Abstract. – OBJECTIVE: Fasting plasma glucose (FPG) is suggested as a potential screening test for further confirmatory testing by oral glucose tolerance test (OGTT) for diagnosing gestational diabetes mellitus (GDM). The diagnostic accuracy of FPG has been investigated in several studies with varying results. This meta-analysis is done to evaluate the diagnostic accuracy of FPG for the screening of GDM.

MATERIALS AND METHODS: We conducted a systematic search for all studies reporting the diagnostic accuracy of FPG with OGTT as the reference standard in the databases of Medline, Scopus, Cochrane and Embase from inception till January 2020. Quality assessment of diagnostic accuracy studies-2 tool was used to assess the quality of trials.

RESULTS: 29 studies with 74,481 patients were included. Eleven studies used the cut-off values of 92 mg/dl for FPG to diagnose GDM, whereas 10 studies used the value of 92 mg/dl. The pooled sensitivity and specificity of FPG for cut-off ≥92 mg/dl was 68.6% (95% CI: 51.8%-81.9%), and 93.2% (95% CI: 80.5%-97.8%) respectively. The AUC was 0.88 (95% CI: 0.79-0.94). The pooled sensitivity and specificity of FPG for cut-off ≥90 mg/dl was 58.5% (95% CI: 41.1%-73.9%), and 89.2% (95% CI: 78.5%-94.9%) respectively. The AUC was 0.83 (95% CI: 0.75-0.91). The overall quality of studies was moderate.

CONCLUSIONS: To summarize, our study found that FPG may have a role in the screening of GDM among pregnant women with satisfactory sensitivity and specificity at a cut-off of 92 mg/dl. Further studies exploring its accuracy in different ethnic populations in reference to a standard OGTT are required to strengthen the evidence.

Key Words: Fasting plasma glucose, Gestational diabetes mellitus, Meta-analysis, Validation studies.

Introduction

Gestational diabetes mellitus (GDM) is one of the most common conditions responsible for adverse maternal and foetal outcomes during pregnancy. World Health Organization (WHO) has stated that about 16% of pregnant women are affected by GDM worldwide. However, it has a wide geographical variation with the prevalence ranging from 1-25%. It is usually apparent in the second half of pregnancy and occurs due to extreme physiologic insulin resistance. Early diagnosis and management of GDM are extremely essential as it can lead to several maternal and perinatal complications of varying severity such as neonatal hypoglycaemia, birth injuries, macrosomia, shoulder dystocia, respiratory distress syndrome, childhood obesity, and perinatal mortality.

Despite the worldwide prevalence and serious nature of the disease, there is a lack of a universally accepted screening test for GDM. Screening tests and diagnostic criteria vary significantly between clinicians, as well as in different geographical areas. The American College of Obstetricians and Gynaecologists (ACOG) and the American Diabetes Association (ADA) recommended that all the pregnant women regardless of the presence or absence of risk factors should be tested by oral...
glucose tolerance test (OGTT) between the 24 and 28th gestational week for the screening of GDM. Early screening is recommended for patients with the presence of risk factors6-8. There is evidence suggesting clinically significant improvements in maternal or neonatal outcomes using the standard OGTT criteria to diagnose GDM, following these criteria leads to a significant increase in healthcare costs, non-user friendly and poorly reproducible. However, the performance of OGTT is known to vary in different geographical centers depending upon the testing resources. The test also leads to a significant burden on the healthcare resources requiring infrastructure and high costs9,10.

