**Diagnostic accuracy of glycated hemoglobin for gestational diabetes mellitus: a systematic review and meta-analysis**

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**Abstract**

**Background:** We conducted a systematic review and meta-analysis to establish the overall accuracy of HbA1c in the diagnosis of GDM. **Methods:** We searched MEDLINE, EMBASE, SCOPUS and ClinicalTrials.gov up to October 2018, using key words related to GDM, HbA1c and diagnosis. Studies were included that carried out with pregnant women without previous diabetes that assessed the performance of HbA1c (index test) compared to 75g OGTT (reference test) for the diagnosis of GDM, that measured HbA1c by standardized methods and presented data necessary for drawing 2x2 tables. **Results:** This meta-analysis included 8 studies, totaling 6,406 pregnant women, of those 1,044 with GDM. The diagnostic accuracy of HbA1c was reported at different thresholds ranging from 5.4% (36mmol/mol) to 6.0% (42mmol/mol), and the area under the curve (AUC) was 0.825 (95% CI 0.751 – 0.899), indicating a good level of overall accuracy. The pooled sensitivities and specificities were 50.3% (95% CI 24.8% - 75.7%) and 83.7% (67.5% - 92.7%); 24.7% (10.3% - 48.5%) and 95.5%(85.7% - 98.7%); 10.8% (5.7% - 19.41%) and 98.7%(96.2% - 99.5%);12.9% (5.5% - 27.5%) and 98.7% (97.6% - 99.3%), for the cutoffs of 5.4% (36mmol/mol), 5.7% (39mmol/mol), 5.8% (40mmol/mol) and 6.0% (42mmol/mol), respectively. **Conclusions:** We observed a high heterogeneity among the studies. The effect of ethnicities, different criteria for OGTT interpretation and the individual performance of HbA1c methods may have contributed to this heterogeneity. The HbA1c test presents high specificity but low sensitivity regardless of the threshold used to diagnose GDM. These findings point out to the usefulness of HbA1c as a rule-in test. HbA1c should be used in association with other standard diagnostic tests for GDM diagnosis.

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**Keywords:** diagnosis; HbA1c; gestational diabetes; meta-analysis.

**INTRODUCTION**

According to the American Diabetes Association (ADA), gestational diabetes mellitus (GDM) is "diabetes that is first diagnosed in the second or third trimester of pregnancy that excludes the possibility of pre-existing type 1 or type 2 diabetes" [1]. This disease is a prevalent and potentially serious condition that may lead to adverse outcomes in both mothers and neonates [2]. It is associated with preeclampsia, increased caesarean rates, and macrosomia [3]. The detection and adequate treatment of this condition reduces the risks for mothers as well as for babies [3,4,5].

The oral glucose tolerance test (OGTT) has been the diagnostic test of choice for diabetes mellitus (DM) in the general population [1]. In the last decades, the diagnostic criteria for GDM have been controversial and a range of recommendations and guidelines to identify women with GDM have been proposed [1, 2, 6-9].

Up to 2013, the World Health Organization (WHO) recommended that the GDM diagnosis should be based on the same criteria used for non-pregnant adults using the 2h 75g OGTT [2]. The UK National Institute for Health and Care Excellence (NICE) recommendations [9] are based on these criteria; however, they recommended a lower cutoff for fasting glucose. More recently, the International Association of the Diabetes in Pregnancy Study Group (IADPSG), after the results of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, a cohort study with about 25,000 pregnant women, recommended a new diagnostic criterion for GDM based also on 2h 75g OGTT but with lowered thresholds for fasting glucose, 1h and 2h glucose. GDM is present if one or more results are altered [10-12]. Since 2013, WHO has adopted these same IADSPG criteria [2]. According to ADA, GDM diagnosis can be performed by the one-step 2h 75g OGTT using the same threshold diagnostic criteria of IADPSG or the two-step strategy with a 1h 50g OGTT screen followed by a 3h 100g OGTT for those who screen positive [1].

Although OGTT is recommended as the diagnostic test for GDM by international organizations, it requires at least 8h fasting, an extensive patient preparation, lacks reproducibility, it is time-consuming and uncomfortable for pregnant women [7].

