

Health Care for Women International



ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/uhcw20

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To cite this article: Silvia Gorban de Lapertosa, Stella Sucani, Susana Salzberg, Jorge Alvariñas, Cristina Faingold, Alicia Jawerbaum, Gabriela Rovira & on behalf of the DPSG-SAD Group (2020): Prevalence of gestational diabetes mellitus in Argentina according to the Latin American Diabetes Association (ALAD) and International Association of Diabetes and Pregnancy Study Groups (IADPSG) diagnostic criteria and the associated maternal-neonatal complications, Health Care for Women International, DOI: 10.1080/07399332.2020.1800012

To link to this article: https://doi.org/10.1080/07399332.2020.1800012



Published online: 04 Sep 2020.





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Prevalence of gestational diabetes mellitus in Argentina according to the Latin American Diabetes Association (ALAD) and International Association of Diabetes and Pregnancy Study Groups (IADPSG) diagnostic criteria and the associated maternal-neonatal complications

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ABSTRACT

In Argentina, gestational diabetes mellitus (GDM) is diagnosed by the Latin American Diabetes Association (ALAD) diagnostic criterion. In this work, we investigated GDM prevalence according to the ALAD and IADPSG diagnostic criteria, evaluated maternal and fetal outcomes and assessed whether fasting glycemia between 92–99 mg/dL was associated with increased risk of macrosomia and maternal obesity/overweight in an Argentine cohort of pregnant women. GDM prevalence was 9.8% with the ALAD diagnostic criterion and 25% considering the IADPSG criterion. Increased prevalence of maternal obesity/overweight was observed in patients with fasting glycemia over 99 mg/dL. A population of high metabolic risk is identified by the ALAD criterion. ARTICLE HISTORY

Received 27 January 2020 Accepted 20 July 2020

Background

The incidence of diabetes mellitus continues increasing and affecting younger people, including women in reproductive age (Burke et al., 1999; Menke et al., 2015). This increase in the incidence of diabetes mellitus is attributable to population aging, urbanization, the obesity epidemics and the physical inactivity. At first sight, the obesity epidemics induced by

changes in the lifestyle seems to be a leading cause of this increase in diabetes prevalence. Obesity and overweight are much extended worldwide, affecting both children and adults across the different ethnic groups (Hales et al., 2017; Poh et al., 2016).

Many studies performed in both developed and underdeveloped countries, although only a few in Latin American countries, have demonstrated an increase in the incidence of type 2 diabetes and gestational diabetes mellitus (GDM) in the last years, which has led to an adverse impact on healthcare systems (Aguayo-Mazzucato et al., 2019; Farrar et al., 2016; Hills et al., 2018; Najafi et al., 2019; Trujillo et al., 2015). GDM, which is defined as the glucose intolerance diagnosed for the first time during pregnancy (American Diabetes Association, 2009; Ben-Haroush et al., 2004; Kjos & Buchanan, 1999), is a prevalent and complex disease when considering both its etiology and pathophysiological mechanisms (Damm et al., 2016; Johns et al., 2018; Plows et al., 2018). The universal screening of GDM allows its diagnosis in all pregnant women by evaluating both fasting glycemia and glycemia values after an oral glucose tolerance test (OGTT). A proper treatment is known to reduce maternal and neonatal complications (Group - HAPO et al., 2008; International Association IADPSG et al., 2010). Most common maternal complications are hypertensive disorders during pregnancy, increased cesarean sections and delivery complications (Bodmer-Roy et al., 2012; Sacks et al., 2015). In addition, frequent adverse neonatal outcomes in GDM pregnancies include large newborns for gestational age, small newborns for gestational age, neonatal hypoglycemia and shoulder dystocia (Ethridge et al., 2014; Kintiraki et al., 2013; Zawiejska et al., 2014).

The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS study) compared the regular obstetric control with a control performed after a specific diagnosis and treatment of GDM, demonstrating the benefits of metabolic control in pregnant women with diabetes, and that GDM is a strong predictor of type 2 diabetes development in the future (Crowther et al., 2005; Greene & Solomon, 2005). The Hyperglycemia and Pregnancy Outcomes study (HAPO) has shown the risks associated with different levels of maternal glucose intolerance and found that these risks are present even when glycemia values are lower than the values used for diagnosis during gestation (Group - HAPO et al., 2008). Indeed, the HAPO study described a close and continuous association between maternal glycemia values and increased weight in newborns, increased levels of peptide C in blood from umbilical cord and other markers of perinatal complications (Group - HAPO et al., 2008). The recent HAPO Follow Up study (HAPO FUS) found also a continuous positive association between glycemia during pregnancy and adiposity in 10- to 14year-old children (Lowe et al., 2019). In 2010, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) established a diagnostic

recommendation based on the HAPO study, with diagnostic values defined considering the glycemia values in which the Odds Ratio for neonatal morbidity is 1.75. According to this criterion, the prevalence of GDM in the HAPO study was 17.8% (International Association IADPSG et al., 2010). This high GDM prevalence led several underdeveloped and developing countries to question and/or delay the use of this diagnostic criterion (Hod et al., 2015; Trujillo et al., 2015).

