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Accuracy of screening tests for gestational diabetes mellitus in Southeast Asia

A systematic review of diagnostic test accuracy studies

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Abstract

Background: To investigate the accuracy of screening tests for gestational diabetes mellitus (GDM) in Southeast Asian pregnant women.

Methods: We searched PubMed (MEDLINE), Web of Science, Cochrane Library, ClinicalTrials.gov, Google Scholar, and Google for relevant articles published in English up to November 2018 using search terms related to GDM, screening tests for GDM and diagnostic performance. The studies were independently screened and selected by both authors. The methodological quality of the included studies was independently assessed by quality assessment of diagnostic accuracy studies 2. A hierarchical summary receiver operating characteristic (HSROC) model was created to estimate the HSROC curve. The summary sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were calculated in a meta-analysis using bivariate random-effects model.

Results: A total of 19 studies were included in which the 100 g oral glucose tolerance test (OGTT) and 75 g OGTT were the two common reference standards for diagnosis of GDM. Most points of diagnostic performance in the HSROC 50 g GCT curve compared with the 100 g OGTT reference standard were clustered in the upper left-hand quadrant. The pooled sensitivity and specificity of the 50 g GCT were 79% (95% confidence interval [CI] 64%–89%) and 74% (95% CI 59%–85%), respectively. For the 75 g OGTT reference standard, the non-fasting 2-hour plasma glucose showed quite similar sensitivity the 50 g GCT compared with the 100 g OGTT reference standard. The pooled sensitivities and specificities of the fasting plasma glucose and hemoglobin A1c were 81% (95% CI 76%–86%) and 70% (95% CI 67%–72%), and 80% (95% CI 66%–90%) and 69% (95% CI 58%–78%), respectively.

Conclusion: Our findings indicate that the 50 g GCT using the threshold of 140 mg/dL is a good screening test for identifying GDM at 24 to 28 weeks' gestational age for both high-risk and universal screening strategies in Southeast Asian countries. The non-fasting 2-hour PG, fasting plasma glucose or hemoglobin A1c are alternative choices for screening.

Abbreviations: AUC = area under curve, DOR = diagnostic odds ratio, FPG = fasting plasma glucose, GCT = glucose challenge test, GDM = gestational diabetes mellitus, HbA1c = hemoglobin A1c, HSROC = hierarchical summary receiver operating characteristic, OGTT = oral glucose tolerance test, PG = plasma glucose, WHO = World health organization.

Keywords: diagnostic test accuracy, gestational diabetes mellitus, screening tests, sensitivity, specificity

1. Introduction

Gestational diabetes mellitus (GDM) mostly occurs in the second and third trimesters of pregnancy due to insulin resistance and glucose intolerance during pregnancy.[1,2] GDM has become a global public health concern due to potentially serious short- and long-term effects on both the pregnant women and their infants including pre-eclampsia, neonatal hypoglycemia, fetal growth, fetal macrosomia, and increased risk of developing future

Editor: Milan Perovic.

This research was supported by a Postdoctoral Fellowship from Prince of Songkla University to Sattamat Lappharat and Targeted Research Grants Program of the Faculty of Medicine, Prince of Songkla University to Tippawan Liabsuetrakul. The research funder was not involved in any steps of conducting the study or the decision of publication submission.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Lappharat S, Liabsuetrakul T. Accuracy of screening tests for gestational diabetes mellitus in Southeast Asia: a systematic review of diagnostic test accuracy studies. Medicine 2020;99:46(e23161).

Received: 26 June 2020 / Received in final form: 9 October 2020 / Accepted: 16 October 2020

http://dx.doi.org/10.1097/MD.0000000000023161

diabetes in both mothers and babies.[3–5] The global GDM prevalences range from 1% to 28% depending on population characteristics, ethnicities, genetic factors, and screening and diagnostic methods or criteria used.[2,6,7] Two review articles reported that Non-Caucasians, particularly Asian ethnicities, had higher rates of GDM than Caucasians.[6,7]

The oral glucose tolerance test (OGTT) has been widely used as a reference standard for diagnosis of GDM, and is normally performed at a late gestational age (24–28 weeks) by either a two-step approach with a 50 g glucose challenge test (GCT) followed by a 3-hour 100 g OGTT or a one-step 2-hour 75 g OGTT. The OGTT requires fasting for at least 8 hours before the procedure,[1,8] and; therefore, screening tests with no requirement of fasting are preferred. The use of 50 g GCT has been widely studied as an index test for screening for GDM, but previous studies have reported accuracy inconsistencies with the GDM across the world depending upon the application of the tests, cut-off thresholds, and population characteristics.[3–5] The use of a 75 g glucose load in a non-fasting state (non-fasting 75 g 2-hour PG), following the Diabetes in Pregnancy Study Group of India criteria, has also been recently studied.[9] Due to the shortcomings of glucose loading with its gastrointestinal side effects on pregnant women, the fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) tests have been alternatively used as screening tests for GDM, but their usefulness is still uncertain.[10–16] Apart from maternal investigation using blood plasma, the fetal biometry measured by ultrasonography has been studied for detection of GDM.[17–19]

Although the detection of GDM is crucial and GDM testing is recommended by the World Health Organization (WHO), a recommendation on whether or how to screen GDM is not definitely determined and routine screening is not suggested. The WHO suggests that identification of effective screening strategies for GDM is prioritized for research in low- and middle-income countries.[20] To date, there is a lack of uniformity in screening and diagnostic methods of detecting GDM, even though screening and diagnosis of GDM is currently applied in routine clinical practice. Due to the high prevalence of GDM and its related complications in the WHO Southeast Asia Region,[6,7,18,21] this systematic review aimed to investigate the accuracy of screening tests for screening GDM in Southeast Asian pregnant women.

2. Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis of Diagnostic Test Accuracy: The preferred reporting items for systematic review and meta-analysis of diagnostic test accuracy statement.[22] The review protocol was registered with the International Prospective Register of Systematic Reviews (CRD42018114375) and approved by the Institute Ethics Committee of the Faculty of Medicine, Prince of Songkla University (REC.61-337-18-1).

2.1. Eligibility criteria

We included various types of studies, such as cross-sectional studies, retrospective and prospective cohort studies, or randomized controlled trials, which had been conducted in countries included in the WHO Southeast Asia Region, and the studies had assessed the accuracy of screening tests for gestational diabetes mellitus. Case-control studies were excluded due to selection and performance bias.[23]

We selected studies in which Southeast Asian pregnant women of any gestational age and risk of GDM, who had received screening tests for GDM during their prenatal visits. Those with known diabetes mellitus before pregnancy or having a history of GDM were excluded. Both the 2- and 1-step approaches for screening for GDM regardless of type of index test or reference standard used were considered.

2.2. Search strategy and data sources

We searched PubMed (MEDLINE), Web of Science, Cochrane Library, and ClinicalTrials.gov for relevant articles published in English up to November 2018 using search terms related to GDM, counties in Southeast Asia, the aforementioned index tests and diagnostic performance. All search term details are provided in Appendix 1 (http://links.lww.com/MD/F201) as supplementary material. We also conducted a manual search using Google Scholar and Google after retrieving articles from the database. Duplicate articles were identified and removed before assessing the remaining articles.

2.3. Study selection

Both review authors independently screened the titles and abstracts of all search results that met the eligibility criteria using Rayyan software.[24] In cases where the titles or abstracts had insufficient information to either include or exclude, the full texts were retrieved and assessed independently. Disagreements and discrepancies were resolved through discussion. The number of included and excluded records was mapped with a preferred reporting items for systematic review and meta-analysis flow diagram.[22]

2.3.1. Data extraction and management. An extraction form was developed with the following information: study details (title, first author, year of publication, country); study characteristics (study design, study site, sample size); participants' characteristics (age, gestational age); index tests characteristics (gestational age, type of GDM screening, type of index test, cut-off value); reference standard test characteristics (gestational age, interval time between index test and reference standard test, glucose loading, diagnostic criteria, cut-off value);and study results (GDM prevalence, true-positive, false-positive, false-negative, true-negative. The data from the included studies were extracted independently. When data were detected to be insufficient or inconsistent to construct a 2×2 contingency table,[25] we contacted the authors for further information. Any discrepancies were resolved by discussion and consensus.

2.3.2. Assessment of methodological quality. The two reviewers independently graded the methodological quality of the included studies, using the signaling questions of the Quality Assessment of Diagnostic Accuracy Studies 2 assessment tool for the 4 key domains (patient selection, index test(s), reference standard, and flow and timing). Each domain was assessed for the risk of bias and applicability, for which each study was classified in all domains as "low risk of bias" and "low concern" as having high methodological quality.[26] Differences were resolved through discussion.

2.3.3. Statistical analysis and data synthesis. The sensitivities and specificities at multiple thresholds of an individual index test

with the same set of reference standards were plotted, and then the optimum threshold of each index test was chosen. The data of the selected optimum thresholds of the index tests were analyzed and overall sensitivities and specificities of various index tests with both reference standards were plotted by coupled forest plots.

A hierarchical summary receiver operating characteristic (HSROC) model was constructed to estimate a HSROC curve.[27] The HSROC model provides equivalent summary estimates for sensitivity and specificity and 95% confidence and prediction regions which describe the uncertainty of the summary sensitivity and specificity. The confidence region is related to the summary estimates of sensitivity and specificity jointly in the HSROC space without consideration of between-studies heterogeneity. The prediction region refers to potential values of sensitivity and specificity that predict the summary sensitivity and specificity of a future study reflecting the between-studies heterogeneity.[28]

The summary sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio (DOR) were calculated in a meta-analysis using a bivariate random-effects model.[29,30] The heterogeneity of the studies was estimated by I^2 and visual inspection of forest plots.[31] A meta-regression considering covariates, namely gestational age at screening, country, sample size, diagnostic criteria of reference standard, and prevalence of GDM, was performed. The possibility of publication bias was tested by using Deek funnel plot.[32] A P-value of $<.05$ was considered statistically significant for all analyses, whereas the Deek funnel plot test considered a value of $P < .10$ as statistically significant. The Review Manager Version 5.3 program (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to construct coupled forest plots. Analyses were performed with Stata Version 15.1 software (StataCorp, College station, Texas, USA) using the "midas" and "metandi" commands.