HbA1c test has been used in clinical practice for monitoring patients with DM since early 80´s [13], but its use in diagnosis was established only in 2010 [14, 15]. Presently, there are more than 100 certified methods/instruments available for routine HbA1c measurement (http://www.ngsp.org/docs/methods.pdf; accessed in 14th December 2018). These methods are mainly based on four principles: immunoassays, ion-exchange chromatography (HPLC), affinity chromatography and enzymatic assays. The International Federation of Clinical Chemistry (IFCC) Working Group on HbA1c Standardization developed a reference system for HbA1c [16] and since the mid 90’s, as well as the National Glycohemoglobin Program (NGSP), work to standardize and align HbA1c methods worldwide [17, 18]. Despite all these international efforts, there are still many situations that may affect HbA1c results, related or not to assay methods, such as the presence of a variant hemoglobin (Hb), anemia and uremia [18, 19]. Recently, the role of race/ethnicity on HbA1c values has been raised [20, 21]. HbA1c values are higher in Blacks, Asians, and Latinos when compared to White persons. These factors have limited the use of HbA1c in specific cases.

The cut-off of HbA1c 6.5% (48 mmol/mol) is recommended for DM diagnosis in the general population (Expert Committee 2010), and this cutoff is endorsed by ADA and WHO [1, 15]. However, its use for the diagnosis of GDM has not been recommended by any current guidelines yet [1, 2, 7, 10]. Results from the HAPO study showed that HbA1c values, like glycemia levels, were significantly associated with all adverse outcomes, and higher levels of maternal HbA1c were related to greater frequency of adverse outcomes [6]. HbA1c test would be more receptive to this group of patients because of its convenience when compared to OGTT. However, due to some physiological and analytical factors that might interfere with HbA1c results, it has not yet been included as a diagnostic tool for GDM [1, 18, 19].

During pregnancy, haemoglobin concentrations change overtime, to accommodate the increasing maternal blood volume and the iron needs of the foetus and also there is a decrease in fasting blood glucose levels [2]. Consequently, HbA1c levels are lower in pregnant women than in non-pregnant women. Due to these factors, different reference values are recommended in pregnancy and HbA1c interpretation should consider these factors [22]. In addition, HbA1c is significantly lower in the first trimesters of gestation and HbA1c trimester-specific reference intervals are required throughout pregnancy [23]. HbA1c values vary from 4.0% (20 mmol/mol) to 6.0% (42 mmol/mol) in pregnant women from different populations [24].

Some studies have evaluated the diagnostic accuracy of HbA1c in DMG [25-29]. In a recent meta-analysis with 2,812 patients and 5,918 controls, which measured HbA1c in Chinese pregnant women, showed that this test is a useful diagnostic tool to confirm GDM [25]. A large cohort study in New Zealand reported that HbA1c ≥5.9% (41 mmol/mol) at the first antenatal visit identified all cases of GDM and was associated with a twofold risk of congenital anomalies, preeclampsia, shoulder dystocia and a threefold risk of perinatal deaths [26]. We also showed that HbA1c levels may be a useful diagnostic tool for GDM in Brazilian pregnant women, the HbA1c cut-off point of 5.8% (40 mmol/mol) was able to diagnose 38% of GDM cases by OGTT and 5% of pregnant women classified as GDM negative by the OGTT were identified according to the HbA1c test [27]. Other studies have also highlighted the potential role of HbA1c in the diagnosis and management of GDM [28, 29]. In this study we carried out a systematic review and meta-analysis to determine the diagnostic accuracy of HbA1c test in the diagnosis of GDM in different populations of pregnant women.

**MATERIALS AND METHODS**

This meta-analysis is in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis: The PRISMA Statement [30] and in according to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy [31]. It was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the number CRD42018041407.

**Search Strategy and Data Sources**

We searched PubMed (MEDLINE), Embase, SCOPUS and ClinicalTrials.gov, with assistance from our Institution’s library professionals, for papers published up to October 2018 using search terms related to GDM, HbA1c and diagnosis combined. Details of all search terms are presented in **Supplementary Material.** From the papers retrieved, a manual search of their references was conducted. Articles published before 1996, duplicate articles and those which less complete were removed and the remaining articles were assessed for eligibility. The revision of titles was followed by the abstracts reading for relevance. Finally, the identification of eligible studies was carried out, based on a full reading of the articles selected by at least 2 researches.

**Study selection**

The inclusion criteria were: (1) cross-sectional or cohort studies that assessed the performance of HbA1c (index test) and 75g OGTT (reference test) for the diagnosis of GDM; (2) HbA1c method certified by the National Glycohemoglobin Standardization Program (NGSP; http://www.ngsp.org/, 13 December 2017, date last accessed) and/or the International Federation of Clinical Chemistry (IFCC) [17-18]; (3) studies that included pregnant women without DM prior to pregnancy or GDM already diagnosed. Exclusion criteria were: (1) studies that did not perform 75g OGTT for the GDM diagnosis; (2) review articles; (3) comments, letters and/or editorials; (4) studies with language other than English, Spanish or Portuguese; (5) articles published before 1996, as from this date on was when the standardization for the HbA1c methods started [16-18]. Three independent reviewers (P.B.R., F.C.C. and J.R.T.T.) decided for studies inclusion based upon eligibility criteria. First, we screened the titles of all papers resulted from the search to identify potentially relevant articles. Afterwards, we evaluated the abstracts of these studies, and relevant articles had their full-text reviewed. Finally, the reviewers selected articles qualified for inclusion and performed data extraction from all included reports. Any disagreements concerning study eligibility or data interpretation were resolved through discussion or, if required, a fourth reviewer was consulted (J.L.C. or A.L.P.).

