Review

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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 glycated hemoglobin (HbA_{1c}) in the diagnosis of gestational diabetes mellitus (GDM) diagnosis.

Methods: We searched MEDLINE, EMBASE, SCOPUS and ClinicalTrials.gov up to October 2018, using keywords related to GDM, HbA_{1c} and diagnosis. Studies were included that were carried out with pregnant women without previous diabetes that assessed the performance of HbA_{1c} (index test) compared to the 75 g oral glucose tolerance test (OGTT) (reference test) for the diagnosis of GDM, that measured HbA_{1c} by standardized methods and presented data necessary for drawing 2×2 tables.

Results: This meta-analysis included eight studies, totaling 6406 pregnant women, of those 1044 had GDM. The diagnostic accuracy of HbA_{1c} was reported at different thresholds ranging from 5.4% (36 mmol/mol) to 6.0% (42 mmol/mol), and the area under the curve (AUC) was 0.825 (95% confidence interval [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 cut-offs of 5.4% (36 mmol/mol), 5.7% (39 mmol/mol), 5.8% (40 mmol/mol) and 6.0% (42 mmol/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 HbA_{1c} methods may have contributed to this heterogeneity. The HbA_{1c} test presents high specificity but low sensitivity regardless of the threshold used to diagnose GDM. These findings point to the usefulness of HbA_{1c} as a rule-in test. HbA_{1c} should be used in association with other standard diagnostic tests for GDM diagnosis.

Keywords: diagnosis; gestational diabetes; HbA_{1c}; 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 cesarean rates and macrosomia [3]. The detection and adequate treatment of this condition reduces the risks for mothers as well as for babies [3–5].

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 as is used for non-pregnant adults

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using the 2 h 75 g OGTT [2]. The UK National Institute for Health and Care Excellence (NICE) recommendations [9] are based on these criteria; however, they recommended a lower cut-off 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 also based on 2 h 75 g OGTT but with lowered thresholds for fasting glucose, 1 h and 2 h glucose. GDM is present if one or more results are altered [10–12]. Since 2013, the WHO has adopted these same IADPSG criteria [2]. According to the ADA, GDM diagnosis can be performed by the one-step 2 h 75 g OGTT using the same threshold diagnostic criteria of IADPSG or the two-step strategy with a 1 h 50 g OGTT screen followed by a 3 h 100 g OGTT for those who screen positive [1].

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

The HbA_{1c} test has been used in clinical practice for monitoring patients with DM since the early 1980s [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 HbA_{1c} measurement (<http://www.ngsp.org/docs/methods.pdf>; accessed 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 HbA_{1c} Standardization developed a reference system for HbA_{1c} [16] and since the mid 1990s, as well as the National Glycohemoglobin Program (NGSP), work to standardize and align HbA_{1c} methods worldwide [17, 18]. Despite all these international efforts, there are still many situations that may affect HbA_{1c} 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 HbA_{1c} values has been raised [20, 21]. HbA_{1c} values are higher in Blacks, Asians and Latinos when compared to White persons. These factors have limited the use of HbA_{1c} in specific cases.

The cut-off of HbA_{1c} 6.5% (48 mmol/mol) is recommended for DM diagnosis in the general population (Expert Committee 2010), and this cut-off is endorsed by the 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 HbA_{1c} values, like glycemia levels, were

significantly associated with all adverse outcomes, and higher levels of maternal HbA_{1c} were related to greater frequency of adverse outcomes [6]. The HbA_{1c} test would be more receptive to this group of patients because of its convenience when compared to the OGTT. However, due to some physiological and analytical factors that might interfere with HbA_{1c} results, it has not yet been included as a diagnostic tool for GDM [1, 18, 19].

