

Suggested consensus for the diagnosis of gestational diabetes



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Practice Points

- There is a continuous relationship between glycemia and adverse pregnancy outcomes.
- Identifying gestational diabetes mellitus (GDM) provides an opportunity for meaningful health interventions to prevent Type 2 diabetes mellitus and other associated morbidities later in life.
- Unified criteria will facilitate research into the area of GDM treatment and outcomes.
- The increased GDM prevalence with new GDM criteria is concordant with the increased prevalence of impaired glucose tolerance in the general population.
- Testing for GDM is cost effective.
- The option of using fasting blood glucose alone for GDM diagnosis requires further investigation in different populations/ethnic groups.
- In resource-poor settings, the use of simplified protocols for testing, including the use of finger-stick glucose measurements, is an area of ongoing investigation.
- The use of the glucose challenge test and a two-step diagnostic process is not recommended.

SUMMARY Recent proposals for the revision of diagnostic criteria for gestational diabetes mellitus (GDM) have engendered worldwide debate. Within and between countries there is disagreement between obstetric, medical and endocrine groups regarding the diagnosis and management of GDM. There have been many articles written recently on this topic in an attempt to clarify opinions and, in some cases, promote a more unified approach. This review aims to discuss the criteria currently in use for the diagnosis of GDM and proposes the universal acceptance of the International Association for Diabetes in Pregnancy Study Group (IADPSG) GDM diagnostic criteria. It also aims to put into perspective the importance of GDM and its increasing prevalence, irrespective of the criteria used for diagnosis. Other factors associated with GDM diagnosis are also covered, including the epidemiology of testing for GDM around the world, the suggested elimination of a two-step diagnostic approach, the cost-effectiveness of testing and the approach to testing in resource-poor settings.

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The debate regarding diagnosis of gestational diabetes mellitus (GDM) has led to some bodies, including the US Preventative Services Taskforce [101] and NIH Panel [102] to recently express concerns regarding the potential increase in the number of GDM diagnoses caused by the change to a one-step process and adoption of International Association for Diabetes in Pregnancy Study Group (IADPSG) criteria for diagnosis of GDM. The authors of this article fundamentally disagree with these contentions and highlight the increasing prevalence of prediabetes and undiagnosed Type 2 diabetes mellitus (T2DM) outside of pregnancy in women of childbearing age [1]. We believe that it is logical to relate the diagnosis of GDM with the risk of adverse pregnancy outcomes [2].

History of the diagnosis of GDM

GDM has historically been defined as the onset or first recognition of abnormal glucose tolerance during pregnancy [3]. New recommendations have modified this to exclude more severe cases that could be considered as ‘overt diabetes’ as a result of the increased prevalence of background T2DM in the general and obstetric populations. The American Diabetes Association (ADA) defines overt diabetes as high-risk women found to have diabetes at their initial prenatal visit, using standard criteria (HbA1c >6.5%; fasting plasma glucose [FPG] >7.0 mmol/l; 2-h oral glucose tolerance test [OGTT] glucose >11.1 mmol/l) [4].

The first published case description of GDM was in 1828 by Heinrich Gottlieb Bennewitz [5], who described a patient exhibiting excess production of sugar who delivered a baby of “such robust and healthy character you would have thought Hercules had begotten”. The realization that diabetes could appear in pregnancy and resolve at the end of pregnancy occurred in the late 1800s; although the term ‘gestational diabetes’ was first coined in 1957 by Carrington [6].

The first use of the OGTT for the diagnosis of diabetes in pregnancy was in the 1950s in Boston (MA, USA). O’Sullivan *et al.* used a 100-g 3-h OGTT for the diagnosis of diabetes in the nonpregnant population, and initially applied the US Public Health Service criteria, which were in common use at the time for OGTTs performed outside pregnancy [7]. The need to define OGTT criteria for the pregnant population was recognized and, following a further cohort study involving 752 women from Boston, O’Sullivan

and Mahan published the first criteria for the OGTT in pregnancy in 1964 [8]. These criteria (based on a 100-g, four-sample, 3-h OGTT) became well established because of their ability to predict the subsequent development of diabetes in the mother, not for the ability to predict adverse pregnancy outcomes. These criteria have since been adjusted to convert the measurements of ‘whole blood sugar’ (glucose and other nonglucose carbohydrate molecules) using the Somogyi–Nelson method to glucose levels in plasma. These corrected criteria for venous plasma glucose are commonly referred to as the Carpenter and Coustan criteria [9].

A growing body of evidence has since accumulated, associating abnormal glucose tolerance in pregnancy with adverse perinatal outcomes. The need for uniformly accepted diagnostic criteria (and management strategies) has been promoted by many clinicians and researchers [10,11], but disputed by others [12–14].