3. Results

3.1. Study selection and study characteristics

Of 286 studies found, 21 studies[14,16,33–51] met the criteria, but the data of 2 studies[36,44] were insufficient to be extracted resulting in a total of 19 studies[14,16,33–35,37–43,45–51] being included in the quantitative analyses. The flow chart of literature screening and selection process is shown in Figure 1. Two common reference standards for diagnosis of GDM, the 3-hour 100 g OGTT and the 2-hour 75 g OGTT, were found. The characteristics of the 11 included studies[33–43] which examined the 100 g OGTT reference standard are shown in Table 1. These studies were conducted in Thailand, India, and Nepal. Of the 11 studies, 10[33–36,38–43] of them used the 50 g GCT test for GDM screening at a gestational age of 24-28 weeks or less. The criteria of the reference standard used for GDM diagnosis were either the Carpenter-Coustan criteria or the National Diabetes Data Group criteria. The characteristics of the 10 included studies[14,16,44–51] using the 75 g OGTT reference standard are shown in Table 2. Most of these studies were conducted in India using a variety of index tests, namely the FPG, non-fasting 2-hour PG, and HbA1c tests, and they were given at a gestational age lower than 24-28 weeks. For diagnosis of GDM the criteria of the International Association of the Diabetes and Pregnancy Study Groups and WHO were used.

3.2. Assessment of methodological quality of included studies

The quality assessment of the included studies is summarized in Figure 2. More than half were at low risk of bias and low applicability concerns in all domains. Of the 21 studies,[14,16,33–51] 14 studies[14,16,33,37–40,43,44,46,48–51] were at low risk of bias for participant selection and 7 studies[34–36,41,42,45,47] were at unclear risk of bias due to insufficient information of exclusion criteria. High applicability concerns of patient selection were found in four studies[33,34,36,41] because only women having positive index tests were tested with a reference test. Thirteen studies[33_37,39_41,43,45,46,48,50] were at low risk of bias for the index test and eight studies[14,16,38,42,44,47,49,51] were at high risk of bias due to either unclearly pre-specified thresholds used or interpreting the results of the index test without being blinded. A low risk of bias for the reference standard was shown in 17 studies[14,16,35,37–40,42–51] while the other four studies[33,34,36,41] were at high risk because the interpretation of the reference standard results was done without being blinded. All studies[14,16,33–51] were judged to have only low applicability concerns for both index test and reference standard. Eleven studies[14,16,35,37,39,40,42,43,46,47,51] were at low risk of bias for the flow and timing of the study and ten studies[33,34,36,38,41,44,45,48–50] were at high risk of bias because of an incomplete number of participants at final analysis, an inappropriate interval between reference standard and index test (over a week), or inconsistency of descriptions in the Results tables and texts.

3.3. Findings of diagnostic test accuracy

Figure 3 presents the overall coupled forest plots of the different index tests compared with the 3-hour 100 g OGTT and the 2-hour 75 g OGTT as reference standards. The sensitivities and specificities of the 50 GCT at the threshold of 140 mg/dL compared with the 3-hour 100 g OGTT ranged from 36% (95% confidence interval [CI] 11%–69%) to 100% (95% CI 88%–100%) and 23% (95% CI 16%–30%) to 92% (95% CI 90%–94%), respectively (Fig. 3A). The sensitivities of the non-fasting 75 g 2-hour PG with the threshold of 140 mg/dL varied from 28% (95% CI 18%–39%) to 98% (95% CI 90%–100%) compared with the 2-hour 75 g OGTT reference standard but specificities were consistently high (Fig. 3B). The sensitivities and specificities of both the FPG and HbA1c were similar, with the variation of their sensitivities better than was found in the non-fasting 75 g 2-hour PG.

The HSROC curve comparing the 50 g GCT and 3-hour 100 g OGTT reference standards is shown in Figure 4. Most points are clustered in the upper left-hand quadrant. The 95% confidence region does not overlap with the diagonal line, but the 95% prediction region does. As there were fewer than four studies comparing the index tests to the 2-hour 75 g OGTT reference standard, the HSROC model could not construct for the HSROC curve.

The pooled diagnostic performances including the DOR of two reference standards with four index tests are shown in Table 3. The pooled sensitivity and specificity of the 50 g GCT with 3-hour 100 g OGTT reference standard with nine studies involving 4,176 pregnant women were 79% (95% CI 64%–89%) and 74% (95% CI 59%–85%), respectively. The area under curve (AUC) was 0.83 (95% CI 0.80–0.86) and the DOR was 10 (95% CI 5–23), indicating high heterogeneity ($I^2 = 99\%$). No publication