**Data collection and analysis**

A data extraction form was developed and the following information were extracted from each report: (1) study details (author, publication year, country of origin); (2) study design; (3) sample size; (4) GDM incidence; (5) participant characteristics (age, gestational age, HbA1c results); (6) test methods (details of methodology and equipment description for HbA1c and OGTT); and (7) test results [true-positive (TP) cases; false-positive (FP) cases; true-negative (TN) cases; and false-negative (FN) cases]. We also attempted to contact authors for further information when data to construct a 2x2 table was unclear or additional data were required. When data were not available from the authors, the study was excluded.

**Quality assessment**

At least two reviewers independently assessed the quality of primary studies by evaluating the risk of bias and applicability, using the Quality Assessment of Diagnostic Accuracy Studies tool QUADAS-2, a questionnaire containing 14 questions assessing risk of bias and applicability concerns [32]. Disagreements were resolved by consensus or by involving a third reviewer (J.L.C. or A.L.P.). We also evaluated if the articles were presented according to Standards for Reporting of Diagnostic Accuracy (STARD) initiative guidelines [33].

**Statistical analysis and data synthesis**

We followed the standard methods recommended for diagnostic accuracy meta-analysis studies [34]. For each study, 2x2 contingency tables were constructed with data extracted for TP, TN, FP and FN rates. By a bivariate model using a random effects approach [35] indexes of HbA1c test accuracy were computed: sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR). PLR >1 for a positive test result is associated with the presence of disease, and NLR <1 for a negative test result is associated with the absence of disease [36]. The DOR is a single indicator that summarizes the diagnostic accuracy of a test, and higher values indicate a better test performance [37]. Overall diagnostic accuracy for HbA1c test for GDM diagnosis was determined by a summary receiver operating characteristic curve (SROC) for the main cut-off points discussed in each study. Afterwards, hierarchical summary ROC curves (HSROC) were used to summarize the HbA1c performance for specific cut-offs if 4 or more studies presented data for the same cut-off [38]. The Fagan nomogram was applied, considering a pre-test probability of 18% for GDM, based on external data from the Metzger et al study [6], to calculate posttest probabilities for GDM using different HbA1c cut-offs [39]. The heterogeneity among studies was evaluated by Chi-square and Cochran Q analysis, I2 (measure of inconsistency, when I2 has a value above 50%, it is considered that there is moderate heterogeneity, 25% is low and 75% is high) and by visual inspection of forest plots. When the studies are reasonably homogeneous, accuracy indexes from individual studies will lie within or near the interval of the pooled accuracy estimate. Deviations may indicate possible heterogeneity or outlier studies [40,41]. We also ran the meta-analyses over again while removing studies one at a time to determine whether a particular study accounted for the heterogeneity. In addition, when data was available, we carried out subgroup analysis by specific cut-off points, HbA1c methods and country of origin. The presence of publication bias was tested by using Deeks’ funnel plots [42]. A P-value <0.05 was considered statistically significant in all analyses, except for Deeks’ test, where a value of P <0.1 was considered statistically significant. Analyses were carried out in Meta-Disc Version 1.4 (Universidad Complutense, Madrid, Spain) and Stata Version 12.1 software (Stata, College Station, TX, USA) by METANDI command. The forest plots were constructed using Review Manager Version 5.3 (Cochrane Collaboration, Oxford, UK). All studies selected for this review were previously approved by an Ethical Review Board and consequently ethical approval was not required by this review study.

**RESULTS**

**Study selection and Study characteristics**

With this strategy 2,927 records were identified. Of those, 49 studies were assessed for eligibility. After full-text reading, 40 articles were excluded (one for different language, 9 for insufficient data, 4 for different reference test criterion, 3 studies performed the diagnostic test in the first gestational trimester and 23 didn’t meet the research question). Lastly, nine studies met our inclusion criteria [27, 29, 43-49], and of these, only 1 article [43] was excluded from the meta-analysis due to lack relevant information to allow a proper extraction of data as it was not clear which diagnostic criterion was used to perform the ROC analysis. Nevertheless, it was included in the qualitative analysis. Eight studies were eligible for systematic review and meta-analysis [27, 29, 44-49](**Figure 1)**.