In 2007, the Latin American Diabetes Association (ALAD) defined a diagnostic criterion (Marquez Guillen & Alad, 2008) quite similar to the one made in 2015 by the British National Institute of Health and Care Excellence (NICE) (National Collaborating Centre for Women's and Children's Health (UK), 2015). According to ALAD, in Argentina and several Latin American countries, the current diagnostic criterion is universal and uses different fasting and post-OGTT glycemia values for diagnosis compared to the IADPSG criterion (Faingold et al., 2009; Salzberg et al., 2016). According to the ALAD criterion, GDM is diagnosed if there are two measurements of fasting plasma glucose higher than 100 mg/dL (5.5 mmol/L) or if glycemia values are higher than 140 mg/dL (7.7 mmol/L) in the second hour of the OGTT (75 g-2h) (Faingold et al., 2009; Salzberg et al., 2016). The evaluation of the prevalence of GDM through both diagnostic methods in Argentina by studying a population from a developing country that has not been previously addressed in this regard, would contribute to the international effort to find a universal screening of GDM. The comparison of these two diagnostic criteria would also allow addressing whether the main adverse outcomes depend on the method of GDM diagnosis and evaluating the contribution of obesity/overweight to these negative birth outcomes.

Considering this, the aim of the present work was to evaluate the prevalence of GDM in Argentina according to both the ALAD and IADPSG diagnostic criteria, to determine the maternal and neonatal complications in an Argentine cohort of pregnant women, and to investigate whether fasting glucose values between 92 and 99 mg/dL (only diagnosed as GDM by the IADPSG criterion) are associated with an increased risk of neonatal macrosomia and maternal obesity/overweight.

Methods

Study design and population

The study population in this cohort study consisted of 1037 pregnant women who attended to 11 obstetric centers in 6 provinces of Argentina from September 2012 to September 2015. Patients with diabetic diagnosis before gestation, patients that were being treated with corticoids, retrovirals and/or betamimetics, patients with intercurrence of infectious pathology, women who

conceived through the use of assisted fertilization methods, gestations with congenital malformations and patients with bariatric surgery were not included in the study. Informed consent was obtained from all individual participants included in the study. The protocol was approved by the Institutional Revision Committee (CRI), Consejo de Evaluación Ética de Investigaciones en Salud (COEIS), Argentina, N° 2012-0003, and was performed in accordance with the ethical standards of the Institution and with the 1964 Helsinski declaration and its later amendments, as revised in Brazil 2013.

GDM diagnosis

The ALAD criterion was used for GDM diagnosis and treatment (Salzberg et al., 2016). According to this criterion, in the first visit to the obstetric centers, all patients received the prescription to make a fasting glycemia measurement. When this measurement showed values higher than 100 mg/dL, the test was repeated during the following three days. GDM was diagnosed with two measurements of fasting glycemia higher than 100 mg/dL. If the fasting glycemia value was lower than 100 mg/dL, a 75 g-2h oral glucose tolerance test (OGTT) was prescribed at 24-28 weeks of gestation. Patients with glycemia values lower than 140 mg/dL in the second hour of the OGTT were considered patients without GDM, while those with values higher than 140 mg/dL were diagnosed with GDM. In patients with normal OGTT at 24-28 weeks of gestation but with risk factors for GDM, the OGTT was repeated at 31-33 weeks of gestation. GDM was diagnosed in any of the instances in which the OGTT was altered. The risk factors considered for GDM were: diabetes in a first degree relative, maternal high or low weight at birth, GDM in a previous pregnancy, maternal age > 30 years old, maternal BMI > 27 kg/m² at the beginning of the pregnancy, fasting glycemia values > 85 mg/dL, polycystic ovary syndrome, macrosomia in a previous pregnancy (newborns with weight higher than 4000 g), previous unexplained perinatal mortality, preeclampsia in previous pregnancies and multiparity (four deliveries or more).

