An Appraisal of Screening Methods for Gestational Diabetes Mellitus

M. Najimudeen¹* and K. Sachchithanantham¹

¹Melaka Manipal Medical College, Malaysia.

Authors’ contributions

This work was carried out in collaboration between both authors. Both authors MN and KS designed the study, involved in the literature search and prepared the article. Both authors read and approved the final manuscript.

ABSTRACT

The importance of screening and diagnosis of gestational diabetes mellitus (GDM) is universally accepted but there is controversy and uncertainty about the most suitable method of screening among various populations. The majority of the patients are asymptomatic. After nearly 60 years of research the screening and diagnosis of GDM, universal screening evades uniform acceptance and remains debatable. Multiple studies, numerous global consensus conferences and several multicenter trials had not identified the unique procedure. Surprisingly still there is uncertainty regarding the most effective method of screening among various populations. The prevalence of GDM varies from less than 1% to more than 10%. It is increasing due to dietary habits, overweight, maternal age, ethnicity, family history and past history. Prevalence vary due to the use of a wide range of definitions and diagnostic test criteria, as well as variations across regions and ethnic groups. The merits of available screening methods such as urine testing for glycosuria, 50g glucose challenge test (GCT), random blood sugar testing, fasting blood glucose (FBS), estimation of glycosylated haemoglobin, fructosamine, 75g oral Glucose Tolerance Test (75g OGTT) and two step approach (Combination of methods) are analysed. In countries where funds are limited, certainly the selective screening is cost effective compared to whole population screening. After many decades of research, only up-to-date considerations are Random blood glucose, O’Sullivan, 75g and Complete OGTT.

*Corresponding author: Email: najim5543@yahoo.com;
Keywords: Gestational diabetes mellitus; screening methods; universal screening; selective screening; combination methods.

1. INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance that begins or is first noticed during pregnancy [1]. This rather a vague definition encompasses a rather heterogenous group of hyperglycemic states in pregnancy that includes undiagnosed pre-existing diabetes mellitus and pregnant women who demonstrate mild glucose intolerance due insulin resistance commonly seen in obesity and the older parous woman. GDM is associated with serious maternal complications like pregnancy induced hypertension, polyhydramnios and caesarean section and foetal problems such as prematurity and large for gestational age, shoulder dystocia and birth injuries, neonatal hyperbilirubinaemia, hypoglycaemia and respiratory distress syndrome. Epidemiological research suggests that women who have gestational diabetes have an increased risk of type 2 diabetes later in life [2].

2. OBJECT

The object of this article is an attempt to appraise the existing screening methods of GDM. The majority of the patients are asymptomatic [3]. The importance of screening and diagnosis of GDM is universally accepted but there is controversy and uncertainty about the most suitable method of screening among various populations. After nearly 60 years of research the screening and diagnosis of GDM is still debatable. Multiple studies, numerous global consensus conferences and several multicenter trials had not identified the unique procedure.

3. WHEN TO SCREEN?

The screening for GDM is normally done between 24-28 weeks. In a normal pregnancy fasting glucose values are lower during the first trimester and early second trimester, compared to the non-pregnant state. Early pregnancy is associated with increased insulin sensitivity. physiological changes in normal pregnancy result in an increase in insulin resistance, so that more insulin is required with advancing gestation to produce [4].

4. SELECTIVE SCREENING OR UNIVERSAL SCREENING?

Screening and diagnosis of GDM are debatable. There have been many international organizations, expert panels and working groups involved in this work. There are many specific guidelines and recommendations available to screen GDM. The U.S. Preventive Services Task Force in 2008 concluded that current evidence was insufficient to establish the balance of benefits and harms for screening for GDM [5].

