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Full length article

Performance of glycated hemoglobin A1c for the diagnosis of gestational diabetes mellitus during the SARS-CoV-2 pandemic in Belgium (2020–2021)

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ABSTRACT

Objectives: During the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, health care access was restricted. To reduce the risk of maternal SARS-CoV-2 infection, simplified screening recommendations for gestational diabetes mellitus (GDM) have been suggested, leading to glycated hemoglobin A1c (HbA1c) being proposed as an alternative to the oral glucose tolerance test (OGTT). This study aimed to assess the optimal HbA1c cutoff to confirm GDM diagnosis according to IADPSG/WHO2013 guidelines.

Methods: In this retrospective study, 3361 pregnancies were followed at the hospital of Mouscron and the Cliniques Universitaires St Luc in Brussels (2020–2021). GDM was universally screened in the third trimester of gestation. The ROC curve was used to evaluate the diagnostic performance of HbA1c with OGTT as the reference. Sensitivity, specificity and likelihood ratios for different HbA1c thresholds were calculated.

Results: In total, 312 women were selected due to HbA1c analysis in addition to OGTT, and 149 had GDM. The area under the ROC curve for GDM detection by HbA1c was 0.73 (95% CI 0.68–0.79, $p < 0.0001$). The cutoff value chosen as a possible threshold was HbA1c 5.5% (37 mmol/mol). The sensitivity, specificity, positive and negative likelihood ratios for this cutoff were 12.0%, 99.4%, 20 and 0.88, respectively. The Fagan nomogram test showed a posttest GDM probability of approximately 70%, corresponding to a 10-fold higher pretest probability. An HbA1c $\geq$ 5.5% (37 mmol/mol) would have avoided OGTT in 18% of women with GDM. These women with an HbA1c $\geq$ 5.5% had significantly higher rates of family history of diabetes, older age, higher BMI and higher blood glucose levels (fasting, 1 h and 2 h) at OGTT.

Conclusion: Our results are consistent with the literature concerning the diagnostic ability of GDM through HbA1c $\geq$ 5.5%.

Introduction

Gestational diabetes mellitus (GDM) is the most common metabolic disease encountered in pregnancy. It is associated with preeclampsia, increased rates of cesarean sections and macrosomia [1]. Screening and treatment of GDM reduces these risks for mothers and newborns [2]. From 2020 to 2021, during the SARS-CoV-2 pandemic, access to laboratories performing oral glucose tolerance tests (OGTTs) was restricted to limit the potential risk of pregnant women being exposed to the virus. Therefore, there was a real risk of GDM not being diagnosed. To avoid missed screening, modified approaches to the diagnosis of GDM during this period of the pandemic have been proposed [3]. The outcomes of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study showed that maternal hemoglobin A1c (HbA1c) was

Abbreviations: SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; GDM, Gestational Diabetes Mellitus; HbA1c, glycated Hemoglobin A1c; OGTT, Oral Glucose Tolerance Test; IADPSG/WHO, International Association of Diabetes and Pregnancy Study Groups/World Health Organization; ROC, Receiver Operating Characteristic; BMI, Body Mass Index.

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associated with some adverse outcomes of GDM diagnosed between 24 and 32 weeks of pregnancy, although the associations were stronger with OGTT than with HbA1c. This was particularly true for birth weight greater than 90th percentile. In contrast, the associations were similar for cesarean section, preeclampsia and preterm delivery. Recently, a French study showed that HbA1c ≥ 5.6% (38 mmol/mol) increased the relative risk of developing a GDM-related complication [4]. Therefore, HbA1c was suggested as an alternative to OGTT for the diagnosis of GDM during the pandemic [1,5,6].

The present study aims to evaluate the performance of HbA1c for the diagnosis of GDM during the 2020–2021 pandemic period in Belgium.