Fasting plasma glucose (FPG) has been widely used as a screening test for GDM owing to several advantages like low cost, universal availability, ease of the procedure and reproducibility. It has been primarily used to screen for the presence of overt diabetes in the first antenatal visit11. It is also suggested that FPG could be used in the screening of pregnant women to further undergo an OGTT for the final diagnosis of GDM. High accuracy of FPG could ease the burden on laboratories and save the resources, as the carrying out a 2-hour 75 g OGTT can be demanding in large populations and limited-resource settings. To date, several studies have evaluated the sensitivity and specificity of FPG for the screening of GDM but with wide variation amongst different geographical regions in the world12-14. Thus, there is a need to establish evidence on the diagnostic accuracy of FPG and delineate the optimal cut-off for the maximum diagnostic accuracy of this test for GDM. To the best of our knowledge, there have been no systematic efforts to synthesize evidence evaluating the diagnostic accuracy of the FPG test. Hence, the aim of the current meta-analysis was to evaluate the diagnostic accuracy of FPG and identify optimal cut-off for the diagnosis of GDM.

Materials and Methods

Inclusion Criteria
We included all types of studies examining the diagnostic accuracy of FPG for GDM. Studies using OGTT as the reference standard were eligible for our review. Studies also should report sensitivity and specificity values or provide data to calculate the same. We included only full text articles while unpublished studies were omitted. Studies with sample size less than 10 or case reports were excluded. Studies not reporting relevant data were also excluded.

Search Strategy
A systematic electronic search was performed in the following databases: Medline, Scopus, Cochrane Library, and Embase. Medical subject headings (MeSH) along with free text terms were applied for carrying out the search. Example of such terms were “Validation Studies”, “Gestational Diabetes Mellitus”, “Fasting Plasma Glucose”, “Oral Glucose Tolerance Test”, “Hyperglycaemia”, “Pregnancy”, “Sensitivity”, “Specificity”, “Diagnosis”, and “Diagnostic Accuracy Studies”. The time limit for the search was from inception to January 2020 without any language restriction. Reference list of primary studies was hand searched to find any other relevant articles to be included in the review.

Selection of Studies
Primary screening of title, keywords, and abstracts was performed by two authors independently. Full-text articles were retrieved for the relevant studies. Secondary screening of the retrieved articles was performed by two authors independently and included the studies satisfying the inclusion criteria. Disagreements during the selection of studies were resolved either via consultation with the third author or through consensus.

Data Extraction and Management
The primary investigator performed the data extraction for obtaining the characteristics of the studies. We extracted the following components: study setting, study design, inclusion and exclusion criteria, reference standards, index test, the total number of participants, patient comorbidities, mean age, sensitivity, and specificity values. The extracted data were entered into STATA software. A comparison of the data in the review and the study reports was done to double-check for the correct entry. The study outcomes measures were: sensitivity, specificity, diagnostic odds ratio (DOR), likelihood ratio positive (LRP), likelihood ratio negative (LRN).

Risk of Bias Assessment in Included Studies
Quality assessment of diagnostic accuracy studies-2 (QUADAS-2) tool was utilized to evaluate the risk of bias by two independent investigators9. It consists of the following domains: patient selection bias, conduct and interpretation of index test and reference standard, the time interval of outcome assessments. The studies were graded as low, high, or unclear based on the presence of any bias.
Statistical Analysis

Meta-analysis was done using STATA 14.2 software (StataCorp, CollegeStation, TX, USA). We obtained the pooled value of sensitivity, specificity, LRN, LRP, and DOR for the FPG using the bivariate meta-analysis method for various cut-offs. The summary receiver operator characteristic curve (sROC) was constructed in which area under the curve (AUC) was obtained. AUC value closer to 1 is indicative of better diagnostic value. We identified the optimal cut-off for diagnosing GDM based on this AUC value.

Forest plot was used to graphically represent the study-specific and pooled estimates of sensitivity and specificity for each of the cut-offs of FPG. The clinical value of the FPG was determined by the LR scattergram for the different cut-offs used in the studies. The probability that a patient has GDM was tested using the Fagan plot. Heterogeneity was assessed graphically using bivariate boxplot and tested using chi-square and I² statistic. Source of heterogeneity was explored with meta-regression using study-related covariates such as study design, year of publication, sample size, study region, quality-related factors. Publication bias was tested using Deek’s test and graphically depicted by the funnel plot. The analysis was performed using the metandi command package.

