Gestational Diabetes Mellitus: Is There an Advantage in Using the Current Diagnostic Criteria?

Diabetes Gestacional: Serão os Atuais Critérios de Diagnóstico Mais Vantajosos?

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ABSTRACT

Introduction: There is no international consensus regarding gestational diabetes mellitus diagnostic criteria. In Portugal, the Carpenter and Coustan criteria were replaced by an adaptation of the International Association of Diabetes and Pregnancy Study Groups criteria. Our aim was to compare the incidence and outcomes of pregnancies complicated by gestational diabetes mellitus according to the current and previous criteria.

Material and Methods: Retrospective analysis of 1218 singleton pregnancies complicated with gestational diabetes mellitus, with surveillance/delivery between 2008-2015. Two groups were considered: identification according to the Directorate-General of Health criteria - International Association of Diabetes and Pregnancy Study Groups (group 1); identification through Carpenter and Coustan criteria (group 2). A comparative analysis was performed.

Results: The incidence of gestational diabetes mellitus doubled (9.4% *vs* 4.6%), and the number of consultations/year increased (~3000 *vs* ~2000). In Group 1, in comparison with group 2, there was a lower risk of macrosomia in newborns [RR 0.44 (IC (95%):0.26 - 0.76)] and a higher risk of small for gestational age infants [RR 1.99 (IC (95%):1.19 - 3.31)]; a 6 - fold and 4 fold higher risk in neonatal hypoglycemia [RR 6.30 (IC (95%): 3.39 - 11.71)] and hyperbilirubinemia [RR 3.89 (IC (95%): 2.25 - 6.72)] were also observed, respectively. There were no differences regarding other outcomes.

Discussion: Outcomes related to the decrease in macrosomia did now show any improvement, with even an increase in Small for Gestational Age and neonatal complications. Given the increased incidence of gestational diabetes mellitus, Directorate-General of Health – International Association of Diabetes and Pregnancy Study Groups criteria may be associated with greater healthcare-related costs due to more frequent consultations, with no apparent obstetrical/neonatal benefit.

Conclusion: The Directorate-General of Health – International Association of Diabetes and Pregnancy Study Groups criteria were associated with a decrease in macrosomia, not accompanied by an improvement of obstetrical/perinatal outcomes. The benefit of using these criteria is open to debate.

Keywords: Diabetes, Gestational/diagnosis; Diabetes, Gestational/epidemiology; Portugal

RESUMO

Introdução: Não existe consenso internacional quanto aos critérios de diagnóstico da diabetes gestacional. Em Portugal, os critérios de Carpenter e Coustan foram substituídos por uma adaptação dos critérios da *International Association of Diabetes and Pregnancy Study Groups*. O objetivo deste estudo foi comparar a incidência e *outcomes* obstétricos/perinatais das grávidas com diabetes gestacional segundo os critérios atuais e prévios.

Material e Métodos: Estudo retrospetivo de 1218 gestações únicas complicadas com diabetes gestacional cuja vigilância/parto ocorreu entre 2008-2015. Consideraram-se dois grupos: diagnóstico pelos critérios da Direção Geral da Saúde – *International Association of Diabetes and Pregnancy Study Groups* (grupo 1); diagnóstico segundo Carpenter e Coustan (grupo 2), tendo sido feita análise estatística comparativa.

Resultados: A incidência da diabetes gestacional duplicou (9,4% *vs* 4,6%) e o número de consultas/ano aumentou consideravelmente (~ 3 000 *vs* ~ 2 000). No grupo 1 verificou-se um risco inferior de recém-nascidos macrossómicos em relação ao grupo 2 [RR 0,44 (IC (95%): 0,26 – 0,76)], e um risco mais elevado de recém-nascidos leves para a idade gestacional (LIG) [RR 1,99 (IC (95%):1,19 – 3,31)]; um risco cerca de seis e quatro vezes superior de hipoglicémia [RR 6,30 (IC (95%): 3,39 – 11,71)] e hiperbilirrubinémia [RR 3,89 (IC (95%): 2,25 – 6,72)] neonatais, respetivamente. Não houve diferenças em relação a outros *outcomes*.

Discussão: A redução dos recém-nascidos macrossómicos não resultou em melhoria dos *outcomes*, havendo um aumento dos recém-nascidos leves para a idade gestacional bem como de complicações neonatais. Os critérios atuais poderão associar-se a maiores gastos em saúde, devido ao aumento considerável da incidência de diabetes gestacional e maior vigilância em consultas, sem benefícios obstétricos/perinatais.

Conclusão: A aplicação dos critérios da Direção Geral da Saúde – *International Association of Diabetes and Pregnancy Study Groups* associou-se a redução da macrossomia, não acompanhada de uma melhoria dos *outcomes*. É discutível o benefício destes critérios em relação aos anteriormente preconizados.