Research design, material and methods

Study population

This study evaluates the performance of the HbA1c test in the diagnosis of GDM, with the reference test being the OGTT according to the criteria of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) and the World Health Organization 2013 (WHO 2013). This investigation is an observational, retrospective multicenter study and involves a population of pregnant women from the Centre Hospitalier de Mouscron (CHM) and the Cliniques Universitaires Saint Luc (CUSL) during the period from March 2020 to July 2021.

The measures taken by the Belgian government at this time imposed several strict quarantine rules and two lockdown periods. Access to GDM testing sites was very limited. However, when screening center appointments were available, some women had HbA1C and OGTT testing at the same time.

The medical records of all women screened for GDM at the two centers were analyzed to determine the maximum number of women who had a third-trimester HbA1c and OGTT.

The study protocol was approved by the Faculty Ethics Committee under reference number CEHF 2021/25JUI/288.

The inclusion criteria were pregnant women who were screened for GDM by HbA1c and who also performed an OGTT between 24 and 28 weeks of pregnancy. GDM was universally diagnosed in both centers according to the 2013 IADPSG/WHO criteria (OGTT with 75 g glucose load, only one pathological value out of three gives a diagnosis of GDM (fasting ≥ 92 mg/dL (5.1 mmol/L), 1 h ≥ 180 mg/dL (10.0 mmol/L), 2 h ≥ 153 mg/dL (8.5 mmol/L) [7].

The exclusion criteria were age < 18 years; type 1 or 2 diabetes, HbA1c ≥ 6.5% or early GDM (glycemia ≥ 92 mg/dl in the first trimester of pregnancy); or severe anemia (≤10 g hemoglobin) [8]. Partial OGTT and/or no HbA1c measured between 24 and 28 weeks' gestation were excluded.

Collected data and outcome measures

Age, weight at the beginning and end of pregnancy, BMI, data on previous pregnancies and risk factors such as a history of macrosomia, GDM and a family history of diabetes were recorded from electronic hospital records. For patients with GDM, we collected data on the date of GDM diagnosis and plasma glucose values (OGTT). Glucose was measured using Abbott Architect c16000 at CHM and Roche c501 and c502 at CUSL. Data on the type of GDM treatment (diet or insulin therapy) were collected, as were data on hemoglobin and HbA1c values, and HbA1c was measured using a high-performance liquid chromatography (HPLC) method on the Tosoh G8 (Tosoh Automated Glycohemoglobin Analyzer HLC-723®G8) at both centers. The performance of the results was compared, and there was no significant analytical difference between the two centers (data not shown).

Statistical analysis

The chi-square test and Fisher's exact test were used for categorical variables, which are expressed as percentages, and independent t-tests were used for continuous variables, which are presented as the mean ± SD. A receiver operating characteristic (ROC) curve was used to analyze the performance of the HbA1c test in diagnosing GDM considering the OGTT as reference diagnostic criteria. Sensitivity, specificity and likelihood ratios for different HbA1c thresholds were calculated to diagnose GDM. All data were analyzed with IBM SPSS version 25 for Windows. A p value of < 0.05 was considered statistically significant. To increase the clinical applicability of the present results, we estimated the posttest probability of GDM using the Fagan nomogram test [9] considering a pretest probability of 10%, which corresponds to the average Belgian prevalence of GDM [2].

Results

Between March 2020 and July 2021, 3361 women gave birth at the two hospitals: CHM 979 and CUSL 2382. After analysis, 343 women met the inclusion criteria (HGPO + HbA1c between 24 and 28 weeks): 262 at the CHM and 81 at the CUSL. Of the 343 pregnant women recruited, 31 were excluded (2 with preexisting diabetes, 5 with no hemoglobin data, 9 with incomplete OGTT, 15 with anemia). A total of 312 were included in the study and were assessed for the presence or absence of GDM according to the 2013 IADPSG/WHO criteria. The flow chart is shown in Fig. 1.