The American College of Obstetricians and Gynecologists (ACOG) recommended selective screening until 1994 but now recommends universal screening in certain high-risk settings [6]. The American Diabetic Association (ADA) recommended universal screening in 1996 but then revised their recommendations in 1997, suggesting selective screening of women at high risk of GDM [7]. The Australasian Diabetes in Pregnancy Society recommended that all pregnant women should be considered for screening dependent on the availability of resources [8]. Others, such as The US Preventive Services Task Force (USPSTF) and the
2003 National Institute of Health and Clinical Excellence (NICE) Antenatal Care guideline, have questioned the role for any screening because of lack of evidence to support its use [9]. Most recently, the International Association of Diabetes and Pregnancy Study Groups has recommended measuring either fasting or random plasma glucose or glycated haemoglobin in either all women or high-risk women at booking depending on the population risk followed by universal testing with an oral glucose tolerance test between 24 and 28 weeks [10].

O’Sullivan et al [11] historically demonstrated that 37–50% of women with GDM may remain undiagnosed using selective screening alone and, thus, recommended routine screening. However, the concept of universal screening has been revised and is still debated by several associations [12]. This is because GDM is not a single disease entity but includes and group of entities that show glucose intolerance at various gestational age.

In 2003, the USPSTF [13] concluded that evidence was insufficient to advise for or against routinely screening all pregnant women for gestational diabetes mellitus. Limited evidence suggests that gestational diabetes treatment after 24 weeks improves some maternal and neonatal outcomes. Evidence is even more sparse for screening before 24 weeks’ gestation [14].

Routine screening protocol requires the consideration of patient comfort, cost to the laboratory and the risk of missing the diagnosis. However ethnicity, nationality are inherent factors and they may warrant screening at an early stage [15].

With this strategy of universal screening, about 20% of women with GDM will remain undiagnosed. Hence, in many parts of Europe, a risk factor approach to GDM is still practiced. In this approach, woman’s age, ethnicity and BMI are considered. Selective screening in risk factor may miss some cases of GDM in the lower risk category, but more cases may be diagnosed in the higher risk category. Hence, there is wide gap between screening practices in European countries and North America. However, in countries like Saudi Arabia, Nigeria and China, 1h 50g GCT at 24–28 weeks of gestation is considered as a reliable universal screening test for GDM. This approach inevitably introduces a two stage process in those who are positive at the GCT contributing to increased inconvenience, anxiety and cost. This approach inevitably introduces a two stage process in those who are positive at the GCT contributing to increased inconvenience, anxiety and cost.

Except as part of specific study, screening the entire pregnant mothers for GDM has never been widely adopted in the United Kingdom. The whole population screening was not done due to uncertainty about the relevance of the condition and logistical problems. However little evidence to support universal screening for glucose intolerance during pregnancy [16].

A large Danish cohort involving over 5000 women considered that risk factor-based screening was as effective as universal screening [17].

5. PREVALENCE OF GDM

The prevalence of GDM varies widely from 1% to 10%. Difference of values in the screening procedure is an important contributory factor. Race and ethnicity also influence the prevalence. Populations of oriental origin appearing to be more susceptible [18]. Asians having a higher mean screening test value [19].
This is an example how the prevalence can vary depending on the diagnostic criteria [20]

<table>
<thead>
<tr>
<th>Institution</th>
<th>Glucose load</th>
<th>FBG</th>
<th>2 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDDG</td>
<td>100 g</td>
<td>5.8mmol/l</td>
<td>9.1mmol/l</td>
</tr>
<tr>
<td>ADA(2000-10)</td>
<td>75 g</td>
<td>5.3</td>
<td>8.6</td>
</tr>
<tr>
<td>CDA (2008)</td>
<td>75 g</td>
<td>5.3</td>
<td>8.9</td>
</tr>
<tr>
<td>WHO</td>
<td>75 g</td>
<td>6.1</td>
<td>7.8</td>
</tr>
</tbody>
</table>

NDDG- National Diabetes Data Group- USA; ADA- American Diabetes Association; CDA- Canadian Diabetes Association; WHO- World Health Organization.