In addition, GDM was diagnosed by the IADPSG criterion. In this case, the same patients were considered as having GDM through the IADPSG criterion when fasting glycemia values were higher than 92 mg/dL. Besides, if 75 g OGTT glycemia values in the first hour were higher than 180 mg/dL or glycemia values in the second hour were higher than 153 mg/dL, GDM according to the IADPSG criterion was diagnosed.

OGTT methodology

The conditions established for the OGTT were that patients received a regular diet three days before the OGTT (with a minimum of 150 g of

carbohydrates). During the test, the patients did not smoke, consume food or make physical activity. The test was made during the morning and women had fasted for 8 h. The first blood sample was obtained in fasting condition, and after extraction, the patients ingested 75 g of anhydrous glucose dissolved in water (20%) in a period of 5 min. Blood samples were taken 1 h and 2 h after the glucose intake for glycemia measurement.

The glycemia values were informed to the medical doctor to perform the GDM diagnosis according to the ALAD criterion. The values of the first hour of the OGTT were kept blind until the end of the study.

Variables evaluated

Data were obtained from prenatal control, birth and neonatology registers. The maternal quantitative variables evaluated were: maternal age (age at the beginning of the study), height (cm) and weight (kg) for BMI calculation and gestational weeks at enrollment. The maternal outcomes evaluated were: hypertensive disorders (arterial hypertension, gestational hypertension, preeclampsia, eclampsia), preterm birth and cesarean section. The neonatal outcomes evaluated were: small size for gestational age (SGA) (live newborns with a weight lower than the percentile 10 for gestational age), macrosomia (newborns with weight higher than 4000 g), neonatal hypoglycemia (glycemia values lower than 40 mg/dL) and hyperbilirubinemia (according to Bhutani curves).

Statistical analysis

The prevalence of GDM, obesity/overweight and macrosomia, as well as the percentage of each maternal or neonatal outcome were analyzed by chi-square test in the total population, including relative risk calculation with the corresponding CI 95%. Maternal and neonatal outcomes in the population with macrosomic newborns were analyzed by exact Fisher test and the corresponding relative risk with the CI 95% was calculated. Two-way ANOVA together with Bonferroni test was used to compare quantitative variables between patients diagnosed or not with GDM by the ALAD or IADPSG criteria. A p value < .05 was considered significant. The analyses were made using Infostat software (Córdoba, Argentina, http://www.infostat.com.ar/).

Results

Prevalence of GDM by the ALAD and IADPSG diagnostic criteria

The prevalence of GDM was evaluated using the ALAD and the IADPSG diagnostic criteria. According to the ALAD diagnostic criterion, 9.8% of

the women evaluated presented GDM, whereas according to the IADPSG diagnostic criterion 24.9% of the patients were diagnosed with GDM (Figure 1a). There was a significant increase in the prevalence of GDM when the IADPSG criterion was applied compared to the ALAD criterion (p < .001; relative risk (RR) 2.53). When comparing the two diagnostic criteria, the results showed that 8.3% of the patients were diagnosed by both criteria, while 1.5% of the patients were diagnosed only by the ALAD criterion and 16.6% were diagnosed only by the IADPSG criterion (Figure 1b).

Regarding the patients with the GDM diagnosis made by the OGTT, there was a significant difference in the percentage of women diagnosed in each instance of the test according to the criterion used. When the fasting glycemia was considered, 22.5% of the patients were diagnosed with the ALAD criterion and 79.6% with the IADPSG criterion (p < .001; RR 3.59). When the glycemia from the second hour of the OGTT was considered, 79.4% of the patients were diagnosed by the ALAD criterion and 16.7% with the IADPSG criterion (p < .001; RR 4.05). With the IADPSG criterion, 32.2% of the women were diagnosed in the first hour of the OGTT (Figure 1c). As only a reduced proportion of GDM patients (16.7%) were diagnosed with the IADPSG criterion by the 2h OGTT (Figure 1d), we addressed whether an increased number of patients would have been identified at the 2h OGTT if the cutoff values had been reduced to the value suggested by the ALAD criteria (140 mg/dL) (Figure 1e). When considering this value, the percentage of patients identified at 2h OGTT increased significantly (27.3%, p < .01) compared to that found with the cutoff value of 153 mg/dL (16.7%). Besides, considering this lower cutoff value, the number of patients diagnosed at 2h OGTT was similar to that diagnosed at 1 h OGTT (28%), but still markedly lower than that diagnosed by the fasting glycemia values (68.6%, p < .001). Moreover, although the percentage of patients diagnosed at fasting was much higher, there was no large overlap between them and those diagnosed at 1 h and 2 h OGTT, considering the cutoff values of either 153 mg/dL or 140 mg/dL (Figure 1d and e).