All studies included in this review totalized 6,848 pregnant women, who performed OGTT and HbA1c tests in the second or third trimesters of pregnancy for GDM diagnosis, of those 1,128 were diagnosed with GDM (15.2%). **Table 1** summarizes the characteristics of all selected studies. Three studies had prospective design [43, 47, 48], one was a retrospective study [49] and five were cross-sectional studies [27, 29, 44-46]. All studies were written in English and published between 2005 and 2017. Four studies were from India, while Arab Emirates, Australia, Brazil, China and Turkey contributed with one study each.

**Quality Assessment**

The quality assessment of the studies by QUADAS-2 criteria is summarized in **Table 2**. Most studies presented a low risk of bias and applicability concerns. One study [44] presented a high risk of bias in the patient selection, flow and timing; in this study 1,459 pregnant women participated, 33 of which were in the first trimester of pregnancy while the remaining women were in the second trimester of pregnancy. Another study [43] had a high risk of bias in the reference standard; this study used two different diagnostic criteria for the diagnosis of GDM and it was not clear which criterion was used in the analyses. For this reason, we did not perform the data extraction. One study [27] presented unclear risk of bias in flow and timing, since 120 pregnant were diagnosed by WHO 1999 diagnostic criteria and 142 were diagnosed by IADPSG criteria. Only one article followed the recommendations and was presented according to the STARD guidelines [27].

**Meta-analysis**

*Overall diagnostic accuracy*

For this analysis we considered the main HbA1c cut-offs discussed in each article [27, 29, 44-49]. HbA1c threshold ranged from 5.4% (36 mmol/mol) to 6.0% (42 mmol/mol). A total of 6,406 pregnant women were included in this analysis, of those, 1,044 were diagnosed with GDM. Using data from these eight studies, DOR was 6.97 (95% CI 4.17 – 11.65) and the area under the curve (AUC) was 0.825 (95% CI 0.751 – 0.899); indicating a good level of overall accuracy (**Figure 2**).

*Effect of HbA1c threshold on diagnostic accuracy*

The forest plot in **Figure 3** shows the sensitivity and specificity of HbA1c for the detection of GDM across all 8 included studies. For studies reporting accuracy at more than one threshold, 2x2 tables were built for each cutoff. The cutoffs 5.4% (36 mmol/mol), 5.7% (39 mmol/mol), 5.8% (40 mmol/mol) and 6.0% (42 mmol/mol) were reported by at least 4 studies and their data were included in the forest plots. **Table 3** summarizes the accuracy measures for these cutoffs.

HbA1c ≥5.4% (36 mmol/mol) for diagnosis of GDM

Four studies evaluated the cutoff of 5.4% (36 mmol/mol) [27, 29, 44, 45], totaling 2,808 pregnant women. HSROC curve showed an AUC of 0.779 (95% CI 0.739 – 0.819; **Figure 4A**). The DOR was 5.20 (95% CI 3.33 – 8.12; I2 =57.6%). Sensitivity ranged from 26% to 86% and specificity from 61% to 96% (**Figure 3**). The pooled sensitivity for these studies was 50.3% (95% CI 24.8% - 75.7%) and the pooled specificity was 83.7% (95% CI 67.5% to 92.7%) (**Table 3**). After re-running the meta-analysis by removing one paper at a time, when removing the study by Bhavadharini et al [44], no DOR heterogeneity was found (I2 = 0%), pooled sensitivity decreased and pooled specificity was the same [39% (95% CI 33% - 44%) and 83% (95% CI 81% to 84%)], respectively. However, after carefully reviewing this study, we were unable to explain the reasons why it contributed to the increase in heterogeneity for this cutoff and the results from the primary meta-analysis were considered.

HbA1c ≥5.7 (39 mmol/mol) for diagnosis of GDM

Five studies presented data for cutoff of 5.7% (39 mmol/mol) [27, 45, 47-49], totaling 3,540 pregnant women. HSROC curve showed an AUC of 0.741 (95% CI 0.675 – 0.807; **Figure 4B**). The DOR was 7.03 (95% CI 4.50 – 10.96; I2 =55.7%). Sensitivity ranged from 9% to 73% and specificity from 76% to 100% (**Figure 3**). The pooled sensitivity for these studies was 24.7% (95% CI 10.3% - 48.5%) and the pooled specificity was 95.5% (95% CI 85.7% to 98.7%) (**Table 3**). After re-running the meta-analysis by removing one paper at a time, no article explained the moderate DOR heterogeneity for this cutoff and we were unable to explain the reasons for this heterogeneity.