Results

Selection of Studies

On systematic search of literature a total of 3930 records were found, of which 1497 studies were from Medline, 1102 from Scopus, 896 from Embase, and 441 from the Cochrane library. After the first stage of screening, 298 studies based on relevance were retrieved. The full text of these studies was extracted for assessing as per the eligibility criteria. Finally, 29 studies with 74,481 participants satisfying the inclusion criteria were included (Figure 1).
Characteristics of the Included Studies

Characteristics of the included studies are described in Table I. Majority (19 studies) of the included studies were prospective studies. The mean age of the participants ranged from 16.1 to 32.1 years. In total, 74,481 participants were assessed in the included studies with sample size varying from 18 to 29,251. Eleven studies used the cut-off values of ≥92 mg/dl for FPG to diagnose GDM, whereas 10 studies used the value of ≥90 mg/dl. All the included studies have performed standard OGTT as a reference standard. The time interval between the index test and reference standard varied from 2 hours to 20 weeks.

Methodological Quality of the Included Studies

Figure 2 depicts the assessment of the risk of bias among the included studies. A high risk of patient selection bias was found in almost 20% of the included studies. 13 out of 29 studies had a high risk of bias in conduct and interpretation of the index test. All the studies had a low risk of bias in the conduct and interpretation of reference standards. 19 studies had low risk of bias in patient flow and interval between index tests and reference standards.

Diagnostic Performance of Fasting Plasma Glucose (FPG) with a Cut-Off of ≥92 mg/dl

In total, 11 studies reported the diagnostic accuracy of FPG with a cut-off of ≥92 mg/dl for GDM. The pooled sensitivity and specificity of FPG for cut-off ≥92 mg/dl was 68.6% (95% CI: 51.8%-81.9%), and 93.2% (95% CI: 80.5%-97.8%) respectively (Figure 3A). The DOR was 29.84 (95% CI: 6.68-133.18). LRP was 10.04 (95% CI: 3.12-32.34) and LRN was 0.33 (0.20-0.56). LRP and LRN values are in the right upper quadrant of the LR scattergram indicating that the FPG can be used for confirmation but not for the exclusion (Figure 4A). The AUC was 0.88 (95% CI: 0.79-0.94) indicating a higher diagnostic performance of FPG using the cut-off ≥92 mg/dl (Figure 5A). Fagan's nomogram (Figure 6A) showed good clinical utility of FPG with cut-off ≥92 mg/dl for GDM diagnosis, as the post-test probability (Positive=77%; Negative=10%) was significantly different from pre-test probability (25%).

There was considerable heterogeneity with a significant chi-square test ($p<0.001$) and an I$^2$ value of 100%. Bivariate box plot (Figure 7A) found 2 out of 11 studies outside the circle implying the possibility of between-study heterogeneity. Figure 8A shows the meta-regression results which indicates that none of the study related factors were responsible for between-study heterogeneity ($p>0.05$). The funnel plot was symmetrical (Figure 9A) indicating the absence of publication bias and it was confirmed by non-significant Deek's test ($p=0.72$).

Diagnostic Performance of Fasting Plasma Glucose (FPG) with a Cut-Off of ≥90 mg/dl

In total, 10 studies reported the accuracy of FPG with cut-off of ≥90 mg/dl for the diagnosis of GDM diagnosis. The pooled sensitivity and specificity of FPG for a cut-off ≥90 mg/dl was 58.5% (95% CI: 41.1%-73.9%), and 89.2% (95% CI: 78.5%-94.9%) respectively. (Figure 3B). The DOR was 11.65 (95% CI: 3.64-37.26). LRP was 5.42 (95% CI: 2.36-12.41) and LRN was 0.46 (0.30-0.72). LRP and LRN values are in the right lower quadrant of LR scattergram indicating that the FPG can neither be used for confirmation nor exclusion (Figure 4B). The AUC was 0.83 (95% CI: 0.75-0.91) indicating higher diagnostic performance of FPG using the cut-off ≥90 mg/dl (Figure 5B). Fagan's nomogram (Figure 6B) showed limited clinical utility of FPG with cut-off ≥90 mg/dl for GDM diagnosis, as the post-test probability (Positive=45%; Negative=7%) was significantly different from pre-test probability (13%).