Evaluation of maternal variables, maternal outcomes and neonatal outcomes

Maternal age, BMI and week of gestation at enrollment (gestational week of the OGTT test) of the 1037 patients were recorded. In the population studied, the mean and standard deviation of the maternal age, BMI and weeks of gestation at enrollment were 26.5 ± 6.4 years old, 27.8 ± 4.9 weeks and 27.3 ± 6.2 kg/m², respectively. As shown in Table 1a, both maternal age



Figure 1. Prevalence of GDM by ALAD and IADPSG diagnostic criteria. a. Percentage of patients diagnosed with GDM by ALAD and IADPSG criteria. Statistics: Chi-square test. ***p < .001. **b.** Percentage of patients with GDM diagnosed only by ALAD, only by IADPSG and by both ALAD and IADPSG criteria. **c.** Percentage of patients diagnosed with GDM according to the three instances of the OGTT in each criterion. **d.** Percentage of patients with GDM diagnosed according to the IADPSG criterion by fasting glucose, 1 h OGTT or 2 h OGTT values. **e.** Percentage of patients with GDM diagnosed according to the IADPSG criterion by fasting glucose, 1 h OGTT or 2 h OGTT. Statistics: Chi-square test. ***p < .001.

and BMI in patients with GDM, diagnosed by either the ALAD and IADPSG diagnostic criteria, were higher than in the patients without GDM (p < .001). No differences were found in maternal age or BMI between the GDM patients diagnosed by ALAD and those diagnosed by IADPSG. There were no differences in weeks of gestation at enrollment between the group of patients without GDM and those with GDM diagnosed either by the ALAD or the IADPSG diagnostic criteria (Table 1a).

Regarding the maternal outcomes, as shown in Table 1b and 1c, women diagnosed with GDM by the ALAD criterion presented higher percentage of cesarean section than women without GDM according to the same criterion (p < .01). If the IADPSG criterion was used, no differences were found in the percentage of cesarean section between patients with and without GDM. Besides, both criteria detected an increase in the prevalence of hypertensive disorders in the patients with GDM (p < .001). No differences were found regarding the percentage of preterm birth according to the ALAD or IADPSG criteria between women with and without GDM. There were no differences when the ALAD and IADPSG diagnostic criteria were compared regarding these maternal outcomes (Table 1c).

Regarding the neonatal outcomes evaluated, as shown in Table 1b and 1c, the results showed higher percentage of cases of hypoglycemia and macrosomia in the newborns from patients with GDM than from healthy patients when either the ALAD or IADPSG diagnostic criterion were used (p < .05). No significant differences were found in the percentage of cases of hyperbilirubinemia and small size for gestational age if either the ALAD or IADPSG criterion was used and compared to the group without GDM. There were no differences in the percentage of these neonatal outcomes when the patients with GDM diagnosed by the ALAD and IADPSG criteria were compared (Table 1c).

Macrosomia

The sensitivity, specificity and positive predicted value (PPV) of the ALAD and IADPSG diagnostic criteria to detect macrosomia were evaluated. The ALAD criterion had low sensitivity for identification of macrosomia (0.17; CI 95%:0.09–0.26), while the IADPSG criterion had a sensitivity of 0.39 for identification of macrosomia (CI 95%: 0.28 - 0.50). The specificity was high in the ALAD (0.91; CI 94%: 0.89 - 0.93) and IADPSG criteria (0.76; CI 95%: 0.74 - 0.99), while a very low PPV was found for both the ALAD (0.13; CI 95%: 0.11 - 0.22) and IADPSG criteria (0.11; CI 95%: 0.09 - 0.28). A subgroup including the cases that presented macrosomic newborns was separately evaluated according to the same variables used before. When maternal variables were measured in the mothers of macrosomic newborns, no differences were

		ALAD		IADPSG			CDM	
Maternal Variables	Without GDM (n 935)	GDM (n 102)	p-value	Without GDM (n 779)	GDM (n 285)	p-value	ALAD v. IADPSG p - value	
Maternal age	26.16 ± 6.56	30.53 ± 7.26	.001	25.53 ± 6.33	29.77 ± 6.99	.001	.36	
BMI	27.77 ± 6.33	31.17 ± 5.67	.001	27.18 ± 5.87	30.87 ± 6.90	.001	.69	
Weeks of gestation at enrollment	27.79 ± 5.23	27.28 ± 5.41	.35	27.86 ± 5.05	27.39 ± 5.77	.21	.86	

Table 1. Maternal variables, maternal outcomes and neonatal outcomes. a)

b)