HbA1c ≥5.8% (40 mmol/mol) for diagnosis of GDM

Four studies evaluated the threshold of 5.8% (40 mmol/mol) [27, 44, 45, 49], totaling 4,160 pregnant women. HSROC curve showed an AUC of 0.624 (95% CI 0.482 – 0.766; **Figure 4C**. The DOR was 8.54 (95% CI 4.89 – 14.90; I2 =38.3%). Sensitivity ranged from 6% to 27% and specificity from 95% to 100% (**Figure 3**). The pooled sensitivity for these studies was 10.8% (95% CI 5.7% - 19.41%) and the pooled specificity was 98.7% (95% CI 96.2% to 99.5%) (**Table 3**). This meta-analysis showed low heterogeneity thus sensitive analysis was not carried out.

HbA1c ≥6.0% (42 mmol/mol) for diagnosis of GDM

Five studies reported data at the threshold of 6.0% (42 mmol/mol) [27, 29, 44-46], totaling 3,608 pregnant women. HSROC curve showed an AUC of 0.927 (95% CI 0.840 – 1.014; **Figure 4D**). The DOR was 11.40 (95% CI 5.34 – 24.36; I2 =77.0%). Sensitivity ranged from 4% to 47% and specificity from 97% to 100% (**Figure 3**). The pooled sensitivity for these studies was 12.9% (95% CI 5.5% - 27.5%) and the pooled specificity was 98.7% (95% CI 97.6% to 99.3%) (**Table 3**). After re-running the meta-analysis by removing one paper at a time, by removing the Saxena et al [46] study, the DOR heterogeneity was 1.4%. After a careful evaluation, this study was the only one using the WHO 1999 criteria to diagnose GDM instead of the IADPSG criteria, this fact could explain the DOR heterogeneity in this subgroup meta-analysis. However, pooled sensitivity and pooled specificity for HbA1c ≥6.0% (42 mmol/mol) after excluding this study were practically unchanged and were 10.2% (95% CI 7.6% - 13.2%) and 98.8% (95% CI 98.3% to 99.2%), respectively.

Effect of other variables on diagnostic accuracy

We also investigated the effect of different methods of HbA1c measurement and the country of origin of patients to explain the variability among studies. For this analysis, we considered the main HbA1c cut-offs discussed in each article. Four studies used HPLC [27, 44, 48,49]and 4 used immunoassay [29, 45-47]to measure HbA1c. We observed low variability when we pooled studies with HbA1c results based only on HPLC methods (DOR =5.48 (95% CI 3.78 – 7.94; I2 =38.4%). The variability among studies was high when we pooled only immunoassay methods (DOR =8.38 (95% CI 2.79 – 25.1; I2 =88.6%), however when we excluded the study by Saxena et al [46] a low heterogeneity was observed (DOR =4.92 (95% CI 3.12 – 7.75; I2 =11.3%). The heterogeneity was also low when we pooled only studies from Asia [29, 44, 46-49][DOR =4.77 (95% CI 3.55 – 6.40; I2 =38.4%) and absent when we evaluated non-Asian studies [27, 45] [DOR =7.21 (95% CI 4.15 – 12.54; I2 =0.0%)]. There was no data available to investigate the effect of anemia, iron supplementation and presence of variants hemoglobin on results heterogeneity.

Publication Bias

Although investigation of reporting bias in diagnostic accuracy data is not well established, we used the method of Deeks [42], that appears to be most appropriate, which indicated that there was no potential publication bias (p =0.112).

Probabilities post-test

Considering the pre-test probability of 18% for GDM and the PLR and NLR for cutoffs 5.4% (36 mmol/mol), 5.7% (39 mmol/mol), 5.8% (40 mmol/mol) and 6.0% (42 mmol/mol) we calculated the post-test probabilities for GDM applying the Fagan´s nomogram (**Figure 5**). The post-test probabilities were 40% and 12% for HbA1c ≥5.4% (36 mmol/mol) and <5.4% (36 mmol/mol); 55% and 15% for HbA1c ≥5.7% (39 mmol/mol) and <5.7% (39 mmol/mol); 64% and 17% for HbA1c ≥5.8% (40 mmol/mol) and <5.8% (40 mmol/mol); 69% and 16% for HbA1c ≥6.0%(42 mmol/mol) and <6.0% (42 mmol/mol); respectively.