The prevalence of GDM varies from less than 1% to more than 10% [21]. The prevalence is increasing due to dietary habits and overweight [22] maternal age, ethnicity, obesity, family history and past history are found to increase the GDM prevalence.

Prevalence vary due to the use of a wide range of definitions and diagnostic test criteria, as well as variations across regions and ethnic groups. Cheung and Wasmer [23] examined the records of 2139 Asian women. The incidence of GDM was 9.2%; among women born in China, it was 8.6%, the Philippines 6.7%, Sri Lanka 10.5%, and Vietnam 10.6%. However in Korea it is 2.0% and in Thailand 2.0%.

International Association of Diabetes and Pregnancy Study Groups (IADPSG) [24], which led to an increased GDM prevalence of up to 18% in the general population, using criteria from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study [25].

Although it is customary to do the screening procedures between 24-28 weeks of gestation, it has been shown that a substantial proportion of patients with GDM can be detected by first trimester screening.

The original development by O’Sullivan and Mahan of criteria for the diagnosis of GDM was largely driven by early observations relating a prior history of pregnancy loss and/or the delivery of heavy infants to the occurrence of frank diabetes mellitus some years later [26].

In a subsequent publication they showed the ability of non-fasted 50g lh screening blood glucose estimation to give 79% sensitivity and 87% specificity for a diagnosis of GDM by subsequent GTT in their population [27].

6. WHICH SCREENING TECHNIQUE?

The Australian Association of Diabetes in Pregnancy Society (ADIPS) recommends screening for GDM with 50 or 75g oral glucose irrespective of meal intake, with 1h plasma glucose level 7.8mmol/L or 8.0mmol/L respectively. If the results are more than these values, OGTT is required for diagnosis [28].

In the year 2008, Holt [29] had suggested that fasting plasma glucose (FPG) can be used as a screening test.

In North America, screening was done with 1 h 50g GCT at 24–28 weeks of gestation with cut off value of 7.8mmol/L. 14–18% were reported as test positive. They were subjected to either 75 g or 100 g OGTT as diagnostic test gave the sensitivity and specificity of 80% and 90%, respectively, whilst the positive and negative predictive values varied according to the prevalence of GDM in the population tested [30].
Recently, the International Association of Diabetes and Pregnancy Study Group (IADPSG) [31] has published new diagnostic recommendations for GDM using one-step OGTT after careful consideration of the data from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study [32]. The IADPSG values are one or more of FPG 5.1mmol/L, 1h plasma glucose 10.0mmol/L and 2-h plasma glucose 8.5mmol/L following a 75g OGTT. However, in 2011, Huynh et al. [33] reported that using IADPSG criteria 19% women were diagnosed with GDM. The screening GCT had a sensitivity of 83%, specificity of 75% and this would miss 17% of cases. Hence, they concluded that OGTT alone is the best procedure without prior GCT. The ADA [34] recommends that women with high risk for GDM should undergo testing as early in pregnancy as possible. All pregnant women should be screened for GDM between 24 and 28 weeks of gestation including those high risk patients who tested.

The best screening method is still debatable. 50g glucose challenge test (GCT) or fasting blood glucose level considered as acceptable screening tests prior to diagnostic testing [35].

Guidance from the ADA favours a two-step approach with an initial GCT followed by a diagnostic test, at least in low-risk populations [36]. The implications of cost-benefit and patient inconvenience are implicit if this approach is accepted universally.

The World Health Organization (WHO) (2002) has recommended a one-hour venous plasma glucose threshold of \( \geq 7.8 \text{ mmol/L} \) for the GCT if a two-step screening process is used [37].

However, the ADA has not set a specific threshold for one-hour venous plasma glucose level for the GCT with thresholds of \( \geq 7.2 \text{ mmol/L (130mg/dL)} \) or \( \geq 7.8 \text{ mmol (140mg/dL)} \) considered as being acceptable with quoted sensitivity for diagnosing GDM at 90% and 80% for each threshold, respectively [38].