During pregnancy, hemoglobin concentrations change overtime, to accommodate the increasing maternal blood volume and the iron needs of the fetus and also there is a decrease in fasting blood glucose levels [2]. Consequently, HbA_{1c} levels are lower in pregnant women than in non-pregnant women. Due to these factors, different reference values are recommended in pregnancy and HbA_{1c} interpretation should consider these factors [22]. In addition, HbA_{1c} is significantly lower in the first trimesters of gestation and HbA_{1c} trimester-specific reference intervals are required throughout pregnancy [23]. HbA_{1c} 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 HbA_{1c} in DMG [25–29]. In a recent meta-analysis with 2812 patients and 5918 controls, which measured HbA_{1c} in pregnant Chinese women, showed that this test is a useful diagnostic tool to confirm GDM [25]. A large cohort study in New Zealand reported that HbA_{1c} ≥5.9% (41 mmol/mol) at the first antenatal visit identified all cases of GDM and was associated with a two-fold risk of congenital anomalies, preeclampsia, shoulder dystocia and a three-fold risk of perinatal deaths [26]. We also showed that HbA_{1c} levels may be a useful diagnostic tool for GDM in pregnant Brazilian women, the HbA_{1c} 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 HbA_{1c} test [27]. Other studies have also highlighted the potential role of HbA_{1c} 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 the HbA_{1c} 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 is in accordance with 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, HbA_{1c} 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 were not complete were removed and the remaining articles were assessed for eligibility. The revision of titles was followed by reading the abstracts for relevance. Finally, the identification of eligible studies was carried out, based on a full reading of the articles selected by at least two researchers.

Study selection

The inclusion criteria were: (1) cross-sectional or cohort studies that assessed the performance of HbA_{1c} (index test) and 75 g OGTT (reference test) for the diagnosis of GDM; (2) the HbA_{1c} 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 with GDM already diagnosed. Exclusion criteria were: (1) studies that did not perform the 75 g OGTT for the GDM diagnosis; (2) review articles; (3) comments, letters and/or editorials; (4) studies with a language other than English, Spanish or Portuguese; (5) articles published before 1996, as from this date on was when the standardization for the HbA_{1c} methods started [16–18]. Three independent reviewers (PBR, FCC and JRTT) decided which studies were included based upon the eligibility criteria. First, we screened the titles of all papers resulting 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 the included reports. Any disagreements concerning study eligibility or data interpretation were resolved through discussion or, if required, a fourth reviewer was consulted (JLC or ALP).

Data collection and analysis

A data extraction form was developed and the following pieces of 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, HbA_{1c} results); (6) test methods (details of methodology and equipment description for the HbA_{1c} test and the 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 2×2 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 (JLC or ALP). 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, 2×2 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 HbA_{1c} 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]. The overall diagnostic accuracy for the HbA_{1c} 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 HbA_{1c} performance for specific cut-offs if four 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 HbA_{1c} cut-offs [39]. The heterogeneity among studies was evaluated by chi-square and Cochran Q analysis, I^2 (measure of inconsistency, when I^2 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, HbA_{1c} 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 2927 records were identified. Of those, 49 studies were assessed for eligibility. After full-text reading, 40 articles were excluded (one for different language, nine for insufficient data, four for different reference test criterion, three studies performed the diagnostic test in the first gestational trimester and 23 did not meet the research question). Lastly, nine studies met our inclusion criteria [27, 29, 43–49], and of these, only one article [43] was excluded from the meta-analysis due to a lack of 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 totaled 6848 pregnant women, who performed the OGTT and HbA_{1c} test in the second or third trimesters of pregnancy for GDM diagnosis, of those 1128 were diagnosed with GDM (15.2%). Table 1 summarizes the characteristics of all selected studies. Three studies had a 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 the 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 1459 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 an unclear risk of bias in flow and timing, as 120 pregnant were diagnosed using the WHO 1999 diagnostic criteria and 142 were diagnosed using the 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 HbA_{1c} cut-offs discussed in each article [27, 29, 44–49]. HbA_{1c} thresholds ranged from 5.4% (36 mmol/mol) to 6.0% (42 mmol/mol). A total of 6406 pregnant women were included in this analysis, of those, 1044 were diagnosed with GDM. Using data from these eight studies, DOR was 6.97

PRISMA 2009 Flow Diagram

Figure 1: Flowchart of the article selection process (from [30]).

(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 the HbA_{1c} threshold on diagnostic accuracy

The forest plot in Figure 3 shows the sensitivity and specificity of HbA_{1c} for the detection of GDM across all eight included studies. For studies reporting accuracy at more than one threshold, 2×2 tables were built for each

cut-off. The cut-offs 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 four studies and their data were included in the forest plots. Table 3 summarizes the accuracy measures for these cut-offs.