Palavras-chave: Diabetes Gestacional/diagnóstico; Diabetes Gestacional/epidemiologia; Portugal

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INTRODUCTION

Gestational diabetes mellitus (GDM) has been defined as carbohydrate intolerance first detected in pregnancy and leading to varying degrees of maternal hyperglycaemia, which has been associated with different obstetric and perinatal outcomes, particularly foetal macrosomia, traumatic delivery and hypertension.[1] These may be prevented through non-pharmacological (lifestyle changes, including diet and physical activity) and pharmacological approaches (insulin and/or oral antidiabetic drugs).[2]

An adequate identification of which pregnant mothers would benefit from these strategies is the main challenge. Different GDM screening and diagnostic criteria have been developed and those by O'Sullivan and Mahan (1964) were the first to be used, based on the risk for the development of diabetes following pregnancy, including an oral glucose tolerance test (OGTT).[3] These were updated by Carpenter and Coustan[4] in 1982 and intermediate cut-off values between O'Sullivan and Mahan criteria and those developed by the *National Diabetes Data Group* (NDDG) were established. These were widely used in the United States of America (USA) as well as in some European countries including Portugal until early 2011[5] and consisted of a two-step approach with a 50-g glucose challenge test (GCT) followed by a 100-g OGTT in the presence of a positive GCT. Blood samples were taken and blood glucose levels were measured at fasting and 1 h, 2 h and 3 h following a glucose overloading. At the same time, a one-step approach with fasting (≥126 mg/dL) and 2-h (≥ 140 mg/dL) plasma glucose following a 75 g oral glucose load has been recommended by the World Health Organization (WHO) (1999).[6]

New criteria for the diagnosis and classification of pregnancy-related hyperglycaemia were recommended in 2010 by the International Association of Diabetes and Pregnancy Study Groups – IADPSG,[7] based on the conclusions of a large multi-centric study (Hyperglycemia and Adverse Pregnancy Outcome – HAPO study)[8] and showing the presence of a linear relationship between maternal blood glucose and maternal and perinatal outcomes.

In Portugal, the use of the IADPSG diagnostic criteria was recommended by the Consensus on Diabetes and Pregnancy (*Consenso sobre Diabetes e Gravidez*)[9] and subsequent updates,[10,11] on which the Standardisation Newsletter (*Circular Normativa*) that was issued by the General Directorate of Health (*Direcção-Geral da Saúde [DGS]*) in Jan 2011 was based.[12] GDM may be diagnosed within the first trimester of pregnancy as the presence of fasting blood glucose ≥ 92 mg/dL [and <126 mg/dL] in the first antenatal medical visit. A re-assessment OGTT carried out between 24 and 48 gestational weeks is recommended in pregnant mothers with blood glucose < 92 mg/dL, according to the criteria shown in Table 1.

The IADPSG criteria were adopted by other international medical societies and organisations such as the American Diabetes Association – ADA),[13] the International Federation of Gynecology and Obstetrics – IFGO),[14] the International Diabetes Federation – IDF)[15] and the WHO.[1] However, based on cost-effectiveness, other recognised Societies have adopted different GDM screening and diagnostic strategies, such as the American College of Obstetricians and Gynecology – ACOG[16] and the National Institute for Health and Care Excellence – NICE.[17] No evidence was found by the Spanish Group of Diabetes and Pregnancy (GEDE)[18] as to change their diagnostic criteria, which includes a two-step strategy based on studies in the Spanish population.

There are no randomised studies in the Portuguese population on the comparison of obstetric and perinatal outcomes between patients with GDM diagnosed according to the different criteria. The new criteria (DGS – IADPSG) were associated with a decline in the number of large for gestational age (LGA) infants, according to the retrospective study by Massa *et al.*[19]

This study aimed at the evaluation and comparison of GDM incidence, clinical activity of the department and obstetric and perinatal outcomes between pregnant mothers diagnosed with GDM according to the Carpenter and Coustan *vs.* DGS – IADPSG criteria.

MATERIAL AND METHODS

Study design

This was a retrospective study of the clinical information regarding all singleton births from pregnant mothers diagnosed with GDM attending a tertiary healthcare centre, who had delivered at the same institution throughout 2008-2015. Due to the presence of a relevant amount of incomplete clinical records, all 2013 data were excluded from the study in order to prevent from an information bias and therefore our final sample regarded a seven-year period.