		ALAD			IADPSG			
	Without GDM (n 935)		GDM (n 102)		Without GDM (n 779)		GDM (n 258)	
Maternal Outcomes	%	n	%	n	%	n	%	Ν
Cesarean Section	47.3 %	442	59.8 %	61	46.9 %	365	53.1 %	138
Hypertensive Disorders	10.7 %	100	18.6 %	19	7.6 %	59	15.7 %	41
Preterm Birth	7.7%	72	6.8 %	7	7.7 %	60	7.3 %	19
Neonatal Outcomes	%	n	%	n	%	n	%	n
Hypoglycemia	1.2 %	12	4.9 %	5	1.0 %	8	3.4 %	9
Hyperbilirubinemia	4.0 %	99	2.9 %	3	4.0 %	31	3.8 %	10
Small for gestational age	5.2 %	49	3.9 %	4	5.4 %	42	4.2 %	11
Macrosomia	6.6 %	62	12.7 %	13	5.9 %	46	11.2 %	29

c)

	ALAD	LAD IADPSG			GDM ALAD v. IADPSG		
	Without GDM v. GDM		Without GDM v.	GDM			
Maternal Outcomes	RR (CI 95%)	p value	RR (CI 95%)	p value	RR (CI 95%)	p value	
Cesarean Section Hypertensive Disorders Preterm Birth	1.57 (1.08 - 2.30) 2.15 (1.36 - 3.39) 0.89 (0.42 - 1.88)	.01 .004 .99	1.20 (0.97 - 1.48) 2.07 (1.43 - 3.01) 0.94 (0.57 - 1.55)	.09 .0002 .89	1.20 (0.86 - 1.68) 1.14 (0.77 - 1.76) 0.95 (0.51 - 1.91)	.29 .50 .95	
Neonatal Outcomes	RR (CI 95%)	p value	RR (CI 95%)	p value	RR (CI 95%)	p value	
Hypoglycemia Hyperbilirubinemia Small for gestational age Macrosomia	3.8 (1.37 - 10.6) 0.72 (0.22 - 2.30) 0.74 (0.22 - 2.3) 1.92 (1.09 - 3.37)	.02 .79 .81 .04	3.3 (1.31 - 8.62) 0.96 (0.47 - 1.39) 0.78 (0.40 - 1.49) 1.88 (1.20 - 2.93)	.02 1.01 .51 .008	1.27 (0.65 - 2.78) 0.81 (0.33 - 2.48) 0.94 (0.43 - 2.40) 1.11 (0.70 - 1.84)	.75 .91 .88 .71	

a. Maternal variables. Values are shown as Mean ± SD. Statistics: two-way ANOVA. b. Maternal and neonatal outcomes shown as percentage. c. Statistics: Chi square test. Relative risk: RR, Confidence Interval 95%: CI 95%.

found in maternal age, BMI or weeks of gestation at enrollment between patients without GDM and patients with GDM diagnosed with either the ALAD or IADPSG diagnostic criterion (Table 2a). Regarding maternal outcomes, in this subgroup, there were no significant differences in the percentage of cesarean section, hypertensive disorders and preterm birth between patients

		ALAD		IADPSG			CDM	
Maternal Variables	Without GDM (n 62)	GDM (n 13)	p-value	Without GDM (n 46)	GDM (n 29)	p-value	GDM ALAD v. IADPSG p – value	
Maternal age	27.27 ± 6.04	27.85 ± 5.54	.75	26.63 ± 6.36	28.55 ± 5.04	.18	.71	
BMI	30.50 ± 6.91	31.35 ± 5.08	.68	30.23 ± 6.93	31.34 ± 6.08	.48	.99	
Weeks of gestation at enrollment	28.47 ± 5.91	29.69 ± 3.44	.48	29.03 ± 5.44	28.14 ± 5.83	.51	.38	

Table 2. Maternal variables, maternal outcomes and neonatal outcomes in cases of macrosomia. a)

b)

		ALAD				i		
Maternal Outcomes	Without GDM (n 62) GDM		GDM (n	13)	Without GDM (n 49)		GDM (n 26)	
	%	n	%	n	%	n	%	n
Cesarean Section	51.6 %	32	69.2 %	9	60.9 %	28	44.8 %	13
Hypertensive Disorders	12.9 %	8	15.4%	2	13.0 %	6	13.8 %	4
Preterm Birth	3.2 %	2	0 %	0	4.4 %	2	0 %	0
Neonatal Outcomes	%	n	%	n	%	n	%	n
Hypoglycemia	6.5 %	4	0 %	0	2.2 %	1	10.3 %	3
Hyperbilirubinemia	0 %	0	0%	0	0 %	0	0 %	0

c)