The development of a sound epidemiologic basis for diagnostic criteria for GDM based on pregnancy outcomes was the driving force behind the HAPO study [15]. The relationship between fasting, and 1- and 2-h glucose concentrations during a 75-g OGTT and adverse pregnancy outcomes was investigated in this multinational blinded epidemiologic study. Primary outcomes were the frequency of large-for-gestational-age babies, cesarean section, clinical neonatal hypoglycemia and neonatal hyperinsulinemia. All of these outcomes, as well as fetal adiposity, pre-eclampsia and birth trauma/shoulder dystocia were related to the maternal OGTT glucose results in a continuous fashion, with no obvious inflection point to suggest a ‘natural’ diagnostic threshold. It was recognized that current testing practices were failing to identify at-risk pregnancies, with poor pregnancy outcomes occurring in patients with glucose levels that had previously been considered normal [16].

At this time, diverse diagnostic criteria were used for GDM, with many different countries and organizations supporting and promoting their own criteria, largely developed on an *ad hoc* basis. In an attempt to achieve consensus on uniform diagnostic criteria from the diverse available criteria, and in response to the HAPO data [16] and two large randomized controlled trials showing an outcome benefit in diagnosing and treating even mild GDM [17,18], the IADPSG organized a workshop conference

Table 1. Comparison of criteria for diagnosis of gestational diabetes.

Criteria	IADPSG 75-g 2-h OGTT; mg/dl (mmol/l)	Carpenter and Coustan [9] [†] 50-g GCT and 100-g 3-h OGTT; mg/dl (mmol/l)	NDDG [‡] 100-g 3-h OGTT; mg/dl (mmol/l)
Fasting	>92 (>5.1)	>95 (5.3)	>105 (5.8)
1 h	>180 (>10.0)	>180 (10.0)	>190 (10.5)
2 h	>153 (>8.5)	>155 (8.6)	>165 (9.2)
3 h	–	>140 (7.8)	>145 (8.0)

[†]American College of Obstetrics and Gynecology accepts either of these criteria.
GCT: Glucose challenge test; IADPSG: International Association for Diabetes in Pregnancy Study Group; NDDG: National Diabetes Data Group; OGTT: Oral glucose tolerance test.

in June 2008. Following this conference, the IADPSG consensus panel developed outcome-based criteria for the diagnosis of GDM, which were published in 2010 (Table 1) [19].

The IADPSG consensus panel of 50 individuals with extensive clinical and research expertise in diabetes in pregnancy considered a variety of possible diagnostic strategies, including some based on the detection of two or more elevated values of the OGTT. Initially, consensus was reached on the proposition that diagnostic criteria should be based on odds ratios for markers of diabetic fetopathy (large for gestational age, excess fetal adiposity and fetal hyperinsulinemia) compared with the mean of the HAPO study cohort. Potential cut-off points representing odds ratios of 1.5, 1.75 and 2.0 were specifically evaluated. The IADPSG consensus panel recommended that cut-off points for the OGTT fasting, and 1- and 2-h plasma glucose levels associated with fully adjusted odds ratios of 1.75 for adverse outcomes compared with the rates seen at mean glucose levels of the HAPO cohort should be designated the diagnostic levels for GDM [103]. Translating these numbers from odds ratios to unadjusted hazard ratios (HRs), these thresholds correspond to HRs of approximately 2.0 (twofold) for the major outcomes considered [19].

These IADPSG criteria have been accepted by a variety of professional and other healthcare bodies, including the Endocrine Society, ADA, Australasian Diabetes in Pregnancy Society and WHO, but challenged by others, including the NIH Consensus Panel and American College of Obstetricians and Gynecologists (ACOG). Therefore, there is still a lack of international acceptance of any universally recognized diagnostic criteria for GDM.

Testing for GDM around the world

Consensus between countries and even within countries regarding GDM diagnostic strategies is lacking. Therefore, GDM prevalence remains

difficult to define and compare between countries, and development and implementation of management strategies is challenging.

A recent multicenter study reported the results of a survey sent to 173 nations asking them to estimate their local prevalence of GDM, provide information on the screening methods used, diagnostic criteria and standard management. The investigators received and collated data from 47 countries [20]. The reported prevalence of GDM was highly variable between countries and even within countries. Estimates of the prevalence of GDM ranged from <1 to 28% of pregnant women. Many of the surveyed countries had guidelines for GDM diagnosis or management, but there was not always clear evidence that these guidelines were being followed [20]. In some countries, it was estimated that only 10% of pregnant women with GDM received active management after diagnosis. Most nonresponding countries were of low income and it appears likely that GDM may be a lower priority in areas where resources are limited.

Risk factors for GDM and T2DM are similar. Therefore, it follows that as the prevalence of T2DM increases in many populations then so will the prevalence of GDM. The estimated prevalence across the USA of impaired glucose metabolism in women aged 18–44 years outside of pregnancy (impaired fasting glucose, impaired glucose tolerance and T2DM) is 30.7% [21]. Therefore, it is not surprising that GDM may also be prevalent in women of a similar age.