Study groups

Pregnant mothers were diagnosed with GDM between

Table 1 – GDM diagnostic criteria according to Carpenter and Coustan and to DGS – IADPSG

	Carpenter e Coustan ‖	DGS – IADPSG ¶
Hours upon glucose overload*	Blood glucose, mg/dL (mmol/L)	
0	95 (5.3)	92 (5.1)
1	180 (10.0)	180 (10.0)
2	155 (8.6)	153 (8.5)
3	140 (7.8)	

* Ingestion of a solution with 100g of glucose in 400cc water and assessment according to Carpenter and Coustan criteria or ingestion of a 75g glucose solution in 250 - 300 cc water and assessment according to DGS-IADPSG criteria. ‖ Positive test when ≥ 2 values are met or exceeded. ¶ Positive test when ≥ 1 value is met or exceeded

2008 and 2011 by following a two-step procedure: 50-g GCT carried out between week 24 and 28 (or within the first trimester in mothers at increased risk of developing GDM, as well as within week 32 in pregnant mothers with negative GCT up to that moment); patients with blood glucose ≥140 mg/dL at 1 hour following a glucose overloading were subsequently submitted to a 100-g OGTT and were diagnosed with GDM according to Carpenter and Coustan criteria, as described in Table 1.

From 2011 onwards, pregnant mothers were diagnosed with GDM according to the updated DGS – IADPSG criteria: presence of blood glucose level ≥ 92 mg/dL in any moment of pregnancy or presence of a positive 75-g OGTT carried out between week 24 and 28, as described in Table 1.

Data were therefore analysed considering two groups:

- Group 1 with pregnant mothers diagnosed according to the more recent criteria (DGS – IADPSG);
- Group 2 with those diagnosed according to the Carpenter and Coustan (CC) criteria.

GDM follow-up and therapy

Pregnant mothers with GDM attended a specialist outpatient clinic with a multidisciplinary team involving obstetricians, endocrinologists (Endocrinology and Metabolic Medicine), nutritionists and nurses. Mostly pregnant mothers with GDM are referred to this clinic, even though pregnant mothers with type-1 and type-2 diabetes, together with other endocrine disorders, mainly thyroid diseases, also attend the clinic.

Optimal metabolic control was established with blood glucose levels of 60-90 mg/dL and 100-120 mg/dL at 1 hour following a glucose overloading. Insulin therapy was started in patients in whom these targets were not reached through diet and physical exercise within one to two weeks. The same therapeutic approach has been followed throughout the whole study period, even when diagnostic criteria were changed.

Metabolic, obstetric and perinatal outcomes

Initially, the incidence of GDM [(annual number of new cases) / (total annual number of childbirths)] and the number of initial and subsequent examinations at the Obstetrics/Endocrinology unit in each group were analysed. The impact of the most recent DGM criteria on the number of consultations may have been estimated by some margin, as considered by the authors, assuming that patient referral by other pathologies has remained unchanged over the years.

Our group of pregnant mothers was subsequently characterised as regards age, parity, pre-pregnancy body mass index (BMI), first-trimester glycated haemoglobin (HbA1c) level, medical history and first GDM recognition during pregnancy (first or second / third trimester).

Metabolic outcomes were assessed through (i) the need for insulin therapy, (ii) gestational age at which it was started, (iii) weight gain throughout pregnancy and (iv) first-trimester HbA1c levels. Weight gain during pregnancy was rated as optimal, suboptimal or excessive according to the recommendations of the Diabetes and Pregnancy Consensus (*Consenso de Diabetes e Gravidez*).[9]

Obstetric and perinatal outcomes were assessed through (i) caesarean section rate (all causes), (ii) preterm delivery, (iii) assisted delivery, (iv) hypertensive disorders of pregnancy, (v) birth weight and weight classification, (vi) 1 and 5 minute Apgar score, (vii) intrapartum-related complications (shoulder dystocia, clavicle fracture, brachial plexus injury), (ix) need for admission to a neonatal intensive care unit - NICU, (x) neonatal morbidity (neonatal respiratory distress syndrome, hypoglycaemia and hyperbilirubinaemia requiring phototherapy), (xi) major birth defects (defined as those producing significant external or functional anomalies, those requiring surgery or any life-threatening defect) and (xii) postpartum OGTT (75-g OGTT followed by fasting and 2-h blood glucose determination). Small for gestational age (SGA) and large for gestational age (LGA) infants were defined as those with birth weight below the tenth and greater than the 90th percentile, respectively. Macrosomia was defined as birth weight ≥ 4,000 g in a term infant.

Statistical analysis

Group 1 and 2 were compared through Student's t-test and chi-square test / Fisher's exact test for continuous and categorical variables, respectively. The association between categorical variables was assessed through odds ratio (OD) and relative risk (RR) calculation.

Data regarding birth weight classification led to a subsequent analysis aimed at the identification of predictors of SGA and LGA infants. A multivariate analysis based on univariate analysis was carried out in order to identify independent parameters related to the presence of SGA and LGA infants. Adjusted OR were calculated through logistic regression models.

The statistical analysis was carried out using IBM SPSS Statistics® version 20.0 software and a p-value < 0.05 was considered as statistically significant.

RESULTS

A slightly increased GDM incidence rate has been found between 2008 and 2010 and greatly increased over the subsequent years, when the DGS – IADPSG criteria were applied (Fig. 1). A 9.4% incidence rate has been found in 2015, around the double of the rate found in 2008 (4.6%). Similarly, a slightly increased total number of consultations has been found between 2008 and 2010 and greatly increased from 2011 onwards, when the current GDM diagnostic criteria were applied. A similar number of initial medical visits has remained throughout two years upon the application of the current criteria and a slightly increasing trend was found in 2014 and 2015 (Fig. 1).