	ALAD		IADPSG		GDM ALAD v. IADPSG		
	Without GDM v.	GDM	Without GDM v.	GDM			
Maternal Outcomes	RR (CI 95%)	p value	RR (CI 95%)	p value	RR (CI 95%)	p value	
Cesarean Section Hypertensive Disorders Preterm Birth	0.75 (0.48 - 1.15) 0.84 (0.20 - 3.50) -	.36 1.00 N/A	1.36 (0.86 - 2.29) 0.95 (0.29 - 3.07) -	.23 .93 N/A	1.54 (0.89 – 2.66) 1.12 (0.23 – 5.34) –	.19 .96 N/A	
Neonatal Outcomes	RR (CI 95%)	p value	RR (CI 95%)	p value	RR (CI 95%)	p value	
Hypoglycemia Hyperbilirubinemia	-	.95 N/A	0.92 (0.81 - 1.05) -	.29 N/A		.54 N/A	

a. Maternal variables evaluated in cases of macrosomia. Values are shown as Mean±SD. Statistics: two-way ANOVA. b. Maternal and neonatal outcomes in patients that had macrosomic newborns. Data shown as percentages. c. Statistics: Exact Fisher test. Relative risk: RR, Confidence Interval 95%: CI 95%. N/A: Not analyzable data.

without GDM and patients with GDM diagnosed by either the ALAD or IADPSG diagnostic criterion (Table 2b and 2c). Similar results were found when neonatal outcomes were evaluated, as there were no differences in hypoglycemia, hyperbilirubinemia or small size for gestational age between patients without GDM and patients with GDM diagnosed by either the ALAD or IADPSG diagnostic criterion (Table 2b and 2c). The comparison between the ALAD and IADPSG diagnostic criteria showed no differences in the variables evaluated (Table 2c).



Figure 2. Prevalence of macrosomia. Percentage of macrosomic newborns according to the maternal fasting glycemia values. FPG: fasting plasma glucose values. Statistics: chi-square test. *p < .05.

To further understand possible differences between the ALAD and IADPSG diagnostic criteria and considering that fasting glucose values detected almost 80% of the GDM diagnosed by the IADPSG criterion, the prevalence of macrosomia was determined in the population of women with fasting glycemia values between 92 and 99 mg/dL with no GDM diagnosed by the p75 OGTT (patients diagnosed with GDM exclusively by the IADPSG criterion and thus untreated patients). This prevalence was then compared with the prevalence of macrosomia in the population with fasting glycemia values lower than 92 mg/dL and the population with fasting glycemia values higher than 99 mg/dL (patients that received treatment to achieve glycemic control). As shown in Figure 2, the prevalence of macrosomia was higher in the group of patients with fasting glycemia values between 92 and 99 mg/dL and over 99 mg/dL compared to the group with fasting glycemia values lower than 92 mg/dL (p < .05). No differences were observed when the group with fasting glycemia values between 92 and 99 mg/dL and that with values over 99 mg/dL were compared (Figure 2).

Prevalence of obesity/overweight

To address the role of obesity/overweight according to the fasting glycemia value groups, all patients of this study were classified according to the fasting glycemia values in the three mentioned groups: values lower than 92 mg/dL, between 92 and 99 mg/dL, and over 99 mg/dL, and prevalence of obesity/overweight was determined. There was an increase in the



b)



Figure 3. Prevalence of obesity/overweight. a. Percentage of patients with obesity/overweight according to the maternal fasting glycemia values. **b.** Prevalence of GDM according to ALAD and IADPSG diagnostic criteria in patients with obesity/overweight. Values are shown as percentage. Statistics: chi-square test. ***p < .001.

prevalence of obesity/overweight in the groups with glycemia values between 92 and 99 mg/dL and over 99 mg/dL compared to the group with glycemia values lower than 92 mg/dL (p < .001) (Figure 3a). Obesity/overweight prevalence was increased in the group that had fasting glycemia values over 99 mg/dL compared to the group with glycemia values between 92

and 99 mg/dL (p < .001) (Figure 3a). Finally, the prevalence of GDM diagnosed by ALAD or IADPSG was evaluated in the obesity/overweight and the normal weight groups. GDM prevalence was increased in the obesity/ overweight group in the patients diagnosed with GDM either by ALAD or IADPSG compared to the normal weight group (p < .001) (Figure 3b). Besides, in both the normal weight group and the obesity/overweight group, there was an increased prevalence of GDM diagnosed by the IADPSG criterion compared to those diagnosed by the ALAD criterion (p < .001) (Figure 3b).