Until 2011, ADA guidance recommended to test for gestational diabetes with a 100-g OGTT be based on women’s risk profiles [39].

In 2011, ADA guidance changed in the light of International Association of Diabetes and Pregnancy Study Group (IADPSG) discussions following the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study [40].

The ADA recommendations now closely reflect International Association of Diabetes and Pregnancy Study Group recommendations [41]. International Association of Diabetes and Pregnancy Study Group guidance recommends a 75g OGTT at 24–28 weeks for all women not previously diagnosed with diabetes by random or fasting plasma glucose testing at the first antenatal visit with gestational diabetes diagnosed according to International Association of Diabetes and Pregnancy Study Group [42]. The World Health Organization protocol is more inclusive and simple, with an oral glucose tolerance test recommended at 24–28 weeks for all women with risk factors for gestational diabetes or an abnormal fasting or random plasma glucose level and diagnostic thresholds the same as those for impaired glucose tolerance and diabetes mellitus outside pregnancy. The Diabetic Pregnancy Study Group (DPSG) of the European Association for the Study of Diabetes (EASD), recommended separate diagnostic thresholds based on a 75g oral glucose tolerance test, intended to be more in line.
7. PREDICTIVE VALUES OF RISK INDICATORS

The strongest independent predictor was a history of GDM, followed by increased maternal age (‡40 years) and BMI (‡35 kg/m²).

The most potent predictors of GDM were previous GDM, glucosuria, and the presence of more than one other risk indicator. Diabetes heredity, BMI 27 kg/m² or more, and previous macrosomia were moderate predictors [43].

The risk-factor screening can detect large numbers of women who do have abnormal glucose tolerance. This has relatively poor sensitivity and specificity. There is high prevalence of GDM in some populations. Therefore other methods or combinations of methods for screening are required [44].

8. SCREENING METHODS

8.1 Urine Testing for Glycosuria

While testing the urine sample routinely for protein in the antenatal clinic, it could be tested for glycosuria as well. This is very simple and cheap. Testing all the pregnant women for glycosuria cannot be taken as a total population screening. There is high prevalence of glycosuria and high proportion of false-negative results. Specificity of the test is high, but sensitivity is poor with results ranging from 7-46% [45] and the UK NICE (National Institute of Clinical Excellence) guidelines [46] did not recommend the continuation of this method of screening.

8.2 50g Glucose Challenge Test (GCT) and 50g/75 OGT T

Glucose challenge test (GCT) plasma screening would cost approximately US$84 to identify one person with previously unrecognised diabetes or prediabetes. GCT screening for prediabetes and previously unrecognised diabetes would be accurate, convenient and inexpensive. Widespread use of GCT screening could help improve disease management by permitting early initiation of therapy aimed at preventing or delaying the development of diabetes and its complications. GCT plasma was unaffected by time after meals or time of day [47].

GCT plasma was a strong indicator of unrecognized glucose intolerance. GCT plasma screening appears to be accurate, convenient and widely applicable, and the test would be relatively inexpensive.

The plasma glucose value of 140mg/dl (7.7mmol/l) in the GCT should be used because of its high sensitivity and higher specificity than does the 130mg/dl (7.2mmol/l) screening value. GDM is unlikely to be present if the venous plasma glucose level is less than 140mg/dl, one hour after administration of 50g oral glucose load at 24 to 28 weeks gestational age [48].

The sensitivity, specificity, and positive and negative likelihood ratios for the OGCT at a threshold of 7.8mmol/l (140mg/dl) were 70% to 88%, 69% to 89%, 2.6 to 6.5, and 0.16 to 0.33, respectively. At a threshold of 7.2mmol/l (130mg/dl), the test characteristics were 88% to 99%, 66% to 77%, 2.7 to 4.2, and 0.02 to 0.14, respectively. For a fasting plasma glucose threshold of 4.7mmol/l (8mg/dl), they were 87%, 52%, 1.8, and 0.25, respectively.
The OGCT and fasting plasma glucose level at a threshold of 4.7mmol/L by 24 weeks' gestation are good at identifying women who do not have GDM. The OGCT is better at identifying women who have GDM [49].