A total of 660 (54.2%) and 558 (45.8%) from a total of 1,218 pregnant mothers were diagnosed with GDM according to the DGS – IADPSG criteria (group 1 pregnant mothers) and to the Carpenter and Coustan criteria (group 2), respectively. Diagnosis was established within the first

trimester in 45.2% of the pregnant mothers in group 1 and in 3.6% in group 2 ($p < 0.0001$) (Table 2).

Both groups were similar, except regarding GDM personal history, which was more prevalent in group-2 pregnant mothers and regarding the fact that more underweight pregnant mothers were found in group 1.

The comparison of metabolic outcomes is shown in Table 3. On average, a 1.4 kg lower weight gain has been found in group 1 pregnant mothers when compared to group 2 ($p < 0.0001$). Different weight gain percentages based on pre-pregnancy BMI were found in both groups ($p < 0.0001$). A slightly higher percentage of pregnant mothers with an optimal weight gain based on pre-pregnancy BMI was found in group 2 (37.8% *vs.* 30.1%). Suboptimal weight gain has been found in around half of the pregnant mothers in group 1 (50.5%) while an excessive weight gain has been found in 27.8% of patients in group 2. On average, 0.3% lower third-trimester HbA1c levels have been found in group 1 ($p < 0.0001$). Significantly higher and earlier need for insulin therapy was found in group 1 *vs.* group 2 patients.

Data regarding the comparison of obstetric and perinatal outcomes are shown in Table 4. Lower macrosomic (3.0% *vs.* 6.8%, $p = 0.002$) and LGA infant (10.0% *vs.* 18.5% $p < 0.0001$) rate was found in group 1 patients. Half the risk of delivering a macrosomic infant was found in group 1 pregnant mothers when compared to group 2 [RR 0.44 (95% CI: 0.26 – 0.76)]. Conversely, double the risk of delivering a SGA infant was found in group 1 patients [RR 1.99 (95% CI: 1.19 – 3.31)] when compared to group 2. Higher rate of neonatal complications has been found in group 1 patients, with a six times greater risk of neonatal hypoglycaemia [RR 6.30 (95% CI: 3.39 – 11.71)] and four times greater risk of presenting with hyperbilirubinaemia [RR 6.30 (95% CI: 3.39b – 11.70)]. A lower C-section rate was found in group 1 patients (31.1% *vs.* 37.5%, $p = 0.019$) when compared to group 2 and this difference was related to "failed induction", with no differences between both groups regarding the rate of C-section related to suspected foetal macrosomia and cephalopelvic disproportion. No significant differences were found between both groups as regards hypertensive disorders of pregnancy, preterm and assisted delivery, intrapartum delivery complications, birth defects, number of admissions to NICU and 1 and 5 minute Apgar score.

Very similar percentage of patients in both groups were diagnosed through post-partum OGTT with diabetes mellitus (DM) (0.4% *vs.* 0.6%), impaired fasting glucose (0.9% *vs.* 0.6%) and impaired glucose tolerance (3.9% *vs.* 3.4%) and 94.8% and 95.3% of the pregnant mothers were diagnosed with GDM in group 1 and 2, respectively.

The study of predictors of SGA and LGA birth were based on birth weight data. A univariate analysis was initially carried out, with the comparison of means and the study of associations between the incidence of SGA and LGA birth and the following variables: maternal age, pre-pregnancy BMI, obesity, weight gain during pregnancy, chronic