**DISCUSSION**

**Summary of main results**

In this meta-analysis we included 8 studies, covering 6,406 pregnant women, and of those 1,044 were diagnosed with GDM. The diagnostic accuracy of HbA1c was reported at different thresholds ranging from 5.4% (36 mmol/mol) to 6.0% (42 mmol/mol). AUC was 0.825 (95% CI 0.751 – 0.899) with a Q\* value of 0.758, indicating a good level of overall accuracy of HbA1c test. Four studies evaluated the cutoff of 5.4% (36 mmol/mol) [27, 29, 44-45], totaling 2,808 pregnant women. The pooled sensitivity and specificity for these studies was 50.3% (95% CI 24.8% - 75.7%) and 83.7% (95% CI 67.5% to 92.7%), respectively. For a cutoff of 5.7% (39 mmol/mol), five studies presented data [27, 45, 47-49], totaling 3,540 pregnant women. Pooled sensitivity and specificity for these studies was 24.7% (95% CI 10.3% - 48.5%) and 95.5% (95% CI 85.7% to 98.7%), respectively. Four studies evaluated the threshold of 5.8% (40 mmol/mol) [27, 44, 45, 49], totaling 4,160 pregnant women yielding a pooled sensitivity and specificity of 10.8% (95% CI 5.7% - 19.41%) and 98.7% (95% CI 96.2% to 99.5%). Five studies reported data for the threshold of 6.0% (42 mmol/mol) [27, 29, 44-46], totaling 3,608 pregnant women. The pooled sensitivity and specificity for these studies was 12.9% (95% CI 5.5% - 27.5%) and 98.7% (95% CI 97.6% to 99.3%), respectively.

**Our results compared with other reports**

As far as we know, this is the first meta-analysis including a multi-ethnic population to evaluate the accuracy of HbA1c test in the diagnosis of GDM. A recent study in Chinese pregnant women [25] that aimed to establish the overall accuracy of HbA1c for the diagnosis of patients with GDM, after systematic review, included 5,918 controls and 2,812 patients with GDM. Meta-analyzed data in this report showed sensitivity of 0.762 (95% CI 0.746 – 0.777), specificity of 0.917 (95% CI 0.910 - 0.924) and an AUC of 0.93 with a Q\*value of 0.841, indicating a high level of overall accuracy for HbA1c test in the diagnosis of GDM.

In a prospective study that enrolled 1,989 pregnant Taiwanese women [50], the AUC was 0.70 and the optimal HbA1c cut-off point to predict GDM was 5.7% (39 mmol/mol) (sensitivity = 45.2% and specificity = 84.1%). However, the reference test adopted in this study was the two steps OGTT recommended by National Health Institute (NHI). The results are in agreement with this review, showing low sensitivity and relative high specificity for HbA1c to diagnose GDM. Additionally, the study by Li et al [51] reported a positive correlation of HbA1c with blood glucose in pregnancy affected by GDM. They showed an AUC for HbA1c of 0.854 (P<0.01). When HbA1c was 5.43% (36 mmol/mol), sensitivity and specificity were 0.832 and 0.764, respectively. Hanna et al [52] examined the concordance between different criteria for GDM diagnosis and observed an increased proportion of women with an HbA1c ≥6.0% (42 mmol/mol) in the discordant cases. They, then, evaluated the performance of this HbA1c threshold in the diagnosis of GDM and found a similar sensitivity and specificity of HbA1c, around 22% and 97%, respectively, irrespective of the criteria used to diagnose GDM. They concluded that HbA1c test alone is unlikely to replace the OGTT in GDM diagnosis. Indeed, an optimal test to diagnose GDM is still desired. The recent study by Farrar et al [53] evaluated through systematic review a different test strategy for the diagnosis of GDM and concluded that there is insufficient evidence to suggest which strategy is best for diagnosing GDM, although HbA1c data were not included in this study.

**Strengths and weaknesses of the review**

This study was conducted through an extensive and systematic literature search; we included papers from different countries that analyzed different populations of pregnant women. At least two independent reviewers extracted the data and the overall quality of original studies was checked by a QUADAS-2 tool to perform quality assessments and most studies presented low risk of bias and applicability concerns. As limitations for this study, we highlight: First, although we only included studies that measured HbA1c with standardized methods, the individual performance of each laboratory was not available. Second, we observed a high heterogeneity among the studies, mainly regarding data for HbA1c sensitivity. Despite our efforts to analyze and exlpain the heterogeneity among studies, scarcy of data regarding interferent factors, such as anemia, iron supplemmentation and presence of variants hemoglobin in the original papers limited our analyses. However, we were able to draw attention to the likely effect of ethnicity and the use of different criteria for OGTT interpretation. One study used the WHO 1999 criteria [44] and after its exclusion a low heterogeneity was observed. Heterogeneity was also low when we pooled only studies from Asia [29, 44,46-49]and absent when we evaluated non-Asian studies [27,45], pointing to the effect of ethnicity on HbA1c values in different populations [20,21]. All these possible interferences might have affected in different ways HbA1c levels measured by the method used in the primary studies. Third, only one article [27] followed the recommendations and was presented according to the STARD guidelines [33] which may have affected the quality of reporting of the other studies.

