15.9%)	
Glycemic difference at 0′[a]	−10 (−17; 0)	−8 (−15; 1)	0.005
Glycemic difference at 60′ [a]	1 (−21; 12)	6.5 (−12; 26.5)	<0.001
Glycemic difference at 120′ [a]	2 (−21; 14)	13.5 (1.5; 30)	<0.001
Total glycemic difference in OGTT[b]	−17.7 ± 45.0	21.2 ± 79.4	<0.001
Maternal initial characteristics			
Maternal age (years)[b]	33.6 ± 5.1	34.6 ± 5.1	0.012
DM family history	978 (46.0%)	101 (59.1%)	0.001
Previous GDM	249 (11.6%)	23 (13.1%)	0.552
Previous macrosomia	82 (3.8%)	10 (5.8%)	0.216
Maternal BMI (Kg/m^2)[a]	25.2 (22.6–29.4)	26.0 (23.3–30.1)	0.086
Factors related to present pregnancy			
Maternal excessive weight gain	453 (22.7%)	47 (29.9%)	0.039
Maternal insufficient weight gain	868 (43.5%)	59 (37.6%)	0.147
Insulin	967 (44.3%)	98 (56.0%)	0.003
Oral agents	25 (3.7%)	3 (5.2%)	0.577

BMI body mass index, *DM* diabetes mellitus, *GDM* gestational diabetes mellitus, *OGTT* oral glucose tolerance test

[a]Median (P25–P75) (minimum-maximum)

[b]Mean ± SD

women were treated with insulin and a similar proportion had insufficient weight gain during pregnancy. The fact that most women had only one slightly elevated parameter in OGTT and, therefore, a near-normal glycemic metabolism, could have contributed to the relatively low prevalence of prediabetes/diabetes after delivery.

In this study, we included a large number of patients, representing a significant percentage of the total number of Portuguese women with GDM in the study period. All patients were diagnosed with GDM using the IADPSG diagnostic criteria, were regularly followed by multidisciplinary teams and were treated with the same glycemic targets. Reclassification of maternal glucose metabolism after delivery was done using the same standard procedure in all women. However, this study has some limitations to the generalizability of its findings. As it was a multicentric retrospective study, OGTT determinations were not performed in the same laboratory and we cannot exclude the existence of interlaboratory variability in glucose determinations. We only had a small number of patients with three altered parameters and, thus, with greater glycemic dysfunction, which may also have underestimated differences between groups. As all patients received some form of medical intervention through pregnancy, the differences between groups regarding hyperglycemic dysfunction and its effect in the occurrence of LGA may be underestimated. Also, we cannot exclude differences among centers regarding insulin therapy and strategies for weight control during pregnancy, namely the number of medical visits, number of plasma glucose measurements, different thresholds for insulin treatment, and different nutrition plans. All patients participated in nutritional consultations at all

Table 4 Logistic regression models for primary and secondary outcomes

	LGA[a]			Reclassification after delivery[b]			SGA[c]		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Model 1: Number of diagnostic criteria in OGTT									
1 criterion	1.0			1.0			1.0		
2 criteria	1.063	0.637–1.774	0.815	1.942	1.373–2.746	<0.001	1.041	0.813–1.333	0.751
3 criteria	3.024	1.672–5.471	<0.001	3.926	2.415–6.381	<0.001	0.628	0.362–1.089	0.098
Model 2: Which OGTT value is diagnostic									
0 min	2.088	1.320–3.304	0.002	1.762	1.223–2.539	0.002	0.549	0.401–0.752	0.001
60 min	1.703	1.082–2.683	0.022	1.568	1.129–2.179	0.007	1.069	0.839–1.362	0.564
120 min	1.171	0.755–1.818	0.481	3.111	2.116–4.574	<0.001	1.008	0.784–1.297	0.870
Model 3: Glycemic difference from proposed cutoffs (mg/dl)									
0 min	1.019	1.004–1.034	0.014	1.016	1.003–1.030	0.017	0.979	0.969–0.989	<0.001
60 min	1.004	0.996–1.011	0.343	1.003	0.997–1.009	0.300	1.002	0.998–1.006	0.254
120 min	0.996	0.990–1.003	0.300	1.022	1.015–1.028	<0.001	1.001	0.997–1.005	0.611

AUC area under the curve, *CI* confidence interval, *LGA* large for gestational age, *OR* odds ratio, *OGTT* oral glucose tolerance test, *SGA* small for gestational age

[a]LGA-covariates included in all models: previous macrosomia, maternal BMI and excessive weight gain during pregnancy. $p < 0.001$ for all covariates in all models. Covariates tested but excluded after backward elimination: family history of diabetes, previous GDM, maternal age and insulin treatment. AUC between 0.775–0.776 for the three models

[b]Reclassification after delivery (prediabetes or diabetes diagnosis)—covariates included in all models: family history of diabetes and insulin treatment. $p < 0.05$ for family history of diabetes in all models; $p < 0.05$ for insulin treatment in model 2 ($p = 0.047$) and $p > 0.05$ in models 1 and 3. Covariates tested but excluded after backward elimination: previous GDM, maternal age, maternal BMI, and excessive weight gain during pregnancy. AUC between 0.650–0.701 for the three models

[c]SGA-covariates included in all models: maternal BMI and insufficient weight gain during pregnancy. $p < 0.05$ for insufficient weight gain in all models; for BMI, $p = 0.025$ in model 1 and $p > 0.05$ in models 2 and 3. Covariates tested but excluded after backward elimination: insulin treatment. AUC between 0.584–0.605 for the three models

medical centers. Nutrition plans were adjusted according to the clinical condition of the patients, namely the presence of GDM, the pre-pregnancy BMI and the trimester of pregnancy. However, there was no standard protocol shared by all centers. As this is a retrospective study, we cannot assess patients' compliance.

In conclusion, we confirmed our hypothesis that women diagnosed with IADPSG criteria in the second trimester of pregnancy constitute a heterogeneous group regarding some neonatal and maternal outcomes. We found that the number of abnormal OGTT values identifies groups with different risks for LGA and prediabetes/diabetes after delivery. Fasting hyperglycemia and glycemia at 60 min seem to be the most important glycemic alterations associated with LGA, while all glucose values seem to be associated with the risk for glucose metabolism dysfunction after pregnancy. Our findings are supported by other recent studies [7, 8, 11]. We also found that, in women with lower BMI and lower fasting glycemic values, strict glycemic targets may lead to high insulin treatment rates and insufficient weight gain in pregnancy, with consequent SGA newborns. These findings suggest that different management strategies should be adopted for different subsets of patients with GDM to obtain ideal pregnancy outcomes, both for the mother and the child.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the

institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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