There was considerable heterogeneity with a significant Chi-square test ($p<0.001$) and an I$^2$ val-
A bivariate box plot (Figure 7B) found 1 out of 10 studies outside the circle implying the possibility of between-study heterogeneity. Figure 8B shows the meta-regression results which indicates that none of the study related factors were responsible for between-study heterogeneity ($p>0.05$). The funnel plot was symmetrical (Figure 9B) indicating the absence of publication bias and it was confirmed by non-significant Deek’s test ($p=0.09$).
<table>
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<th>First author and year</th>
<th>Country</th>
<th>Study design</th>
<th>Sample size</th>
<th>Type of diagnostic modality</th>
<th>Gold standard comparator</th>
<th>Cut-off for diagnosis</th>
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Table I. (Continued). Relationship between COVID-19 transmission and weather parameters.

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Diagnostic Performance of FPG Using Other Optimal Cut-Offs

In our review, 8 out of 29 studies have used differing cut-offs with two studies reported 91 mg/dl as optimal cut-off while each of the other studies reported 81 mg/dl, 83 mg/dl, 84.5 mg/dl, 86 mg/dl, 86.8 mg/dl, and 89 mg/dl as the optimal cut-off respectively. Hence, the pooled estimate could not be obtained for any of these cut-offs. However, sensitivity and specificity ranged from 60-80% for most of these cut-offs in these studies.

Discussion

Owing to several maternal and fetal complications attributed to GDM, the importance of screening and adequately managing the disease cannot
be underestimated. Currently, universal screening is recommended by the majority of the available guidelines for accurately diagnosing GDM in a given population. However, it is estimated that in countries with limited health-care resources, lack of universal screening can risk missing up to 43% of GDM patients. While OGTT is the gold standard diagnostic test for GDM, it is associated with several potential problems. It is recommended that OGTT be performed between 24-28 weeks of gestation. The absence of regular early ultrasounds and inconsistent antenatal consultations can lead to difficulties in the accurate planning of OGTT. Furthermore, the high costs, laboratory requirement is another limitation. Thus screening all patients with OGTT can be difficult. FPG has been suggested as a screening test for GDM as it is less time consuming and user-friendly and can reduce the health-care costs involved with universal OGTT testing. However, it is important to determine the diagnostic performance and optimal cut-off of FPG in the screening of GDM. Hence, the current review was conducted to estimate the diagnostic accuracy of FPG as a screening test for GDM.

Figure 5. SROC Curve for FPG in the screening of GDM.

Figure 6. Fagan nomogram evaluating the overall value of FPG for the diagnosis of GDM.
In an ideal scenario, a good screening test should have high sensitivity i.e., low false negatives to enable inclusion of all patients with the disease. Secondly, the test should have high specificity i.e., low false positive so that the final diagnosis is confirmed by the diagnostic test. On a systematic review of the literature, we found that several different cut-off values of FPG have been used by the included studies for diagnosing GDM. In an attempt to better clarify current evidence we carried out separate assessments of the diagnostic accuracy of FPG for these different cut-offs. Most studies assessed the accuracy of cut-offs of 92 mg/dl or 90 mg/dl for FPG. Out of these two, the better cut-off for diagnosing GDM was found to be 92 mg/dl with a pooled sensitivity of 68.6% and a pooled specificity of 93.2% with a higher diagnostic value (AUC=0.88). In comparison, the sensitivity and specificity of FPG for cut-off ≥90 mg/dl were 58.5%, and 89.2% respectively. The diagnostic accuracy of FPG (92 mg/dl) was found to be somewhat similar to the diagnostic accuracy of HbA1c for the screening of GDM. In a meta-analysis of 41 studies, Tian et al have reported the sensitivity of HbA1c to be 76.2% and specificity to be 91.7% when used as a screening test for GDM. The pooled accuracy of ≥92 mg/dl FPG was also similar to the use of other predictive biomarkers such as circulating adiponectin, leptin, and genetic biomarkers.