**Applicability of ﬁndings to the review question**

To make sense for the results of the meta-analysis and to asses false-error rates, we calculated the post-test probabilities for GDM applying the Fagan´s nomogram, we considered the test performance estimates based on external data from the Metzger et al study [6], with pre-test probability of 18% for GDM and the PLR and NLR for cutoffs 5.4% (36 mmol/mol), 5.7% (39 mmol/mol), 5.8% (40 mmol/mol) and 6.0% (42 mmol/mol). The post-test probabilities for a positive test were 40%, 55%, 64% and 69% for HbA1c ≥5.4% (36 mmol/mol), HbA1c ≥5.7% (39 mmol/mol), HbA1c ≥5.8% (40 mmol/mol) and HbA1c ≥6.0% (42 mmol/mol); respectively. The post-test probabilities for a negative test for these cutoffs were low and ranged from 12 to 17%, like the pre-test probability of 18%. HbA1c results ≥5.4% (36 mmol/mol) increase at least 2-fold the probabilitiy for GDM whereas HbA1c results <5.4% (36 mmol/mol) do not alter the initial probability of GDM.

**CONCLUSION**

Limited evidence provided by the studies included in this review suggests that HbA1c tests, regardless of the threshold used to diagnose GDM, result in few false-positives GDM cases but very high levels of false negative GDM cases, with a high level of specificity across all population groups described here. These findings point to the usefulness of HbA1c cut-offs of 5.7% (39 mmol/mol), 5.8 (40 mmol/mol) or 6.0% (42 mmol/mol) as rule-in test for the diagnosis of GDM. However, it means that irrespective the cut-off adopted, a negative result will require further investigation through a more sensitive test for confirmation of diagnosis. The prognostic value of HbA1c for GDM adverse outcomes needs further evaluation by prospective studies and it is beyond the scope of this review.

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**Table 1.** Characteristics of selected studies.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Country** | **Study design** | **Age (years)** | **Diagnostic criteria**  **75g OGTT** | **HbA1c**  **(%)** | **GDM incidence**  **(%)** | **Pregnancy weeks** | **HbA1c cut-off (%)**‡ | **Total N** | **HbA1c method** |
| Agarwal 2005 | Árab Emirates | Prospective | 26.6 ±5.5 | WHO/ADA | Without GDM 5.95 ±0.75  With GDM 6.0 ±0.81 | 19 by WHO  11 by ADA | 24-28 | 6.0/5.0/ **5.5** | 442 | Immunoassay LX20 SynchronPro |
| Bhavadharini 2017\* | Índia | Cross-sectional | 26.1 ±3.9 | IADPSG | Without GDM 4.9 ±0.5  With GDM 5.2 ±0.5 | 13 | 12-26 | 5.4/**5.8**/6.0 | 1459 | HPLC (Variant II Turbo analyzer) Biorad Laboratories |
| Khalafallah 2016 | Australia | Cross-sectional | 18 - 47 | ADIPS | 4.8 ±0.36 | 12 | 24-28 | **5.4**/5.7/ 5.8/6.0 | 480 | Imunoassay by DCA 2000 Siemens |
| Rajput 2012 | Índia | Cross-sectional | 16 - 30 | ADA/IADPSG | With GDM 5.73 ±0.34 | 7 byADA  24 by IADPSG | 24-28 | **5.95**/5.45 | 607 | Immunoassay Conelab30i |
| Renz 2015† | Brazil | Cross-sectional | 23 - 35 | WHO and/or IADPSG | Without GDM 5.1 ±0.4  With GDM 5.5 ±0.5 | 33 | 22-32 | 5.3/5.7/ **5.8**/6.0 | 262 | HPLC (Variant II Turbo analyzer) Biorad Laboratories |
| Saxena 2017 | Índia | Cross-sectional | 25 ±3.6 | WHO/DIPSI | Without GDM 5.06 ±0.54  With GDM 6.43 ±0.78 | 6.38 | 24-32 | **6.0** | 800 | Immunoassay AU480, Randox reagent |
| Servket 2014 | Turkey | Prospective | 27.9 ±5.2 | IADPSG | Without GDM 5.0 ±0.5  With GDM 5.5 ±0.7 | 16 | 24-28 | 5.2/**5.7** | 339 | Immunoassay Roche Hitachi Tokio |
| Soumya 2015 | Índia | Prospective | No GDM 25.8 ±3.1 GDM 28.6 ±1.2 | IADPSG | Without GDM 5.4 ±0.5  With GDM 6.2 ±0.6 | 9 | 24-28 | 5.3/**5.7** | 500 | HPLC BioRad Laboratories, Hercules CA,USA |
| Ye 2016 | China | Retrospective | No GDM 29.5 (±3.7) GDM 31.6 (±4.3) | IADPSG | Without GDM 4.9 ±0.3  With GDM 5.1 ±0.4 | 21 | 24-28 | 5.3/**5.5**/ 5.7/5.8 | 1959 | HPLC (Variant II Turbo analyzer) Biorad Laboratories |