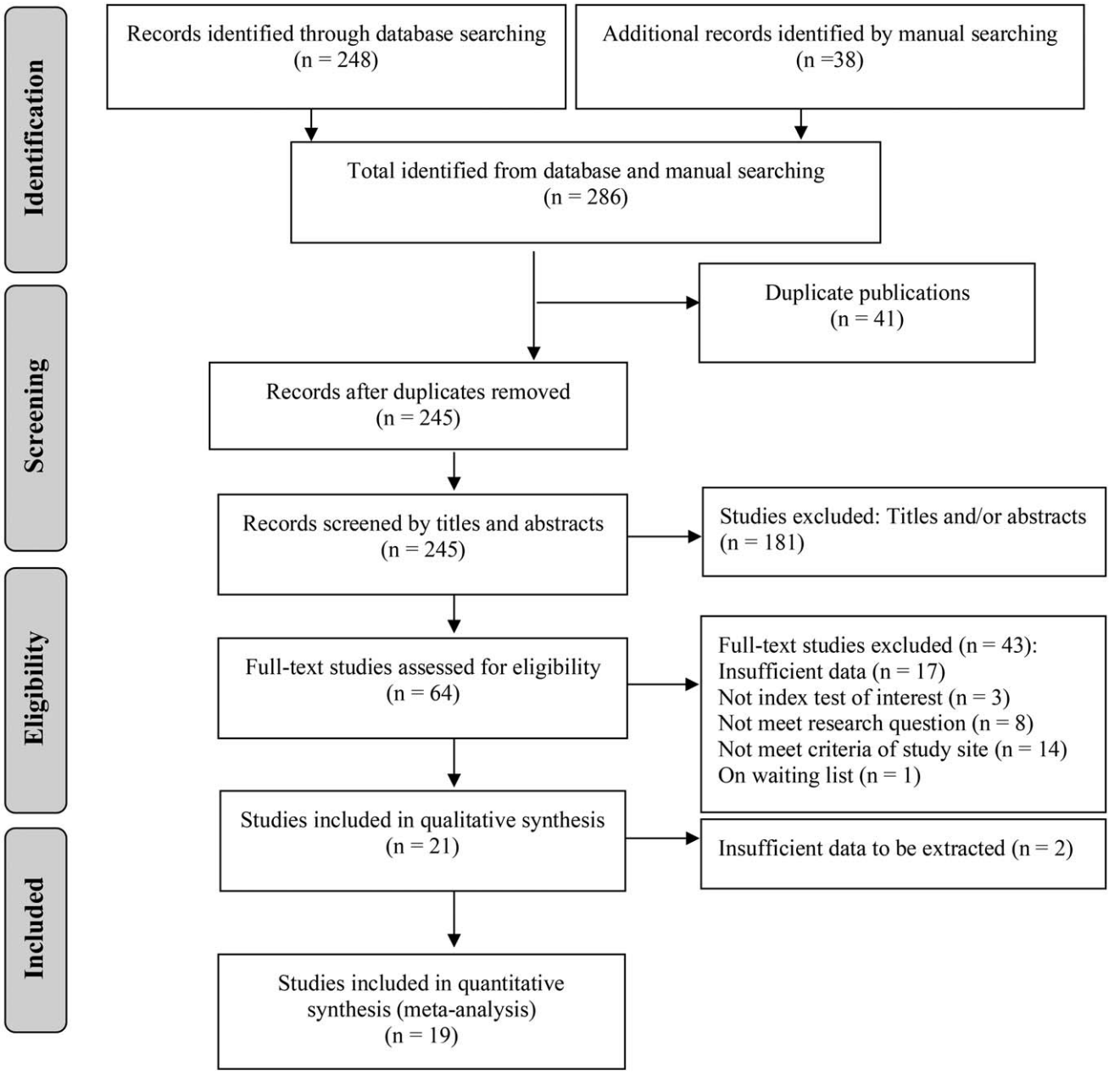

Figure 1. Flow chart of literature screening and selection process.

bias was found ($P = .40$). There were no statistically significant covariates revealed in the meta-regression analysis.

For the 2-hour 75 g OGTT reference standard, the non-fasting 75 g 2-hour PG was examined in 3 studies involving 2,767 pregnant women, and found quite similar sensitivity of the 50 g GCT comparing to the 3-hour 100 g OGTT reference standard. High specificity with an AUC of 0.98 (95% CI 0.96–0.99) and DOR with extremely wide confidence intervals for the non-fasting 75 g 2-hour PG were found. The diagnostic performances and DORs of the FPG and HbA1c tests compared to the 2-hour 75 g OGTT were similar. For the FPG, three studies involving 2,514 pregnant women showed pooled sensitivity and specificity of 81% (95% CI 76% to 86%) and 70% (95% CI 67%–72%), respectively, with a DOR of 10 (95% CI 7–14) with AUC of 0.83 (95% CI 0.79–0.86). The pooled sensitivity and specificity of the HbA1c test in 2 studies involving 1,107 pregnant women were 80% (95% CI 66%–90%) and 69% (95% CI 58%–78%), respectively, with a DOR of 9 (95% CI 5–16) and AUC of 0.81 (95% CI 0.77–0.84). There was no potential publication bias for the aforementioned index tests compared with the 2-hour 75 g OGTT reference standard ($P = .50$). Meta-regression could not be performed due to too few studies to conduct the analysis.

4. Discussion

Two common reference standards, the 3-hour 100 g OGTT and the 2-hour 75 g OGTT were used to diagnosis of GDM, and we found various index tests using the 50 g GCT followed by non-fasting 75 g 2-hour PG, FPG, and HbA1c in GDM screening in Southeast Asia. The majority of studies were found to have a low

Table 1

Characteristics of included studies by 100 g OGTT reference standard.