HbA_{1c} ≥ 5.4% (36 mmol/mol) for the diagnosis of GDM

Four studies evaluated the cut-off of 5.4% (36 mmol/mol) [27, 29, 44, 45], totaling 2808 pregnant women. The HSROC curve showed an AUC of 0.779 (95% CI

Table 1: Characteristics of selected studies.

Reference	Country	Study design	Age, years	Diagnostic criteria, 75 g OGTT	HbA _{1c} , %	GDM incidence, %	Pregnancy, weeks	HbA _{1c} cut-off, % ^c	Total, n	HbA _{1c} method
Agarwal 2005	Arab 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
Bhavadharini 2017 ^a	India	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	SynchronPro 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	Immunoassay by DCA 2000 Siemens
Rajput 2012	India	Cross-sectional	16–30	ADA/IADPSG	With GDM 5.73 ± 0.34	7 by ADA 24 by IADPSG	24–28	5.95/5.45	607	Immunoassay Conelab30i
Renz 2015 ^b	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	India	Cross-sectional	25 ± 3.6	WHO/DIPS	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	India	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. ^aThirty-three pregnant in 1st gestational trimester; ^b120 pregnant by the WHO 1999 diagnostic criteria; ^cprincipal HbA_{1c} cut-off in bold; OGTT, oral glucose tolerance test; ADA, American Diabetes Association; WHO, World Health Organization; IADPSG, International American Diabetes Pregnancy Study Group; DIPS, Diabetes in Pregnancy Study group India; ADIPS, Australasian Diabetes in Pregnancy Society.

Table 2: Quality assessment using QUADAS-2 criteria.

Study	Checklist QUADAS-2						
	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
1. Agarwal 2005				?			
2. Bhavadharini 2017							
3. Khalafallah 2016							
4. Rajput 2012							
5. Renz 2015				?			
6. Saxena 2017							
7. Servket 2014							
8. Soumya 2015							
9. Ye 2016							

, low risk; , high risk; ?, unclear risk.

Figure 2: Summary receiver operating characteristic curves (SROC) of HbA_{1c} for all eight studies.

0.739–0.819; Figure 4A). The DOR was 5.20 (95% CI 3.33–8.12; $I^2=57.6\%$). 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%–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 ($I^2=0\%$), pooled sensitivity decreased and the pooled specificity was the same (39% [95% CI 33%–44%] and 83% [95% CI 81%–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 cut-off and the results from the primary meta-analysis were considered.

HbA_{1c} ≥ 5.7 (39 mmol/mol) for the diagnosis of GDM

Five studies presented data for cut-off of 5.7% (39 mmol/mol) [27, 45, 47–49], totaling 3540 pregnant women. The 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; $I^2=55.7\%$). 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

HbA_{1c} 5.4%

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bhavadharini 2017	62	147	133	1117	0.32 [0.25, 0.39]	0.88 [0.86, 0.90]		
Khalafallah 2016	15	19	42	404	0.26 [0.16, 0.40]	0.96 [0.93, 0.97]		
Rajput 2012	37	219	6	345	0.86 [0.72, 0.95]	0.61 [0.57, 0.65]		
Renz 2015	54	42	32	134	0.63 [0.52, 0.73]	0.76 [0.69, 0.82]		

HbA_{1c} 5.7%

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Khalafallah 2016	6	2	51	421	0.11 [0.04, 0.22]	1.00 [0.98, 1.00]		
Renz 2015	27	16	59	160	0.31 [0.22, 0.42]	0.91 [0.86, 0.95]		
Servket 2014	14	27	39	259	0.26 [0.15, 0.40]	0.91 [0.87, 0.94]		
Soumya 2015	33	111	12	344	0.73 [0.58, 0.85]	0.76 [0.71, 0.79]		
Ye 2016	37	15	376	1531	0.09 [0.06, 0.12]	0.99 [0.98, 0.99]		