One of the methods for the screening and diagnosis of GDM is the 75g glucose load test. In Europe, the 75g 2h OGTT is predominantly used, as recommended by the World Health Organization. To date, the 75g glucose load in pregnancy has been used to a lesser extent than the more traditional 100g load, probably because the 75g test was developed to diagnose diabetes in non-pregnant persons and has had little validation in pregnant women.

Several studies evaluating the cost of GDM screening have also demonstrated that a two-step method using 50g GS is the least costly.

The American Diabetes Association (ADA) suggests that all pregnant women should be screened for GDM between 24 to 28 weeks of gestation unless they are of low risk. Two methods are suggested. In the one step approach 100g OGTT is performed directly without any initial screening. In the two step approach, women are initially screened by measuring the plasma glucose one hour after 50g glucose load. Women with glucose level of 7.2mmol/l to undergo an 100g OGTT on a different day, In both occasions, the diagnosis of GDM is established by the Carpenter and Coustan criteria [50].

8.3 Random Blood Glucose Testing

When the blood is drawn for haemoglobin estimation this sample also could be used to assess the blood glucose level randomly. The value depends on the time of last meal. The original cut offs were taken as and 5.8mmol/l if the last meal is more than 2 hours and 6.4mmol/l if less than 2 hours. The specificity of this test is around 80-90% but sensitivity is around 40%.Therefore this method cannot be regarded as suitable screening test [51].

8.4 Fasting Blood Glucose (FBS) Testing

Mortensen in the year 1980 suggested testing fasting blood glucose as a screening test. This has the advantage of eliminating the effects of food unlike the random blood glucose testing. The sensitivities of this test is in the order of 70- 90% and the specificities of 50-75% [52]. This method is useful as the whole population screening method if the value of 5.3mmol/L is considered, then FBS had an excellent specificity of 97.7%, but a poor sensitivity of 19.4%. The value of 5.1mmol/L, is the threshold proposed in the HAPO study and IADPSG recommendations [53], FBS has 95.2%, specificity sensitivity is only 26.4%.

8.5 Estimation of Glycosylated Haemoglobin and Fructosamine

Estimation of Glycosylated haemoglobin and fructosamine would reflect the blood glucose level in previous weeks and they have no place as screening tests [54].

Between 1989 and 2000, at least seven studies agreed that fructosamine was not a good test for screening of GDM. Despite all the advances in technology, serum fructosamine is a poor test to screen for GDM [55].
8.6 75g Oral Glucose Tolerance Test (75g OGTT)

In its recently published guidelines [56] the National Institute of Clinical Excellence (NICE) recommended that all women with one or more risk factors should be screened using an oral glucose tolerance test (OGTT) [57].

It could be simplified into a single-step definitive screening strategy using an OGTT with a 75g glucose load, as was done in the HAPO study [58], and as recommended by the WHO [59], the IADPSG [12] and the recent French Expert Consensus on GDM [60], even though it may result in an increased prevalence of GDM.

The most sensitive way to screen is to use OGTTs, but these are inconvenient [61]. Since early glucose intolerance is often pathophysiologically similar to gestational diabetes (high glucose levels after a challenge), it seemed possible that screening could be done using a strategy similar to that used for gestational diabetes, i.e. an oral glucose challenge test (GCT), in which 50g glucose are given at any time of day, without a prior fast, and glucose levels are measured 1 h later. If the glucose levels exceed a cut-off, patients then have an OGTT. We hypothesized that such a strategy could constitute an effective, convenient, low-cost method of screening in non-pregnant adults.