Study	Country	Study design	Index test	GA (wk)	Index test cut-off	Diagnostic criteria	GDM prevalence	No. of women	Screening group
Jirapinyo 1993[35]	Thailand	Prospective study	50 g GCT	24–28	140–150 mg/dL	NDDG	10.6%	396	High-risk
Puavilai 1993[40]	Thailand	Prospective study	50 g GCT/ HbA1c	24–28	140 mg/dL and 5.6%	NDDG	7.2%	334	Universal
Mathai 1994[38]	India	NA	50 g GCT	24–28	130–150 mg/dL	CC	4.7%	232	Universal
Thitadilok 1995[42]	Thailand	NA	50 g GCT	24–28	140–150 mg/dL	NA	7.6%	304	High-risk
Chanprapaph 2004[34]	Thailand	Retrospective study	50 g GCT	<24–28	140 mg/dL	NDDG	7.1%	411	Universal
Juntarat 2007[36]	Thailand	Diagnostic study	50 g GCT	24–28	130–150 mg/dL	CC	28.6%	598	Universal
Punthumapol 2008[41]	Thailand	Retrospective study	50 g GCT	<24–28	179 mg/dL	NDDG	13.2%	1,114	High-risk
Poomalar 2013[39]	India	Prospective study	50 g GCT/ FPG	<24–28	130–140 mg/dL and 80–95 mg/dL	CC	7.2%	500	Universal
Wutthibenjarassamee 2014[43]	Thailand	Diagnostic study	50 g GCT/ HbA1c	24–28	140 mg/dL and 4.9%–5.1%	NDDG	24.5%	200	High-risk
Basnet 2018[33]	Nepal	Cross-sectional	50 g GCT	<24–28	130–140 mg/dL	CC	5.4%	685	Universal
Khan 2018[37]	India	Prospective study	Non-fasting 75 g 2-h PG	<24–28	140 mg/dL	CC	13.0%	200	Universal

50 g GCT = 50 grams glucose challenge test, 75 g OGTT = 75 grams oral glucose tolerance test, 100 g OGTT = 100 grams oral glucose tolerance test, ADA = American Diabetes Association, CC = Carpenter-Coustan, FPG = fasting plasma glucose, GA = gestational age, HbA1c = Hemoglobin A1c, IADPSG = International Association of the Diabetes and Pregnancy Study Groups, PG = plasma glucose, NDDG = National Diabetes Data Group, NA = non-available, WHO = World Health Organization.

risk of bias and low applicability concerns in all domains. Out review found a wide range of sensitivities of the 50 GCT compared to the 3-hour 100 g OGTT and the non-fasting 75 g 2-hour PG compared with the 2-hour 75 g OGTT at the same threshold of 140 mg/dL. The FPG and HbA1c tests showed similar sensitivities and specificities and lower variations of sensitivities compared to the non-fasting 75 g 2-hour PG. Overall, our review indicates that the 50 g GCT using the threshold of 140 mg/dL is a good screening test for GDM at 24-28 weeks of gestation with high-risk or universal strategies. The non-fasting 75 g 2-hour PG, FPG or HbA1c tests are alternative options, but there were too few studies to come to any statistical conclusion as to their usefulness.

We found the studies focusing on the WHO Southeast Asia Region used one of the two common reference standards of the 100 g OGTT or the 75 g OGTT after fasting for the diagnosis of GDM, which earlier systematic studies also reported.[4,52] Due to a lack of universal consensus regarding glucose load and diagnostic criteria for GDM, the guidelines and recommendations for screening and diagnosing GDM in pregnant women vary.[1,8,20,53] A 3-hour 100 g OGTT has been proposed and used as a reference standard for diagnosis of GDM since the 1960s, which is administered by loading 100 g of oral glucose and measuring the FPG and PG levels at 1, 2, or 3 hours.[1,54] The 2-hour 75 g OGTT test measures FPG and PG levels at 2 hours after loading with 75 g oral glucose. Although the 75 g OGTT test has a lower sensitivity but higher specificity, it was recommended by the WHO in 1999 as the preferred diagnostic test for GDM.[55] This method is applied and used as a one-step test in some countries due to economical and convenient reasons.[37,56]

The 50 g GCT is the most widely used screening test for GDM, used by administering a 50 g glucose load without fasting followed by a determination of PG at one hour.[57] The common threshold of the 50 g GCT compared with the 3-hour 100 g OGTT ranges from 130 to 150 mg/dL,[58,59] which is in accordance with the findings of our included studies. The best common threshold found in our systematic review was 140 mg/dL as recommended in the American Diabetes Association or WHO guidelines.[1,20] We found better pooled sensitivity than specificity with the 50 g GCT test, similar to the results of previous systematic reviews, even though the criteria of the included studies and study settings in those reviews were different

Table 2

Characteristics of included studies by 75 g OGTT reference standard.

Study	Country	Study design	Index test	GA (weeks)	Index test cut-off	Diagnostic criteria	GDM prevalence	No. of women	Screening group
Siribaddana 1998[49]	Sri Lanka	Prospective study	50 g GCT	24–28	140 mg/dL	WHO 1985	5.5%	721	Universal
Senanayake 2006[47]	Sri Lanka	Comparative study	FPG	NA	80–126 mg/dL	WHO 1999	27.7%	271	High-risk
Wijeyaratne 2006[51]	Sri Lanka	Retrospective study	FPG	24–28	80–126 mg/dL	WHO 1999	16.3%	883	High-risk
Rajput 2012[16]	India	NA	HbA1c	24–28	5.45%–5.95%	ADA	7.1%	607	Universal
Mohan 2014[45]	India	Cross-sectional	Non-fasting 75 g 2-h PG	NA	130–150 mg/dL	WHO 1999	8.0%	1,031	Universal
Soumya 2015[14]	India	Prospective study	HbA1c	24–28	5.3%–6.1%	NA	9.0%	500	Universal
Saxena 2017[46]	India	Cross-sectional	Non-fasting 75 g 2-h PG	24–28	140 mg/dL	WHO 1999	6.4%	800	Universal
Tripathi 2017[50]	India	Prospective study	Non-fasting 75 g 2-h PG	24–28	140 mg/dL	WHO 1999	6.7%	936	Universal
Agarwal 2018[44]	India	NA	FPG	24–28	76–92 mg/dL	IADPSG	18.3%	6,520	Universal
Sharma 2018[48]	India	Prospective study	FPG	<24–28	84.5 mg/dL	IADPSG	6.5%	246	Universal

50 g GCT = 50 grams glucose challenge test, 75 g OGTT = 75 grams oral glucose tolerance test, 100 g OGTT = 100 grams oral glucose tolerance test, ADA = American Diabetes Association, CC = Carpenter-Coustan, FPG = fasting plasma glucose, GA = gestational age, HbA1c = hemoglobin A1c, IADPSG = International Association of the Diabetes and Pregnancy Study Groups, NDDG = National Diabetes Data Group, PG = plasma glucose, WHO = World Health Organization.