All women had a mean age of 30.0 ± 5.0 years and were in the third trimester of pregnancy (gestational age 26 ± 1.6 weeks). In total, of the 312 women, 149 (47.8%) had GDM, and they were compared with 163 women (52.2%) who did not have GDM. The demographic, clinical and laboratory characteristics of the study participants are shown in Table 1.

There was a significant difference between women with and without GDM in terms of age (32.0 ± 5.2 vs. 28.7 ± 4.4, $p < 0.0001$), BMI (26.9 ± 5.8 vs. 24.3 ± 4.7, $p < 0.0001$), history of GDM (15.6% vs. 4.4%, $p < 0.003$), and family history of diabetes (38.1% vs. 3.7%, $p < 0.0001$). The patients were similar in terms of history of macrosomia and hypertension (ns). The HbA1c values of the pregnant women with and without GDM were 5.1 ± 0.3% (32.8 ± 3.7 mmol/mol) and 4.88 ± 0.2% (29.8 ± 2.8 mmol/mol), respectively ($p < 0.0001$). Hemoglobin was similar between the two groups ($p = 0.52$).

The overlap between HbA1c values in the non-GDM and GDM groups is shown in Fig. 2. On analysis of this HbA1c distribution, there is a narrow overlap between the 2 groups, from 4.9% (30 mmol/mol) to 5.1% (32 mmol/mol).

ROC analysis (Fig. 3) using the 2013 IADPSG/WHO criteria as a reference showed an AUC of 0.73 (95% CI 0.67–0.79, $p < 0.0001$), and the cutoff point obtained by the best sensitivity/specificity balance was HbA1c of 5.0% (31 mmol/mol). This cutoff point renders a sensitivity of 60.4% and a specificity of 72.39% according to the Table 2.

Likelihood ratios (LR+ = positive likelihood ratio; LR− = negative likelihood ratio) for different HbA1c thresholds were also calculated for the HbA1c values obtained (Table 2).

HbA1c levels at 4.5% (26 mmol/mol) and 5.3% (34 mmol/mol) were the first points on the ROC curve with sensitivity and specificity values greater than 95%, respectively. HbA1c levels at 4.5% (26 mmol/mol) rendered an LR + of 1.10 (95% CI 0.08–4.02) and an LR− of 0.23 (95% CI 0.60–31), whereas HbA1c ≥ 5.3% (34 mmol/mol) had an LR + of 6.57 (95% CI 1.84–98) and an LR− of 0.79 (95% CI 0.07–3.69).

However, when considering HbA1c ≥ 5.5% (37 mmol/mol), this value had a specificity greater than 99%, with an LR + of 20 (95% CI 9.26–621) and LR− of 0.88 (95% CI 0.07–3.57), though HbA1c ≥ 5.6% (38 mmol/mol) had an LR + of 17 (95% CI 9.26–621) and an LR− of 0.90 (95% CI 0.07–3.57).

Therefore, the probability of diagnosis of GDM is high if HbA1c is ≥ 5.5% as it is associated with the high LR + values.

Using the Fagan nomogram test, it is possible to estimate the probability of a pregnant woman being diagnosed with GDM from the likelihood ratios and the prevalence rate of GDM in Belgium [2].