8.7 Two Step Approach (Combination of Methods)

The two-step method (Glucose Screening ± OGTT) accomplished this better than the one-step method (75g OGTT). Worldwide controversy exists with regard to the best method and criteria for GDM screening and diagnosis. The two-step approach, using GS and either 2 hour, 75g or 3 hour, 100g OGTT, was found to be less expensive with equivalent diagnostic power to the one-step approach (2 hour, 75g OGTT alone) [62].

The disadvantage of the 75g OGTT is that few pregnant women vomit with 75g glucose and 300 ml of water. They have to wait for 2 hours with few impatient children in the clinic.

100g Glucose tolerance test was compared with fasting glucose level with risk factors (FG+RF) combined with 50g Glucose Tolerance Test [63]. The study concluded that diagnostic efficiency with simplicity, practicality and low cost make FG+RF more appropriate for screening for GDM. The equivalence of one hour plasma glucose allows a new, cheaper and less uncomfortable protocol to be proposed for screening and diagnosing GDM. The 50g GTT is considered to be a reliable test for the screening of GDM. The fasting glucose and risk factor (FG+RF) combination and the 50g GTT has high specificity in comparison with the 100g GTT.

9. CONCLUSION

There are still no evidence-based arguments to help in deciding between selective or universal screening for GDM

The combination methods appears better but costly and inconvenient to the patients.

When gestational diabetes mellitus risk is less than 1%, the no screening/treatment strategy is cost-effective. Where the risk is between 1.0% and 4.2% the fasting plasma glucose
followed by OGTT is most likely to be cost effective. If the risk is more than 4.2%, the universal OGTT is most likely to be cost-effective. [64]

Despite the increasing frequency of pregnancies complicated by GDM, there is still no international consensus on optimal screening programmes and the current guidelines have varied performances. There is no ideal strategy, and local circumstances including the financial health care burden of universal screening will need to be taken into account when deciding who to screen in any health care setting [65].

There is a need to establish true prevalence of GDM in communities and develop specific guidelines on use of a cost effective screening tool which could be used in the first trimester probably based on risk criteria and a universal screening between 24-28 weeks based on the results of the HAPO study macrosomia, caesarean section are linearly related to fasting, 1hr and 2hr blood sugars.

If a woman’s individual risk of gestational diabetes could be accurately predicted, then healthcare resource allocation could be improved by providing an individualized screening strategy.

There is a need to establish true prevalence of GDM in communities and develop specific guidelines on use of a cost effective screening tool which could be used in the first trimester probably based on risk criteria and a universal screening between 24-28 weeks based on the results of the HAPO study macrosomia, caesarean section are linearly related to fasting, 1hr and 2hr blood sugars.

It is time to move from academic discussion focusing on sensitivity and specificity to reality of practicing on a very basic care level.

10. RECOMMENDATIONS

Malaysia is marching forward to become a developed country. Along with that the eating habit among teenagers is changing. The fast foods and food containing high oil and fat are becoming very popular. The obesity and related diseases are rapidly increasing. Sedentary life style and occupation are on the increase. Delayed marriage and older maternal age cannot be ignored. The GDM prevalence in Malaysia from 8.3% in 1996 had increased to14.9% in 2006. 50g GCT threshold value of >or=7.6mmol is appropriate for the Malaysian population at high risk of GDM [66]. The selective screening at 24-28 weeks of pregnancy is cost effective in countries like Malaysia.

Women with one or more risk factors should be offered a single-step definitive screening strategy using an OGTT with a 75g glucose load

CONSENT

Review article and consent of the patients are not applicable.

ETHICAL APPROVAL

Not applicable.
COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

64. Wilson Ayach. Roberto Antonio Araújo Costa Comparison between 100g glucose tolerance test and two other screening tests for gestational diabetes: combined fasting glucose with risk factors and 50g glucose tolerance test. Sao Paulo Med. J. 2006;124(1).