Data are expressed as mean±SD or range. \*33 pregnant in 1stgestational trimester; †120 pregnant by WHO 1999 diagnostic criteria; ‡ principal HbA1c cut-off in bold; OGTT (Oral glucose tolerance test); ADA (American Diabetes Association); WHO (World Health Organization); IADPSG (International American Diabetes Pregnancy Study Group); DIPSI (Diabetes in Pregnancy Study group India); ADIPS (Australasian Diabetes in Pregnancy Society).

**Table 2.** Quality assessment using QUADAS-2 criteria.

**Checklist QUADAS-2**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Risk of bias | | | | Applicability concerns | | |
|  | Patient selection | Índex test | Reference standard | Flow and timing | Patient selection | Índex test | Reference standard |
| 1. Agarwal 2005 | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Triste sem Preenchimento | ? | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento |
| 1. Bhavadharini 2017 | Rosto Triste sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Triste sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento |
| 1. Khalafallah 2016 | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento |
| 1. Rajput 2012 | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento |
| 1. Renz 2015 | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | ? | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento |
| 1. Saxena 2017 | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento |
| 1. Servket 2014 | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento |
| 1. Soumya 2015 | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento |
| 1. Ye 2016 | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento | Rosto Sorridente sem Preenchimento |

Rosto Sorridente sem Preenchimentolow risk; Rosto Triste sem Preenchimentohigh risk; ? unclear risk.

**Table 3.** Summary of findings.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Review question:** What is the diagnostic accuracy of HbA1c in the GDM diagnosis?  **Population:** Pregnant women in prenatal care, without previous DM, in the third trimester of pregnancy  **Studies:** cross-sectional diagnostic test accuracy studies, cohort studies, reporting 2x2 data  **Index test:** HbA1c  **Reference standard:** 75 g oral glucose tolerance test - OGTT | | | | | |
| **Subgroup HbA1c (%) [mmomol]** | **Studies (N)** | **Pooled Sensitivity (95% CI)** | **Pooled Specificity (95% CI)** | **AUC** | **Interpretation for every 1,000 pregnant women tested**  **Prevalence = 18%** |
| 5.4 [36] | 4 | 0.503 (0.25- 0.76) | 0.837 (0.67 - 0.93) | 0.779 | 91 cases of GDM will be detected, 89 cases will be missed, and there will be 134 false GDM diagnoses |
| 5.7 [39] | 5 | 0.247 (0.10- 0.48) | 0.955 (0.86 - 0.99) | 0.741 | 44 cases of GDM will be detected, 136 cases will be missed, and there will be 37 false GDM diagnoses |
| 5.8 [40] | 4 | 0.107 (0.06- 0.19) | 0.987 (0.96 - 0.99) | 0.626 | 19 cases of GDM will be detected, 161 cases will be missed, and there will be only 11 false GDM diagnoses |
| 6.0 [42] | 5 | 0.129 (0.05- 0.27) | 0.987 (0.98 - 0.99) | 0.927 | 23 cases of GDM will be detected, 157 cases will be missed, and there will be 11 false GDM diagnoses |

AUC, area under the curve; CI, confidence interval.

**Figure 1:** Flowchart of the article selection process.

**Figure 2:** Summary receiver operating characteristic curves (SROC) of HbA1c for all 8 studies.

**Figure 3:** Forest plot of the sensitivity and specificity of HbA1c cut-offs in the diagnosis of GDM. TP = true positive; FP = false positive; FN = false negative; TN = true negative. The blue square depicts the sensitivity and speciﬁcity for each study and the horizontal line represents the corresponding 95% conﬁdence interval for these estimates.

**Figure 4:** Hierarchical summary receiver operating characteristic curves of HbA1c at different cut-off points for GDM: A) 5.4% (36 mmol/mol); B) 5.7% (39 mmol/mol); C) 5.8% (40 mmol/mol) and D) 6.0% (42 mmol/mol).

**Figure 5:** Fagan’s nomograms for HbA1c test, showing posttest probabilities for GDM. (A) HbA1c ≥5.4% (36 mmol/mol); B) 5.7% (39 mmol/mol); C) 5.8% (40 mmol/mol) and D) 6.0% (42 mmol/mol).