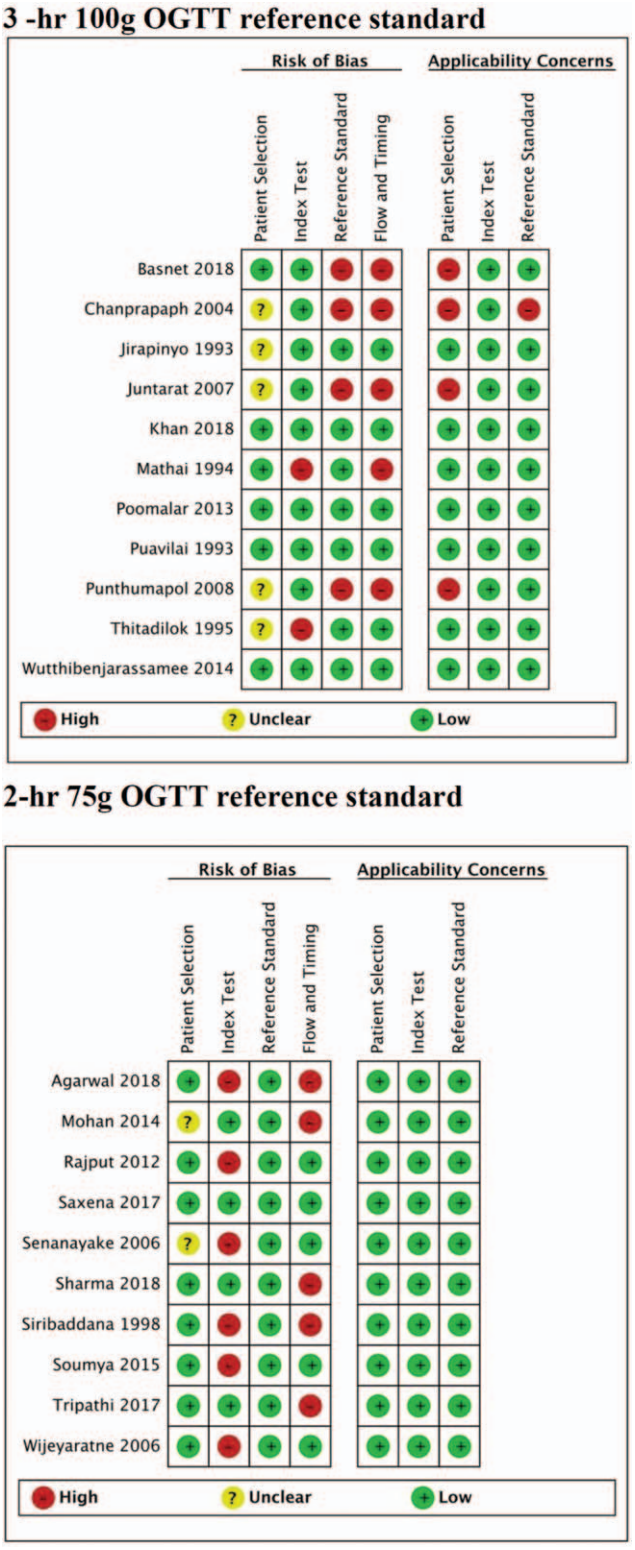

Figure 2. QUADAS-2 risk of bias and applicability assessment of included studies. QUADAS-2 = quality assessment of diagnostic accuracy studies 2.

from ours. Glucose loading may cause nausea and vomiting in some pregnant women, and thus be unpleasant for them.[60] The heterogeneity of the 50 g GCT test was not resolved after meta-regression, though the known covariates were considered. This may be because meta-regression investigates the effects of multiple factors simultaneously thus nine studies may not be sufficient to reveal significant factors.[31]

In the non-fasting 75 g 2-hour PG test, PG is estimated two hours after 75 g glucose loading without overnight fasting.[55] This may cause similar side effect as the glucose loading of the 50 g GCT test. In our study, we found a high variation of summary pooled sensitivity of non-fasting 75 g 2-hour PG, although these results were from three studies only, and all from India.[45,46,50] Due to the high prevalence of GDM in India reported at 16%, the use of non-fasting 75 g 2-hour PG was adapted to be a national guideline of diagnostic test for screening for GDM.[9] We found a high summary pooled specificity with a narrow confidence interval of non-fasting 75 g 2-hour PG, which supports the principle of using it as a diagnostic tool.[9,61] However, the study needs to be repeated with data from other countries for confirmation of clinical applications outside India.