Other accuracy parameters also favoured 92 mg/dl FPG value as the optimal cut-off for diagnosing GDM. In LR scattergram, LRP and LRN occupied the right upper quadrant indicating that the investigation can be used as a test for confirmation of GDM but not for exclusion. The clinical utility of FPG was also better for this cut-off as Fagan’s nomogram showed that a significant increase in the post-test probability compared to pre-test probability. However, while inferring these results, we must consider the quality standards and differences in methodology of the included studies influencing the summary findings. Hence, we evaluated the presence of heterogeneity between the included studies. There was significant heterogeneity among the included studies with significant chi-square test and I² statistic. This can be attributed to the difference in ethnicity of the study populations, the presence of different risk factors amongst the included patients, as well as to the difference in OGTT periods amongst the included studies. However, on further exploration of the source of heterogeneity via meta-regression, we found none of the study related factors to have a significant influence on the between-study variability. Deek’s test and funnel plot results showed that there was no publication bias among the studies reporting diagnostic accuracy of FPG using either of the two cut-offs.

This study has the following strengths. A large number of studies (29 studies with 74,481 patients) were included in our review to evaluate the diagnostic accuracy of FPG as a screening test for GDM. To the best of our knowledge, no other study has conducted a meta-analysis for the same. We also found non-significant publication bias which adds more credibility to the results obtained in our review.

However, this study had some limitations. First, we found some studies to have a high risk of bias and which might have influenced the final estimates. In addition, we have found significant
heterogeneity between the studies included in the review. This limits the study’s ability to interpret the pooled results. However, we tried to overcome this limitation by exploring the potential source of heterogeneity among the included studies. But we could not find any study-related factors responsible for this significant heterogeneity. Secondly, not all studies used the same cut-off value of FPG for the screening of GDM. Hence, the number of studies in the meta-analysis was much less than the total number of included studies. Thirdly, the reference standard of OGTT used in the included studies had variations. This could also have influenced our study results. Lastly, the diagnostic accuracy of any screening test for GDM can depend on several other factors like the ethnicity of the population, timing of the test, and the presence of risk factors for GDM. The influence of these variables could not be judged in our analysis.

Despite these limitations, this study provides valuable insights regarding the diagnostic accuracy of FPG for screening pregnant women in diagnosing GDM. Though FPG had satisfactory sensitivity and specificity, it cannot meet the SnNout triage test criteria for sensitivity and the SpPin criteria for the specificity of a diagnostic test. This means that FPG cannot rule in or rule out a woman to be free from GDM with utmost certainty. These findings are in line with the International Guidelines for the diagnosis of GDM, which suggests OGTT as the first-line modality to rule out a woman from GDM. However, FPG can be used as a preliminary screening test and pregnant women with higher FPG value can then undergo OGTT for confirmation or exclusion of GDM. This shall reduce the time spent in the healthcare facility by pregnant women and also reduces the healthcare costs for the process of screening for GDM.

**Conclusions**

To summarize, our study found that FPG may have a role in the screening of GDM among pregnant women with satisfactory sensitivity and specificity at a cut-off of 92 mg/dl. Further studies exploring its accuracy in different ethnic populations in reference to a standard OGTT are required to strengthen the evidence.
Figure 9. Funnel plot for publication bias.
References


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