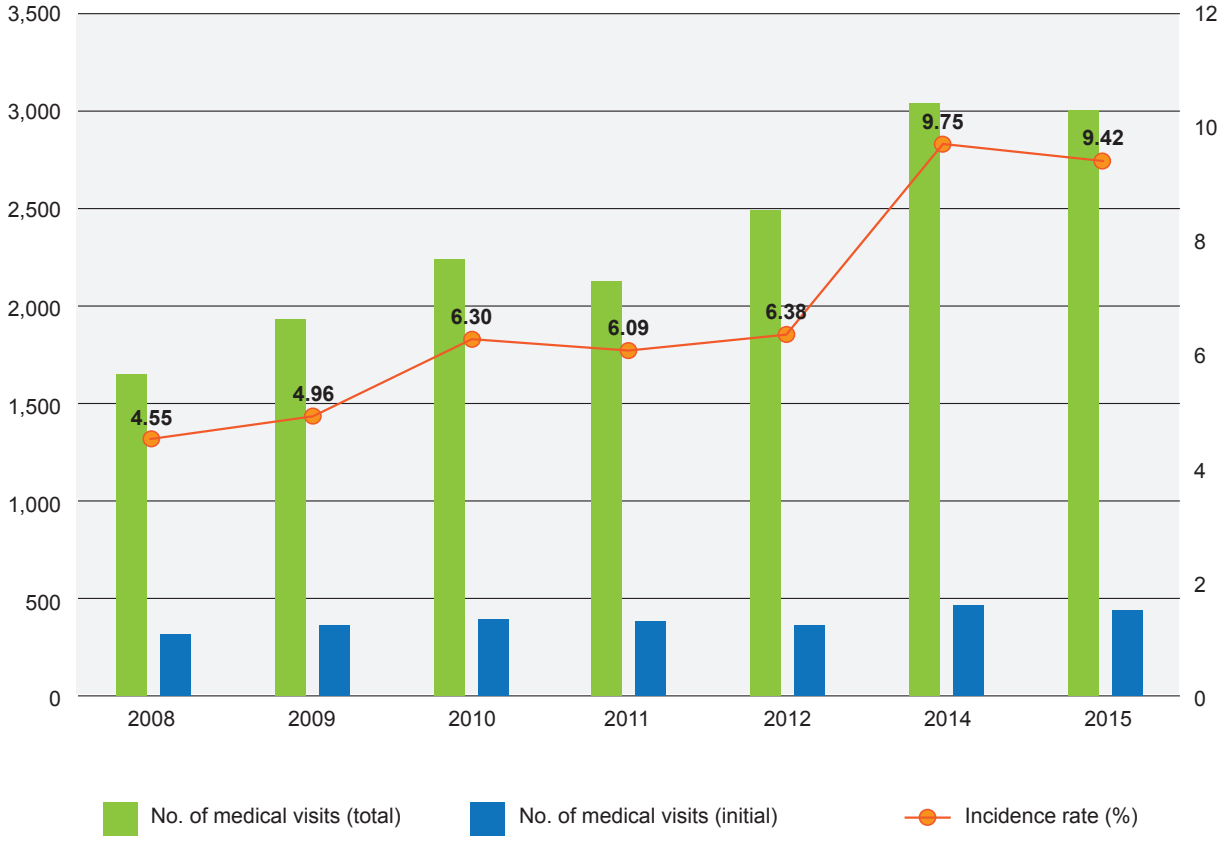

Figure 1 – DGM incidence and no. of medical visits (Obstetrics / Endocrinology outpatient unit)

Table 2 – Clinical characteristics of pregnant mothers diagnosed with GDM according to different criteria

	Group 1 DGS – IADPSG n = 660	Group 2 CC n = 558	
	Mean ± SD or frequency (%)		*p*
Age	33.0 ± 4.9	33.0 ± 4.7	0.877
Pre-pregnancy BMI	26.1 ± 5.3	26.5 ± 5.3	0.149
Classification according to pre-pregnancy BMI ‖			
Low weight	2.0*	0.6*	0.147
Normal weight	47.8	45.5	
Overweight	29.4	31.4	
Obesity	20.8	22.5	
Primiparous	38.0	38.4	0.909
Chronic hypertension	4.2	4.1	0.917
GDM personal history	17.0	25.4	0.010*
GDM family history	45.1	50.2	0.079
Diagnosed in the first trimester	45.2	3.6	< 0.0001*
First-trimester HbA1c level	5.2 ± 0.3	5.4 ± 0.5	0.252

* Significant differences for a 0.05 significance level. ‖ Low weight (BMI < 18.5 kg/m²); normal weight (18.5 kg/m² ≤ BMI < 25.0 kg/m²); overweight (25.0 kg/m² ≤ BMI < 30.0 kg/m²); obesity (BMI ≥ 30.0 kg/m²).
SD: standard deviation; BMI: body mass index; GDM: gestational diabetes mellitus; DM: diabetes mellitus; HbA1c: glycated haemoglobin

hypertension, first and third-trimester HbA1c levels, OGTT with fasting, 1-h and 2-h post-load blood glucose determination and need for insulin therapy (data not shown). Predictors of SGA and LGA birth were subsequently identified and adjusted OR were calculated.

Obesity, pregnancy weight gain and third-trimester HbA1c level were independent predictors of LGA birth and obesity was associated with 3.2 times higher incidence of delivering a SGA infant. A higher incidence of SGA birth was found in older mothers and with lower weight gain during pregnancy and a 3.8 times higher risk per each less unit in third-trimester HbA1c level has been found.

DISCUSSION

The application of the DGS – IADPSG criteria in our institution led to a double incidence of GDM (4.6% *vs.* 9.4%), in line with has been anticipated by other authors[7,20] and found in experimental[21,22] and observational studies.[19,23] A world incidence of GDM between 1 and 14% has been found,[22] which is very variable due to the lack of an international consensus regarding GDM diagnostic criteria. The increasing incidence that was found in our study was mainly due to the fact that patients were mainly diagnosed within the first trimester, which was less frequent when the previous criteria were used (45.2% *vs.* 3.6%), in line with what has been found in the study by Massa *et al.* (30.8% *vs.* 1.8%), which was also carried out in a Portuguese maternity.