The FPG is a plasma value which is one of abnormal findings indicating the diagnosis of GDM using for both the standard 3-hour 100 g and 2-hour 75 g OGTT before glucose loading.[1,62] There is a consensus concerning the abnormal value that indicates a diagnosis of DM (≥126 mg/dL) in general population.[63] For pregnant women, different classifications of diagnostic criteria for GDM are recommended and various thresholds are used.[8,64,65] Three studies conducted in Southeast Asia were found in our review which found that 84.5 to 85.0 mg/dL was the same common screening threshold and gave the optimum pooled sensitivity and specificity compared to the 2-hour 75 g OGTT.[47,48,51] The thresholds of FPG for screening GDM in previous studies varied from 80 to 90 mg/dL and showed a high variation of sensitivities and specificities.[12,60] Compared with the same threshold of 85 mg/dL, the pooled diagnostic performance of FPG in our review was lower than in a cohort study conducted in Brazil.[66]

The HbA1c is generally used in clinical practice to diagnose and monitor DM.[67] Owing to its properties and convenience (non-glucose loading and non-fasting), there has been substantial interest in using it as an alternative measurement for GDM screening.[68] Our review found two studies conducted in India with thresholds of 5.45% and 5.7% which showed optimum pooled sensitivity and specificity comparable to the FPG test.[14,16] A previous systematic review including eight studies from various countries showed different thresholds of HbA1c ranging from 5.4% to 6.0% with low sensitivity and high specificity for screening for GDM.[69] Although the pooled sensitivities and specificities of both FPG and HbA1c were similar to the 50 g GCT test in our review, there was evidence from only 2 or 3 included studies thus more studies using the same thresholds are required for comparisons of multiple tests to identify the suitable threshold and index test for screening GDM in the future.

The diagnostic performances of screening tests for GDM from the included studies in our review were almost all at a low risk of bias and applicability concerns. Nonetheless, there were some limitations. First, we considered high prevalence of GDM in Southeast Asia, therefore, it may be limited for generalizability. Second, a variation of thresholds was presented in each index test and we selected the optimal thresholds for our analyses which might have introduced unexpected selection bias due to our restriction process. Third, there were only a small number of studies in our meta-analyses, which mean it was difficult to perform sub-analyses to reduce heterogeneity among the studies.