HbA_{1c} 5.8%

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bhavadharini 2017	22	27	173	1237	0.11 [0.07, 0.17]	0.98 [0.97, 0.99]		
Khalafallah 2016	5	1	52	422	0.09 [0.03, 0.19]	1.00 [0.99, 1.00]		
Renz 2015	23	9	63	167	0.27 [0.18, 0.37]	0.95 [0.91, 0.98]		
Ye 2016	26	8	387	1538	0.06 [0.04, 0.09]	0.99 [0.99, 1.00]		

HbA_{1c} 6.0%

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bhavadharini 2017	17	11	178	1253	0.09 [0.05, 0.14]	0.99 [0.98, 1.00]		
Khalafallah 2016	2	1	55	422	0.04 [0.00, 0.12]	1.00 [0.99, 1.00]		
Rajput 2012	17	13	127	450	0.12 [0.07, 0.18]	0.97 [0.95, 0.98]		
Renz 2015	13	3	73	173	0.15 [0.08, 0.24]	0.98 [0.95, 1.00]		
Saxena 2017	24	16	27	733	0.47 [0.33, 0.62]	0.98 [0.97, 0.99]		

Figure 3: Forest plot of the sensitivity and specificity of HbA_{1c} 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.

the pooled specificity was 95.5% (95% CI 85.7%–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 cut-off and we were unable to explain the reasons for this heterogeneity.

HbA_{1c} ≥5.8% (40 mmol/mol) for the diagnosis of GDM

Four studies evaluated the threshold of 5.8% (40 mmol/mol) [27, 44, 45, 49], totaling 4160 pregnant women. The 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%–99.5%) (Table 3). This meta-analysis showed low heterogeneity thus sensitive analysis was not carried out.

HbA_{1c} ≥6.0% (42 mmol/mol) for the diagnosis of GDM

Five studies reported data at the threshold of 6.0% (42 mmol/mol) [27, 29, 44–46], totaling 3608 pregnant women. The 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%–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 HbA_{1c} ≥6.0% (42 mmol/mol) after excluding

Table 3: Summary of findings.

Review question: What is the diagnostic accuracy of HbA _{1c} 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 2 × 2 data. Index test: HbA _{1c} Reference standard: 75 g OGTT						
Subgroup HbA _{1c} % [mmol/L]	Studies (n)	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	AUC	Interpretation for every 1000 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.

this study were practically unchanged and were 10.2% (95% CI 7.6%–13.2%) and 98.8% (95% CI 98.3%–99.2%), respectively.

Effect of other variables on diagnostic accuracy

We also investigated the effect of different methods of HbA_{1c} measurement and the country of origin of patients to explain the variability among studies. For this analysis, we considered the main HbA_{1c} cut-offs discussed in each article. Four studies used HPLC [27, 44, 48, 49] and four used immunoassays [29, 45–47] to measure HbA_{1c}. We observed low variability when we pooled studies with HbA_{1c} 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).

Post-test probabilities

Considering the pre-test probability of 18% for GDM and the PLR and NLR for cut-offs 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 HbA_{1c} ≥5.4% (36 mmol/mol) and <5.4% (36 mmol/mol); 55% and 15% for HbA_{1c} ≥5.7% (39 mmol/mol) and <5.7% (39 mmol/mol); 64% and 17% for HbA_{1c} ≥5.8% (40 mmol/

Figure 4: Hierarchical summary receiver operating characteristic curves of HbA_{1c} 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).

mol) and <5.8% (40 mmol/mol); 69% and 16% for HbA_{1c} ≥6.0% (42 mmol/mol) and <6.0% (42 mmol/mol); respectively.