First-trimester fasting blood glucose determination was aimed at the identification of previously undiagnosed pregnant mothers with GDM, due to the globally increased prevalence of obesity and DM in the young population. Therefore, a universal screening or limited only to at-risk mothers was discussed by an expert panel at the IADPSG[7] in which

Table 3 – Comparison of metabolic outcomes between each group

	Group 1 DGS – IADPSG n = 660	Group 2 CC n = 558	
	Mean ± SD or Frequency (%)		*p*
Weight gain during pregnancy (kg)	9.0 ± 6.2	10.4 ± 5.2	< 0.0001*
Weight gain classification			
Optimal	30.1	37.8	< 0.0001*
Suboptimal	50.5	34.4	
Excessive	18.4	27.8	
Third-trimester HbA1c level (%)	5.3 ± 0.5	5.6 ± 0.7	< 0.0001*
GA at which insulin therapy was started	25.7 ± 8.2	31.8 ± 5.4	< 0.0001*
Need for insulin therapy	54.9	35.9	< 0.0001*

* Significant differences for 0.05 significance level
SD: standard deviation; GA: gestational age; HbA1c: glycated haemoglobin

Table 4 – Comparison of obstetric and perinatal outcomes between each group

	Group 1 DGS – IADPSG n = 660	Group 2 CC n = 558		
	Frequency (%)		*p*	RR (95% CI)
Macrosomia	20 (3.0)	38 (6.8)	0.002*	0.44 (0.26 – 0.76)
LGA birth	66 (10.0)	103 (18.5)	< 0.0001*	0.54 (0.41 – 0.72)
SGA birth	47 (7.1)	20 (3.6)	0.007*	1.99 (1.19 – 3.31)
Delivery complications ¶	8 (1.2)	12 (2.2)	0.199	0.56 (0.23 – 1.37)
Assisted delivery	149 (22.6)	130 (23.3)	0.763	0.97 (0.79 – 1.19)
C-section	205 (31.1)	209 (37.5)	0.019*	0.83 (0.71 – 0.97)
Suspected macrosomia	20 (9.8)	25 (12.0)		
NRFS	48 (23.4)	62 (29.7)		
FTL/FPD	46 (22.4)	42 (20.1)		
Pelvic presentation	31 (15.1)	38 (18.2)	0.128	
Maternal indication	17 (8.3)	11 (5.3)		
Failed induction	20 (9.8)*	8 (3.8)*		
Other reasons	19 (9.3)	16 (7.7)		
Neonatal hypoglycaemia	82 (12.4)	11 (2.0)	< 0.0001*	6.30 (3.39 – 11.71)
Hypertensive disorders of pregnancy	15 (2.3)	8 (1.4)	0.284	1.58 (0.68 – 3.71)
Preterm delivery	47 (7.1)	44 (7.9)	0.613	0.90 (0.61 – 1.34)
Neonatal RDS	18 (2.7)	10 (1.8)	0.278	1.52 (0.71 – 3.27)
Neonatal hyperbilirubinaemia	69 (10.5)	15 (2.7)	< 0.0001*	3.89 (2.25 – 6.72)
Admissions to NICU	35 (5.4)	19 (3.4)	0.101	1.57 (0.91 – 2.72)
1-min Apgar score < 7	40 (6.1)	37 (6.7)	0.687	0.92 (0.59 – 1.41)
5-min Apgar score < 7	1 (0.2)	4 (0.7)	0.124	0.21 (0.02 – 1.89)
Major birth defect ‼	27 (5.1)	18 (3.7)	0.284	1.37 (0.77 – 2.46)

* Significant differences for a 0.05 level of significance. ¶ Shoulder dystocia, clavicle fracture, brachial plexus injury. ‼ Significant functional disorder involved.
SD: standard deviation; LGA: large for gestational age; SGA: short for gestational age; NRFS: non-reassuring foetal status; FTL/FPD: failure trial of labour /foeto-pelvic disproportion; RDS: respiratory distress syndrome; NICU: Neonatal intensive care unit; RR: relative risk

the relevance of knowing the specific prevalence of DM in the young population was recognised. Nevertheless, not enough evidence was found by the panel of experts as to recommend a GDM diagnosis and treatment before the 24-28 weeks of pregnancy. Fasting blood glucose screening at the initial antenatal medical visit aimed at GDM identification and treatment is not the recommended procedure by different recognised Societies[13,16,17] and even contradicting the ADA declaration[13] under which GDM is defined as diabetes mellitus that was diagnosed at the second and third trimester of pregnancy, in addition to the definition of the physio-pathological mechanism of GDM as possibly related to a non-physiological increase in insulin resistance, usually starting at the 20-24 weeks. The cause remains unclear and insulin resistance may be explained by the fetoplacental unit, namely regarding an elevated human placental lactogen found in the second half of pregnancy or due to the maternal adipose tissue, as certain adiponectin are known to have an effect on the sensitivity to insulin.[24]