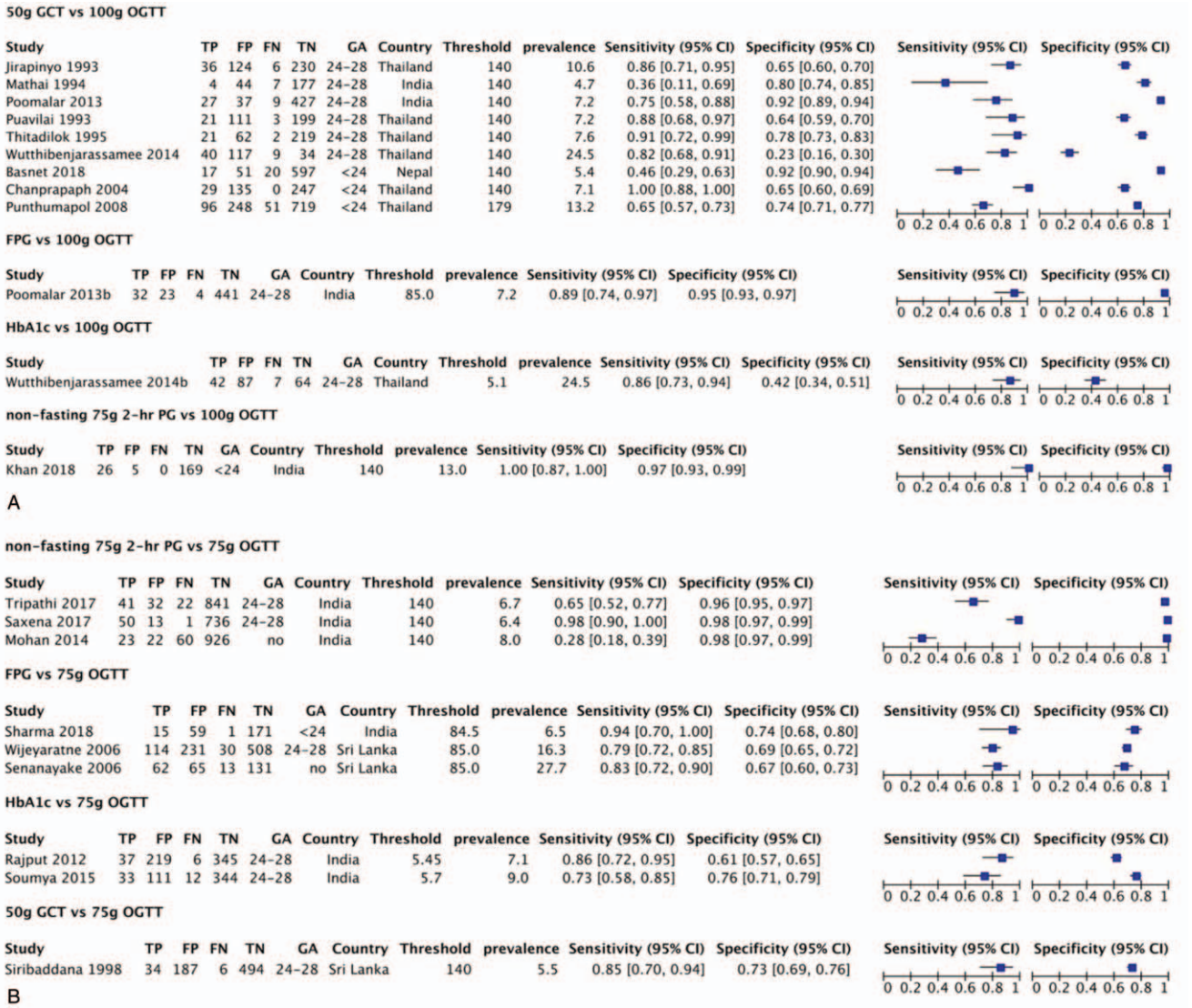

Figure 3. Coupled forest plots of index tests (50 g GCT, FPG, HbA1c and non-fasting 75 g 2-hr PG) for GDM screening with 100 g OGTT reference standard (A) and 75 g OGTT reference standard (B). FPG = fasting plasma glucose, GCT = glucose challenge test, HbA1c = hemoglobin A1c, OGTT = oral glucose tolerance test.

Finally, comparisons of multiple tests could not be performed again due to too few studies.

5. Clinical implications

Our study confirms that the 50 g GCT using the threshold of 140 mg/dL is the most useful screening tests for GDM in Southeast Asian pregnant women. Although the non-fasting 75 g 2-hour PG test is used widely in India, it is more commonly used as a diagnostic test rather than a screening tool. Both the FPG and HbA1c tests can be alternative methods in cases where glucose loading is not feasible. However, the number of included studies was small in our review, and more well-designed studies for diagnostic accuracy of screening tests for GDM are still required.

Table 3

Summary of findings.

Reference standard	Index test	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)	DOR (95% CI)	AUC
100 g OGTT	50 g GCT	0.79 (0.64, 0.89)	0.74 (0.59, 0.85)	3.00 (1.90, 4.70)	0.29 (0.16, 0.50)	10 (5, 23)	0.83
75 g OGTT	Non-fasting 75 g 2-h PG	0.76 (0.23, 0.97)	0.97 (0.96, 0.98)	30.3 (13.50, 68.00)	0.25 (0.04, 1.51)	123 (9, 1,610)	0.98
	FPG	0.81 (0.76, 0.86)	0.70 (0.67, 0.72)	2.7 (2.40, 3.00)	0.27 (0.21, 0.35)	10 (7, 14)	0.83
	HbA1c	0.80 (0.66, 0.90)	0.69 (0.58, 0.78)	2.6 (2.00, 3.30)	0.29 (0.17, 0.48)	9 (5,16)	0.81

50 g GCT = 50 grams glucose challenge test, 75 g OGTT = 75 grams oral glucose tolerance test, 100 g OGTT = 100 grams oral glucose tolerance test, AUC = area under curve, DOR = diagnostic odds ratio, FPG = fasting plasma glucose, HbA1c = hemoglobin A1c, LR+ = positive likelihood ratio, LR– = negative likelihood ratio, PG: plasma glucose.

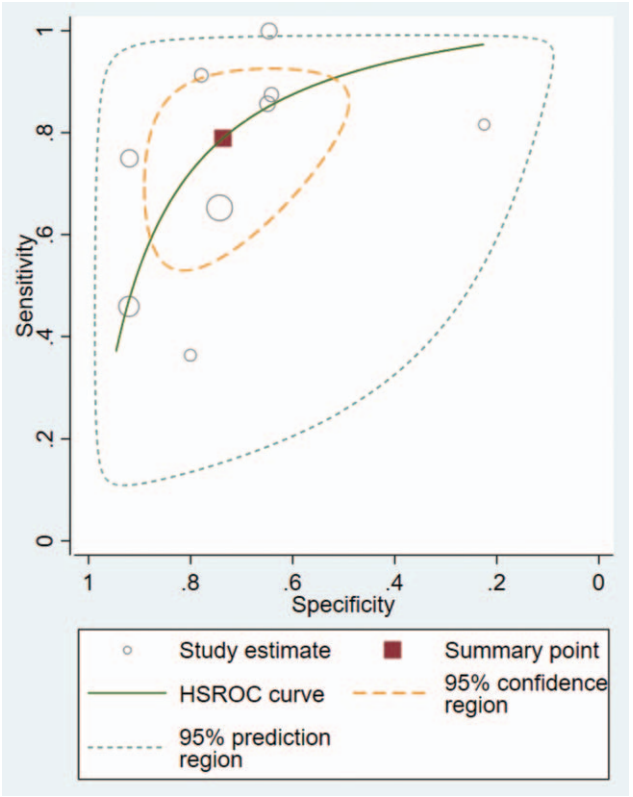

Figure 4. Hierarchical summary receiver operating characteristic (HSROC) curve of 50 g GCT with 100 g OGTT reference standard. GCT = glucose challenge test, OGTT = oral glucose tolerance test.

6. Conclusions

The 50 g GCT with the threshold of 140 mg/dL at 24 to 28 weeks of gestational age is a good screening test for identifying GDM at 24 to 28 weeks' gestation for both high-risk and universal screening strategies in Southeast Asian countries. The non-fasting 75 g 2-hour PG test had better specificity than sensitivity, thus, it should be a diagnostic test rather than a screening test. Although both the FPG and HbA1c tests have high sensitivities and thus may be considered as alternative options for GDM screening, they still lack guidelines and threshold supports. However, all screening tests need to be confirmed by the appropriate reference standard.

Author contributions

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