Discussion

As main findings of this study, the prevalence of GDM in Argentina according to the ALAD and IADPSG criteria showed a 2.5 increased risk of GDM if the IADPSG diagnostic criterion was applied compared to the ALAD diagnostic criterion. Although patients diagnosed with GDM by the ALAD criterion and not those exclusively diagnosed by the IADPSG criterion were treated, maternal and fetal outcomes were similar in both groups and higher than those in patients without GDM. This suggests that, in addition to the glycemic control, a different treatment approach may be necessary to prevent adverse outcomes in patients with GDM. Obesity/ overweight is highly prevalent in patients diagnosed with GDM by the ALAD and more markedly by the IADPSG criterion, suggesting that a focus in prevention of obesity/overweight before pregnancy and improving obesity management from early gestation would benefit maternal and fetal outcomes.

The HAPO study and later the HAPO FUS study showed a linear increase in maternal glycemia associated with adverse maternal, neonatal and childhood outcomes (Group – HAPO et al., 2008; Lowe et al., 2019). The IADPSG 2010/Word Health Organization (WHO) 2013 diagnostic criteria for GDM was based on the glycemia levels related to an OR 1.75 in selected adverse outcomes in the HAPO study (International Association IADPSG et al., 2010). Nevertheless, the IADPSG criterion is still not used worldwide, and not in many undeveloped and developing countries, mainly due to its association with an important increase in GDM prevalence (Bodmer-Roy et al., 2012; Gopalakrishnan et al., 2015; Trujillo et al., 2015). In Argentina and many Latin American countries, the ALAD diagnostic criterion is currently used (Salzberg et al., 2016). The present study was able to update the prevalence of GDM in Argentina and to compare the prevalence and outcomes according to the IADPSG and ALAD diagnostic criteria.

In this work, using the ALAD criterion, we observed an increase from a known prevalence of 5% of GDM in 1995 (Salzberg & Alvariñas, 1995) to the current prevalence of 9.8%, indicating a 2-fold increase in the GDM prevalence in the last 25 years. When comparing the GDM prevalence in the Argentine population with the ALAD and the IADPSG diagnostic criteria, it is interesting to note that the study population presented an average maternal age (27 years old) and BMI (27.3 kg/m²) similar to those observed in the population analyzed by the HAPO study (29 years old and 27.7 kg/m², respectively) (Group – HAPO et al., 2008). In our study, the ALAD criterion led to a GDM prevalence that was markedly lower (9.8%) than the prevalence of patients diagnosed with GDM by the IADPSG diagnostic criterion (24.9%). Besides, 1.5% of the patients were diagnosed by the ALAD criterion but not by the IADPSG criterion. These women were diagnosed by glycemia values higher than 140 mg/dL in the second hour of the OGTT, suggesting a high-risk population as this glycemia value is the threshold to apply treatment.

We also found that women with GDM were diagnosed mostly by the fasting glycemia values using the IADPSG criterion compared to the ALAD criterion. On the other hand, at the second hour of the OGTT, GDM was detected in more patients by the ALAD criterion than by the IADPSG criterion. These results suggest that the increase in the prevalence of GDM established by the IADPSG criterion is mainly caused by an increased number of patients detected by the fasting glycemia values. Indeed, this main detection of GDM patients by fasting glycemia values remained even if the 2h OGTT cutoff values were reduced to those used by the ALAD criterion. Moreover, the relatively limited overlap between the patients diagnosed by IADPSG at fasting, 1 h OGTT and 2 h OGTT considering the cut- off values proposed by the IADPSG and the ALAD criteria suggests different patient populations and a putative different etiology of their GDM, possibly arising through different physiopathological mechanisms. Further studies should be performed to determine whether different treatments should be appropriate to prevent adverse outcomes in these different populations.

Adverse maternal outcomes have been previously associated with GDM diagnosed through different criteria, including IADPSG (Ethridge et al., 2014; Sacks et al., 2015; Trujillo et al., 2015). In this work, together with the analysis of the prevalence of GDM, the maternal and neonatal outcomes were evaluated. Maternal age, BMI and hypertensive disorders were higher in women with GDM diagnosed by either the ALAD or the IADPSG criterion than in women without GDM. When the ALAD diagnostic criterion was applied, there was an increase in the percentage of women with diabetes that presented cesarean section that was not detectable if the IADPSG diagnostic criterion detects a high-risk population. Regarding the neonatal outcomes, there was an increase

in the number of cases with hypoglycemia and macrosomia in patients diagnosed by either the ALAD or IADPSG criterion compared to the patients without GDM. Our results suggest that neither the ALAD nor the IADPSG diagnostic criteria are good predictors of macrosomia, as shown by the low PPV (ALAD criterion: 12.7%, IADPSG criterion: 11.2%) and low sensitivity values (ALAD criterion: 17.3%, IADPSG criterion: 38.7%). These low sensitivity and PPV values of both criteria are limitations to predict macrosomia and warrant further studies and possible inclusion of other parameters needed to increase these values.