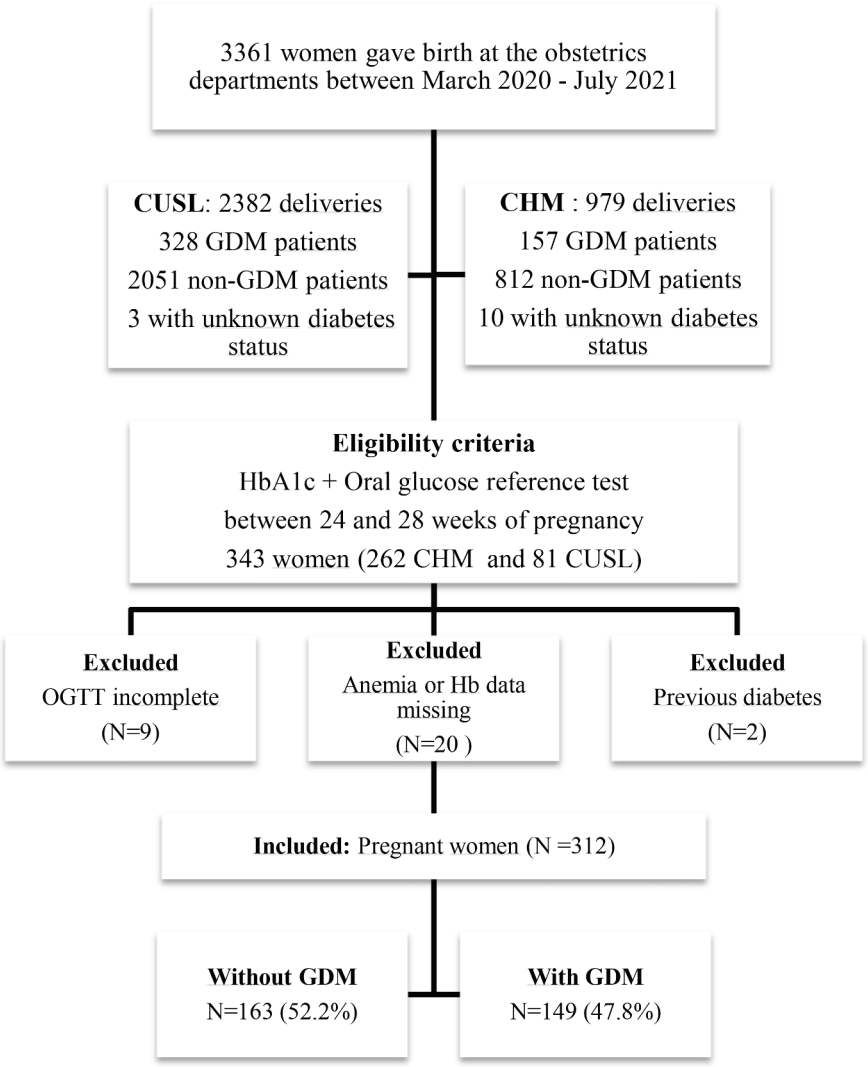

Fig. 1. Flow chart.

Given a pretest probability of 10% for GDM, the posttest probabilities of the women with GDM were 53% for HbA1c ≥ 5.4% (36 mmol/mol), 70% for HbA1c ≥ 5.5% (37 mmol/mol), and 65% for HbA1c ≥ 5.6% (38 mmol/mol) (Fig. 4). For a patient with HbA1c ≥ 37 mmol/mol (5.5%), the blue line on Fagan's nomogram meets the third scale at 70. We therefore estimate the probability for a patient to have gestational diabetes to be 70%. For a patient with a negative test, the red line on the nomogram meets the third scale at 9. The probability for the patient to have GDM is then only 9%.

Based on these data, 27 pregnant women were classified as having GDM using an HbA1c of ≥ 5.5% (37 mmol/mol) as the cutoff for GDM. These women with ≥ 5.5% (37 mmol/mol) had significantly more family history of diabetes (44.4 vs. 19.1%; $p < 0.005$), older age (32.6 vs. 30.0 years, $p < 0.02$), higher BMI (28.3 vs. 25.3 kg/m^2, $p < 0.01$), and higher blood glucose levels (fasting, 1 h, and 2 h) ($p < 0.0001$).

However, there was no difference in history of arterial hypertension ($p = 0.52$), GDM ($p = 0.17$), macrosomia ($p = 0.31$) or insulin treatment ($p = 0.13$).

Discussion

In this study, we evaluated the performance of HbA1c in the detection of GDM in comparison with the conventional OGTT. Our data showed that the HbA1c levels in pregnant women who did not have GDM were significantly lower than those in pregnant women who did have GDM. However, there was some overlap between participants' HbA1c in the two groups. Some studies suggest that anemia may be the cause of the lower HbA1c levels observed during pregnancy [10]. Because women with and without GDM had similar levels of total hemoglobin in our study, anemia could not explain these differences. We also excluded women with anemia with hemoglobin < 10 g.