Discussion

Summary of the main results

In this meta-analysis we included eight studies, covering 6406 pregnant women, and of those 1044 were diagnosed with GDM. The diagnostic accuracy of the HbA_{1c}

test was reported at different thresholds ranging from 5.4% (36 mmol/mol) to 6.0% (42 mmol/mol). The 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 the HbA_{1c} test. Four studies evaluated the cut-off of 5.4% (36 mmol/mol) [27, 29, 44, 45], totaling 2808 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%–92.7%), respectively. For a cut-off of 5.7% (39 mmol/mol), five studies presented data [27, 45, 47–49], totaling 3540 pregnant women. The pooled sensitivity and specificity for these studies was 24.7% (95% CI 10.3%–48.5%) and 95.5% (95% CI 85.7%–98.7%), respectively. Four studies

Figure 5: Fagan's nomograms for HbA_{1c} test, showing post-test probabilities for GDM.
(A) HbA_{1c} ≥ 5.4% (36 mmol/mol); (B) 5.7% (39 mmol/mol); (C) 5.8% (40 mmol/mol) and (D) 6.0% (42 mmol/mol).

evaluated the threshold of 5.8% (40 mmol/mol) [27, 44, 45, 49], totaling 4160 pregnant women yielding a pooled sensitivity and specificity of 10.8% (95% CI 5.7%–19.41%) and 98.7% (95% CI 96.2%–99.5%). Five studies reported data for the threshold of 6.0% (42 mmol/mol) [27, 29, 44–46], totaling 3608 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%–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 the HbA_{1c} test in the diagnosis of GDM. A recent study in pregnant Chinese women [25] that aimed to establish the overall accuracy of the HbA_{1c} test for the diagnosis of patients with GDM, after a systematic review, included 5918 controls and 2812 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 the HbA_{1c} test in the diagnosis of GDM.

In a prospective study that enrolled 1989 pregnant Taiwanese women [50], the AUC was 0.70 and the optimal HbA_{1c} 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 two-step OGTT recommended by National Health Institute (NHI). The results are in agreement with this review, showing low sensitivity and relative high specificity for HbA_{1c} to diagnose GDM. Additionally, the study by Li et al. [51] reported a positive correlation of HbA_{1c} with blood glucose in pregnancy affected by GDM. They showed an AUC for HbA_{1c} of 0.854 ($p < 0.01$). When HbA_{1c} 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 HbA_{1c} $\geq 6.0\%$ (42 mmol/mol) in the discordant cases. They then evaluated the performance of this HbA_{1c} threshold in the diagnosis of GDM and found a similar sensitivity and specificity of HbA_{1c}, around 22% and 97%, respectively, irrespective of the criteria used to diagnose GDM. They concluded that the HbA_{1c} 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 a 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 HbA_{1c} 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 a low risk of bias and applicability concerns. As limitations for this study, we highlight: First, although we only included studies that measured HbA_{1c} 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 HbA_{1c} sensitivity. Despite our efforts to analyze and explain the heterogeneity among studies, scarcity of data regarding interferent factors, such as anemia, iron supplementation and the presence of variants of haemoglobin 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 HbA_{1c} values in different populations [20, 21]. All these possible interferences might have affected in different ways the HbA_{1c} 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 of the results of the meta-analysis and to assess the 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 a pre-test probability of 18% for GDM and the PLR and NLR

for cut-offs 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 HbA_{1c} $\geq$ 5.4% (36 mmol/mol), HbA_{1c} $\geq$ 5.7% (39 mmol/mol), HbA_{1c} $\geq$ 5.8% (40 mmol/mol) and HbA_{1c} $\geq$ 6.0% (42 mmol/mol); respectively. The post-test probabilities for a negative test for these cut-offs were low and ranged from 12 to 17%, like the pre-test probability of 18%. HbA_{1c} results $\geq$ 5.4% (36 mmol/mol) increase at least two-fold the probability for GDM whereas HbA_{1c} results $<$ 5.4% (36 mmol/mol) do not alter the initial probability of GDM.

Conclusions

Limited evidence provided by the studies included in this review suggests that HbA_{1c} tests, regardless of the threshold used to diagnose GDM, result in few false-positive GDM cases but very high levels of false negative GDM cases, with a high level of specificity across all the population groups described here. These findings point to the usefulness of HbA_{1c} cut-offs of 5.7% (39 mmol/mol), 5.8 (40 mmol/mol) or 6.0% (42 mmol/mol) as rule-in tests for the diagnosis of GDM. However, it means that irrespective of the cut-off adopted, a negative result will require further investigation through a more sensitive test for confirmation of the diagnosis. The prognostic value of HbA_{1c} for GDM adverse outcomes needs further evaluation by prospective studies and it is beyond the scope of this review.

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