Although one limitation of this study was that we were not able to treat GDM patients diagnosed by IADPSG, we had the opportunity to address putative differences in the population of women that were only diagnosed by IADPSG (untreated for GDM during pregnancy) and the group that was diagnosed by ALAD (treated for GDM during pregnancy). Thus, we evaluated macrosomia in three groups according to their fasting glycemia values: below 92 mg/dL, between 92 and 99 mg/dL and over 99 mg/dL. In agreement with the well-known studies addressing fasting glycemia as a risk factor for macrosomia (Group - HAPO et al., 2008; Sesmilo et al., 2017; Zawiejska et al., 2014), we found that the increased fasting glycemia values led to a 2-fold increased risk of prevalence of macrosomia. Interestingly, the similar prevalence of macrosomia in both the group with values of 92-99 mg/dL (untreated patients with GDM diagnosed by IADPSG) and the group with values over 99 mg/dL (patients treated due to GDM diagnosed by ALAD) revealed the difficulties in reducing macrosomia by only targeting glycemia. Indeed, several works have shown increased macrosomia despite treatment of maternal hyperglycemia (Billionnet et al., 2017; Bogdanet et al., 2018).

Maternal obesity/overweight is a known risk factor for GDM in different populations (Egan et al., 2017; Kim et al., 2013). In our population, we found that the prevalence of obesity/overweight was clearly associated with increasing fasting glycemia values. Indeed, obesity/overweight was evidenced in 48% of the patients with GDM diagnosed by ALAD and in 45% of the patients diagnosed by IADPSG, data that illustrate the relevance of obesity/overweight as a risk factor in GDM. Moreover, we observed similar adverse maternal and fetal outcomes in all patients that had macrosomic newborns, and this included mothers without GDM and with GDM diagnosed both through the ALAD and the IADPSG diagnostic criteria. It should be noted that the maternal BMI of patients without GDM was lower than that of patients with GDM (diagnosed by either the ALAD or IADPSG criterion), whereas the maternal BMI of patients without GDM that had macrosomic newborns was similar to that of those with GDM diagnosed by either the ALAD or IADPSG criterion. All this points to obesity/overweight as a possible inducer of macrosomia.

Although applying a universal GDM criterion would be the best way to make international comparisons (Hod et al., 2015), this study showed a huge increase in GDM prevalence associated with the change from the ALAD to the IADPSG diagnostic criterion. This suggests that using the IADPSG criterion may be difficult in underdeveloped/developing countries due to the socioeconomic situation, although cost-effectiveness studies are needed to clarify this point. On the other hand, this study identifies the important contribution of obesity/overweight to negative birth outcomes independent of GDM diagnosis regardless of the criteria used for the diagnosis of GDM. This suggests that women with obesity/overweight should be identified for their proper treatment independently of the GDM criteria used.

Conclusions and recommendations

In Argentina, GDM is a prevalent disease affecting almost 10% of the pregnancies. A further 2.5-fold increase in GDM prevalence is expected if the IADPGS criterion is applied in our population. Whether the treatment of patients diagnosed by the IADPSG and not the ALAD criterion is cost-effective remains to be determined. The patients with GDM diagnosed by ALAD (who received treatment to achieve metabolic control) and by IADPSG (who did not receive treatment except a concurrent ALAD diagnosis) showed similar maternal and fetal outcomes, suggesting that glycemic control may not be enough to prevent all adverse outcomes. Obesity/overweight should be identified and treated due to negative adverse outcomes in pregnancy and to its contribution to the increased GDM prevalence. Indeed, obesity/overweight is associated with increased fasting glucose and increased GDM prevalence diagnosed by ALAD and, more markedly, by IADPSG. Strategies that include lifestyle education and nutritional advice prior to pregnancy are encouraged as they are likely to reduce the incidence of both GDM and macrosomia.

Disclosure statement

The authors declare that they have no competing interests.

Supporting Information

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Funding

This study was supported, in part, by grants from the Argentine Society of Diabetes (SAD022-2012).

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