The ROC curve analysis, used to evaluate the performance of the HbA1c test in the diagnosis of GDM, showed AUC values for the 2013 IADPSG/WHO reference criteria at 0.73 (95% confidence interval 0.68 to 0.79). This is in agreement with other studies [11,12]. The HbA1c threshold of 5.0% (31 mmol/mol) had the best balance of sensitivity and specificity. However, the sensitivity value for this cutoff point was not high enough (66.1%) to rule out the diagnosis of GDM. In contrast, when an HbA1c level of 5.5% (37 mmol/mol) was used as the cutoff point, the specificity for the diagnosis of GDM was excellent (99%). A previous New Zealand study [13] proposed an optimal HbA1c threshold of 5.9% (41 mmol/mol) but for a diagnostic period of < 20 weeks of pregnancy. This threshold was associated with greater neonatal complications than the threshold of HbA1c < 5.9%. Another Brazilian study [11] suggested that HbA1c ≥ 5.8% (40 mmol/mol) in the third trimester of pregnancy was associated with a 38% posttest probability of a diagnosis of GDM. A similar study suggested the use of HbA1c 5.8% (40 mmol/mol) as a cutoff point to confirm the diagnosis of GDM in women in Thailand [12].

Table 1
Demographic, history, and laboratory characteristics of pregnant women with and without GDM, according to the 2013 IADPSG/WHO diagnostic criteria.

	Without GDM	With GDM	
	N = 163	N = 149	*P*
Age (years)	28.7 ± 4.3	32.0 ± 5.2	<0.0001
Gestational age (weeks)	26.3 ± 1.7	27.3 ± 2.3	0.1
BMI (kg/m^2) at the beginning of pregnancy	24.3 ± 4.7	26.9 ± 5.8	<0.0001
Weight gain during pregnancy (kg)	13.0 ± 6.3	8.9 ± 6.0	<0.0001
History of GDM	6/136 (4.4%)	23/147 (15.6%)	0.003
History of macrosomia	4/136 (2.9%)	10/147 (6.8%)	0.173
Family history of diabetes	5/136 (3.7%)	56/147 (38.1%)	<0.0001
History of hypertension	5 (3%)	3 (2%)	0.72
GDM treated with a diet	–	107 (71.0%)	
GDM treated with insulin	–	42 (29%)	
OGTT			
GAJ (mg/dl)	81.8 ± 5.2	90.15 ± 11.3	<0.0001
1 h G (mg/dl)	121.1 ± 26.1	170.8 ± 30.4	<0.0001
2 h G (mg/dl)	104.8 ± 19.4	146.2 ± 30.9	<0.0001
HbA1c [mmol/mol (%)]	29.8 ± 2.8 (4.8 ± 0.2)	32.8 ± 3.7 (5.1 ± 0.3)	<0.0001
Hb (g/dL)	11.80 ± 1.01	11.73 ± 0.84	0.52

Data are expressed as the means ± SDs, or n (%). GDM = gestational diabetes, OGTT = oral glucose tolerance test, BMI = body mass index, FPG = fasting blood glucose, 1hG = blood glucose after 1 h glucose loading, 2hG = blood glucose 2 h after glucose loading, Hb = hemoglobin.