In our study, in line with what has been found by Massa *et al.*,[19] a reduced number of pregnant mothers have been diagnosed with GDM through postpartum OGTT, with no

Table 5 – Independent predictors of large (LGA) and small for gestational age (SGA) birth

	Adjusted OR (95% CI)			
	LGA*	*p*	SGA**	*p*
Obesity	3.209 (1.782 – 5.780)	< 0.0001	-	
Weight gain during pregnancy (kg)	1.061 (1.011 – 1.113)	0.016	0.908 (0.826 – 0.998)	0.046
Third-trimester HbA1c level (%)	2.525 (1.322 – 4.823)	0.005	0.261 (0.083 – 0.823)	0.022
Age (years)	-		1.146 (1.033 – 1.270)	0.010

* Adjusted OR for the following co-variables: fasting, 1-h and 2-h OGTT, obesity, weight gain during pregnancy, third-trimester HbA1c level and insulin therapy. ** Adjusted OR for the following co-variables: maternal age, pre-pregnancy BMI class, weight gain during pregnancy and third-trimester HbA1c level.
OR: odds ratio; CI: confidence interval

differences between both criteria (0.4% *vs.* 0.6%). In Portugal, a 1.5% prevalence of DM in young women (20-39) has been found in 2015.[25] Therefore, due to the reduced prevalence of the disease, a selective fasting blood glucose screening only in women at risk at the initial antenatal medical visit should be considered in order to search for the presence of previous diabetes. This selective screening approach based on risk factors was also studied for GDM diagnosis between 24 and 28 weeks of pregnancy by Miailhe, *et al*. Even though one sixth of the patients with GDM remained undiagnosed, these would regard pregnant mothers with slightly elevated blood glucose levels and not associated with complications, according to these authors.

Different authors have found an optimal cost-effectiveness with the implementation of the IADPSG criteria, based on the analysis of health expenditure.[23,26] However, in a revision carried out by the NICE[17] and including five studies, the authors have found that the potential benefits of the introduction of the IADPSG criteria would only be reached at the expense of an unacceptable increased cost. In addition, according to a recent Cochrane Collaboration revision,[21] no comprehensive studies involving the comparison in terms of health expenditure between the applications of different GDM diagnostic approaches have been carried out up to now. Cost-effectiveness of the use of DGS – IADPSG criteria *vs.* previous criteria was not the aim of this study. Nevertheless, a significantly increased number of follow-up medical visits with these pregnant mothers has been found (~3,000 *vs.* ~2,000), as well as an increasing need for insulin therapy (54.9 % *vs.* 35.9%), which was not followed by any improvement in neonatal outcomes (number of admissions to the NICU, birth defects) and even by an increasing number of some complications (hypoglycaemia and hyperbilirubinemia). A reduction in global C-section rate has also been found, even though this conclusion could not be related to the use of different criteria, as no differences regarding the number of C-section procedures due to suspected foetal macrosomia and cephalopelvic disproportion have been found.

A 50% reduction in macrosomic and LGA births, which was one of the major outcomes of GDM diagnosis and treatment, was achieved in our study with the application of the DGS – IADPSG criteria. In addition, higher metabolic control has been found, with lower third-trimester HbA1c levels, lower weight gain and more frequent and earlier insulin use, which may explain for the outcomes. However, at the same time, a doubling of the number of SGA infants has been found when compared to the use of the previous diagnostic criteria. The independent predictive factors of LGA and SGA infants, adjusted to confounding factors, were analysed in order to clarify these outcomes.

Regardless of the fasting, 1-h and 2-h OGTT values, obesity was a predictor of LGA birth, in line with different other studies.[24,27,28] A 3.2 times higher LGA incidence has been found in obese pregnant mothers. First-trimester HbA1c levels and weight gain during pregnancy were also associated with LGA infants, even though with lower OR values. According to the physiopathological model based on the modified Pedersen hypothesis, higher foetal growth is a consequence of maternal hypoglycaemia related to foetal hyperinsulinaemia.[24] However, foetal macrosomia also happens in the presence of an optimal metabolic control[29] and most of the cases of LGA infants have occurred within normal blood glucose categories in the HAPO study,[30] which is probably explained by the presence of high levels of triglycerides, according to the study by Son *et al*,[31] in which hypertriglyceridemia was found to be an independent predictor of LGA birth.