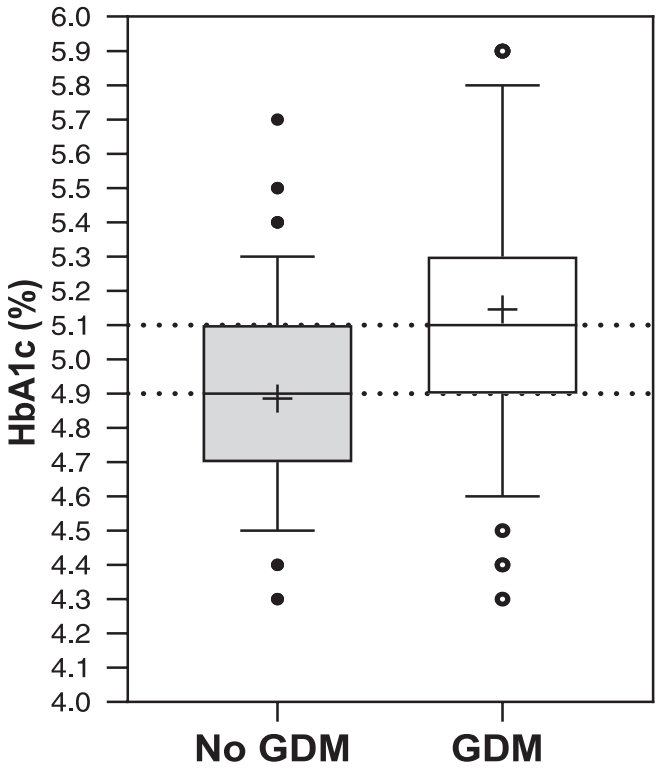

Fig. 2. Glycated hemoglobin (HbA1c) levels in pregnant women without and with gestational diabetes mellitus (GDM). Box-and-whiskers plot of No GDM (grey) and GDM (white); the top and bottom of the boxes indicate the 25th and 75th percentile, the lines represent the overlap between the two groups, and the plus sign represents the mean. The whiskers represent the 5th and 95th percentiles.

However, in these studies, the WHO-1999, IADPSG/WHO-2013, and National Diabetes Data Group criteria for a 3-hour 100-g OGTT were used for comparison.

In comparison, whereas our study compared only HbA1c to the

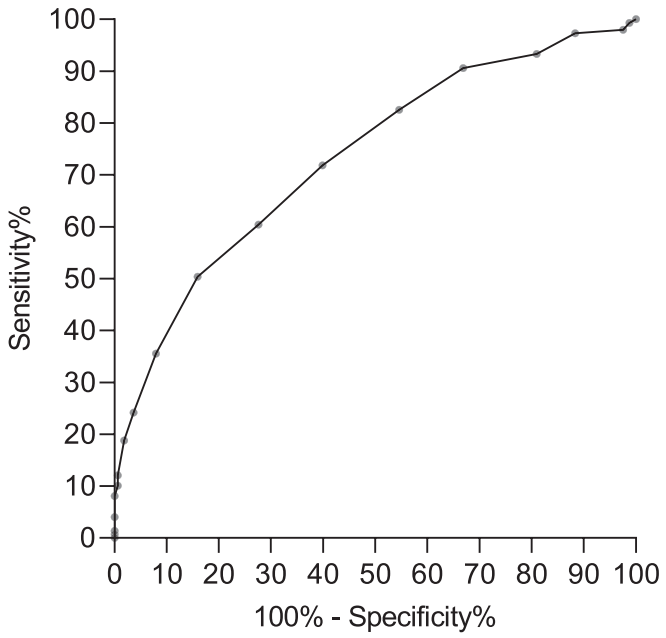

Fig. 3. The ROC curve for the evaluation of the diagnostic performance of HbA1c for GDM. Line: HbA1c vs. ADA/WHO 2013 (N = 312).

Table 2
HbA1c test performance in diagnosing GDM (N = 312).

HbA1c [% (mmol/mol)]	Sensitivity (%) 95% CI	Specificity (%) 95% CI	LR + 95% CI	LR− 95% CI
4.3 (23)	99.33 [96.30–99.97]	1.22 [0.21–4.36]	1.01 [0.07–3.60]	0.54 [5.11–299]
4.4 (25)	97.99 [94.25–99.45]	2,45 [0.95–6.13]	1.00 [0.07–3.64]	0.82 [2.72–148]
4.5 (26)	97.32 [93.30–98.95]	11.66 [7.59–17.49]	1.10 [0.08–4.02]	0.23 [0.60–31]
4.6 (27)	93.29 [88.09–96.31]	19.02 [13.73–25.73]	1.15 [0.09–4.39]	0.35 [0.37–19]
4.7 (28)	90.6 [84.85–94.32]	33.13 [26.36–40.67]	1.35 [0.11–5.31]	0.28 [0.21–11]
4.8 (29)	82.55 [75.66–87.80]	45.4 [37.95–53.06]	1.51 [0.13–6.51]	0.38 [0.15–7.83]
4.9 (30)	71.81 [64.11–78.42]	60.12 [52.46–67.32]	1.80 [0.18–8.91]	0.47 [0.12–5.91]
5.0 (31)	60.4 [52.38–67.90]	72.39 [65.07–78.68]	2.19 [0.25–13]	0.55 [0.10–4.91]
5.1 (32)	50.34 [42.40–58.25]	84.05 [77.65–88.88]	3.16 [0.44–22]	0.59 [0.08–4.23]
5.2 (33)	35.57 [28.33–43.53]	92.02 [86.83–95.28]	4.46 [0.87–45]	0.70 [0.08–3.86]
5.3 (34)	24.16 [17.99–31.63]	96.32 [92.20–98.30]	6.57 [1.84–98]	0.79 [0.07–3.69]
5.4 (36)	18.79 [13.33–25.82]	98.16 [94.73–99.50]	10 [3.55–198]	0.83 [0.07–3.62]
5.5 (37)	12.08 [7.78–18.29]	99.39 [96.61–99.97]	20 [9.26–621]	0.88 [0.07–3.57]
5.6 (38)	10.07 [6.19–15.95]	99.39 [96.61–99.97]	17 [9.26–621]	0.90 [0.07–3.57]
5.7 (39)	8.05 [4.67–13.55]	100 [97.70–100.0]		
5.8 (40)	4.02 [1.88–8.5]	100 [97.70–100.0]		
5.9 (41)	1.34 [0.23–4.7]	100 [97.70–100.0]		
AUC	**0.73**			

LR+ = positive likelihood ratio; LR− = negative likelihood ratio. 2013 ADA/WHO reference criteria.