Despite these considerations, the reduction in the number of LGA and macrosomic infants in our study seems to have been related to blood glucose control, considering that a similar percentage of obese or overweight pregnant mothers have been found in both groups. In addition, the increase in the number of SGA infants may have been related to the reduction in blood glucose levels, with a 3.8 times higher incidence per each less unit in third-trimester HbA1c level. Maternal age and weight gain during pregnancy have also been predictors of SGA birth, in line with other studies.[32,33] It is worth mentioning that less than recommended weight gain has been found in half of the pregnant mothers in group 1 (DGS – IADPSG criteria). Variables in multivariate analysis were not adjusted to patient's smoking habit and, considering that this is an important risk factor of SGA birth, this is a limitation.[33]

An improvement in obstetric and perinatal outcomes (particularly the reduction in C-section and assisted delivery rate, in delivery complications (shoulder dystocia, clavicle fracture, brachial plexus injury) and in neonatal hypoglycaemia and hyperbilirubinemia, as well as in the number of admissions to NICU would be expected in association with the reduction in macrosomic and LGA infants in group 1 (pregnant mothers diagnosed according to the DGS – IADPSG criteria).

The reduction in global C-section rate (due to all causes) that was found in our study may not be directly assigned to the reduction in macrosomic infants, considering the analysis of the indications for C-section (no differences were found regarding the C-section rate due to suspected foetal macrosomia and cephalopelvic disproportion). Therefore, in contrast to what would be expected, no outcome improvement and even an increased number of neonatal complications have been found, with a six times higher risk of hypoglycaemia and four times higher risk of hyperbilirubinemia. These outcomes are also in contradiction to what would be expected. Hypoglycaemia may also have been be explained by an SGA-related acquired hyperinsulinism.[34] Hyperbilirubinemia may relate to the polycythaemia secondary to an increased erythropoiesis, also associated with SGA births.[35]

Apart from the outcomes that were described, DGS – IADPSG criteria were not associated with a reduction in preterm delivery, assisted delivery, hypertensive disorders of pregnancy and birth defects.

Despite the recommendations by the working group of

the IADPSG, supported by the results of the HAPO study, there is still no international consensus regarding GDM screening and diagnosis. Some issues related to clinical guidelines that derived from this large multicentric prospective study were acknowledged: 1) this was an observational study and the benefit of treating moderate hyperglycaemia has not been analysed;[17] 2) there is a linear association between the adverse outcomes and maternal glycaemia and therefore any cut-off used for the diagnosis of GDM is arbitrary, which has been defined by a group of experts as a 1.75 times higher risk of adverse perinatal outcomes[36, 37]; 3) blood glucose and maternal BMI have both contributed to the risk of delivering LGA infants, even though with a greater impact of maternal BMI on all blood glucose categories, except the highest.[30]

There are two randomised clinical trials currently ongoing[38,39] aimed at the comparison of obstetric outcomes between patients diagnosed with GDM through a one-step (as recommended by the IADPSG) *vs.* two-step approach. These trials will bring some light on the way GDM should be diagnosed in order to reach better foetomaternal outcomes.

Therefore, the doubts described by Fagulha 15 year's ago[40] still stands: which is the best approach for the identification of pregnant mothers at risk for maternal and perinatal morbidity? Which is the optimal blood glucose level for the institution of diet and/or insulin therapy?

The limitations of any retrospective study are no exception in our study, apart from the fact that this is a unicentric study. Cost-effectiveness analysis would be relevant in order to study the impact on health resources of the more recent GDM diagnosis criteria. The use of 60 – 90 mg/dL and 100 - 120 mg/dL targets of fasting and 1-h postprandial glucose, respectively, may have had an influence on some of the outcomes (namely on the differences regarding pregnancy weight gain, third-trimester HbA1c level, need and gestational age at which insulin therapy is started, increased SGA births, neonatal hypoglycaemia and hyperbilirubinemia), as a restrictive glycaemic control has been required in a subgroup of pregnant mothers with milder hyperglycaemia. Fasting blood glucose levels ≤ 95 mg/dL and postprandial ≤ 140 mg/dL are currently included in the Portuguese National Consensus (*Consenso Nacional)*[11] recommendations.

Despite these limitations, our study was based on the comparison within a significant number of patients (around 600 in each group), corresponding to all the patients diagnosed with GDM who were followed up and had delivered at our institution, a tertiary maternity, complying with uniform diagnostic and therapeutic criteria. The fact that blood glucose targets have remained unchanged upon the institution of new criteria has allowed for a direct comparison of the clinical outcomes regarding the different diagnostic approaches.

CONCLUSION

According to our study, the identification and treatment of pregnant mothers with moderately elevated blood glucose were associated with a reduction in macrosomic and LGA births. However, this decline was not associated with an improvement in obstetric and perinatal outcomes and was even associated with an increase in SGA births and neonatal complications. Therefore, a controversial benefit from the application of DGS-IADPSG criteria has been found when compared to those previously applied. Further randomised prospective studies with a cost-effectiveness analysis on this subject in the Portuguese population are required.

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HUMAN AND ANIMAL PROTECTION

The authors declare that the followed procedures were according to regulations established by the Ethics and Clinical Research Committee of the ARS LVT (reference 9136/CES/2016) and according to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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