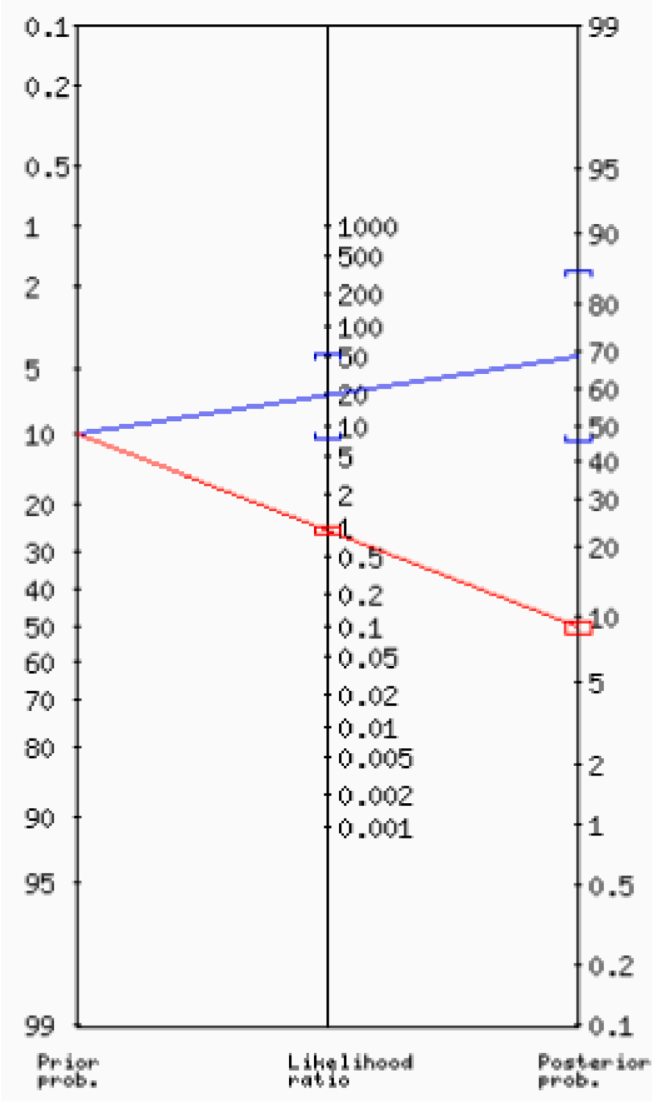

Fig 4. Fagan nomogram for the HbA1c test showing posttest probabilities of gestational diabetes in pregnant women with HbA1c ≥ 5.5% (37 mmol/mol).

IADPSG/WHO-2013 criteria.

As the posttest probability, by using the Fagan nomogram test, of having GDM with an HbA1c cutoff ≥ 5.5% (37 mmol/mol) was 70%, we propose this cutoff level to be the most useful for clinical use.

If we were to consider this HbA1c level as a diagnostic test in the total study population (n = 312), then 25 women would be true positive (HbA1c ≥ 5.5% and abnormal HGPO), and 8.0% of OGTTs would be considered as unnecessary. On the other hand, 2 (0.63%) women were false positive (normal HGPO but HbA1c ≥ 5.5%), 124 (39.7%) were false negative (abnormal HGPO but HbA1c < 5.5%), and 161 (52%) were true negative (normal HGPO and HbA1c < 5.5%). Therefore, 60% of the OGTTs could have been avoided.

These results are consistent with those of other studies that have reported mean HbA1c values of 4.9 to 5.5% (30 to 37 mmol/mol) in pregnant women without GDM [14]. When we used the HbA1c cutoff of ≥ 5.5% (37 mmol/mol) to distinguish between women with and without GDM, we found that those classified as having GDM were more likely to be older, to have a family history of GDM and to have elevated BMI and blood glucose (fasting, 1 h, and 2 h).

Limitations of the study

Firstly, although our results are consistent with those of other studies, our sample of pregnant women may differ from that of other populations. Secondly, the relationship between HbA1c and negative maternal and/or fetal outcomes could have been further analyzed, to clarify risks at different HbA1c levels. Thirdly, as HbA1c is known to be more expensive than glucose-based tests, we could have performed cost-effectiveness analyses, to inform decision-makers further. The strength of this study is that it is the first to evaluate the accuracy of HbA1c in diagnosing GDM compared with the 75 g OGTT (IADPSG/WHO-2013) in a large number of patients. Our results showed that 27 GDM cases were diagnosed by an HbA1c cutoff of ≥ 5.50% (37 mmol/mol), with only 2 false positives.

During the SARS-COV-2 pandemic, the HbA1c test had several advantages over the OGTT, including less biological variation, better reproducibility, better sample stability and no fasting [15]. This makes it a useful parameter to confirm the presence of GDM. However, the low sensitivity of this test makes it a poor option.

Conclusion

The HbA1c test does not have sufficient sensitivity and specificity to be used as the sole test for the diagnosis of GDM. Different HbA1c cutoff points in combination with the OGTT, however, could possibly be used for diagnostic purposes. To avoid even more OGTTs and the inconvenience of this test for pregnant women in situations such as a pandemic, it would also be useful to investigate the combination of HbA1c with fasting blood glucose (greater than 92 mg/dl).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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No potential conflicts of interest relevant to this article were reported.

Author contributions

C.N., P.O. collected data and wrote the manuscript.
A.C., D.G. collected data and validated the data.
P.O. and O.A. directed and conducted the statistical analyses.
C.N., A.C., D.G., P.O. and O.A. reviewed the manuscript.
P.O. and O.A. initiated and directed the study and reviewed the manuscript.
P.O. and O.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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