There is marked variation between countries/ethnic groups in terms of the estimated prevalence of GDM, but also variation in terms of the screening approach used (i.e., universal or selective), the screening steps and the diagnostic criteria. This makes country-to-country comparisons difficult. The acceptance and universal use of a single set of criteria for diagnosis of GDM would allow more direct comparison between the

prevalence of GDM in different countries and, subsequently, comparisons of outcomes when using different treatment strategies/management protocols.

In 2012, the HAPO investigators published a *post hoc* analysis of the frequency of GDM (using the IADPSG criteria) across the different HAPO study centers. This report also assessed the contribution of each glucose measurement to these frequencies (i.e., fasting, 1- or 2-h glucose measurements) [22]. HAPO used a 75-g OGTT performed between 24 and 32 weeks of gestation on 23,957 women. When the IADPSG criteria were applied to this cohort, the overall prevalence of GDM was 17.8%. There were marked variations in the prevalence of GDM diagnosed with these criteria between centers. Differing prevalences persisted after adjustment for maternal age, BMI, chronic hypertension, and family history of diabetes and hypertension. The highest prevalence of GDM was in CA, USA (25.5%), closely followed by Singapore (25.1%), Manchester, UK (24.3%) and Bangkok, Thailand (23%). The countries with the lowest prevalence included Australia (15.5% in Newcastle and 12.4% in Brisbane) and Israel (only 9.3%) [22].

There were also center-to-center variations in which glucose measurement(s) met the threshold for the diagnosis of GDM. Across the entire HAPO cohort, 55% met the criteria based on FPF alone, 33% based on the 1-h glucose and 13% based on the 2-h glucose. This has clear implications for the use of the IADPSG criteria in different populations; for example, it may be possible in some areas to use an alternative 'two-step algorithm'. In such an approach, in a population predominantly with abnormalities of fasting glucose, an initial measurement of fasting glucose could potentially detect most cases of GDM. Full glucose tolerance testing could then be reserved for those not already diagnosed by the fasting test. However, such an approach still requires validation in clinical practice and potential process errors related to the two-step approach may also need to be addressed.

Timing of screening for GDM in pregnancy

Another, sometimes overlooked, recommendation of the IADPSG panel was to develop strategies for early detection of pre-existing diabetes through testing in early pregnancy [19].

It is important to identify pre-existing diabetes as early as possible in pregnancy or, if

possible, prior to pregnancy. Pre-existing diabetes is associated with an increased risk of congenital anomalies and other serious pregnancy complications, including gestational hypertension and pre-eclampsia. Early treatment may help to reduce these risks. Recognition of pre-existing diabetes also has implications for monitoring and treatment of this population in the early postpartum period.

Pre-existing diabetes should be screened for opportunistically at the first antenatal visit, either in high-risk women (according to IADPSG, which left this decision to local discretion) or universally in all women (according to the Endocrine Society Guidelines [23]) using the same diagnostic cut-offs that are recommended in the nonpregnant population.

One abnormal versus two abnormal values

The GDM diagnostic criteria initially developed by O'Sullivan required two elevated OGTT values for a diagnosis of GDM [8]. The arguments in favor of this centered largely around poor reproducibility of whole-blood glucose measurements using the whole-blood Somogyi–Nelson technique commonly employed at that time. This tradition continues across the USA and in some other countries, despite marked improvements in the technical characteristics of venous plasma glucose assays and a large body of evidence suggesting that one abnormal OGTT value carries risks of adverse pregnancy outcomes similar to those found with two or more abnormal values [24]. The requirement for two abnormal values essentially represents another (rough) expression of 'glucose dose' and, although it has validity thanks to familiarity in the USA, it has never gained prominence in other parts of the world.

Single-step process, elimination of the glucose challenge test

In the USA, the ACOG still promotes a two-step process with an initial 50-g nonfasting glucose challenge test (GCT) and progression to a formal OGTT if the venous plasma glucose 1 h after this glucose load exceeds a (variable) threshold. A recent systematic review compared the 50-g GCT and OGTT (either 75 or 100 g) to estimate the sensitivity and specificity of the GCT for GDM [25]. For consecutively recruited patients, the pooled sensitivity was 0.74 (95% CI: 0.62–0.87), meaning that the

process of performing GCT and then OGTT misses approximately 26% of potential GDM diagnoses.

Many other organizations have eliminated the GCT from their algorithms due to its lack of sensitivity and specificity, and the delay in diagnosis and subsequent initiation of appropriate treatment this causes. Instead, all women are screened with an OGTT at 24–28 weeks.

A recent prospective observational study randomized 786 pregnant women to either screen for GDM with a one-step method using a 75-g OGTT following IADPSG criteria ($n = 386$) or a two-step method with 50-g GCT and 100-g OGTT using the Carpenter and Coustan criteria ($n = 400$), and then analyzed the prevalence of GDM using each method. This study also aimed to determine whether women diagnosed as having normal glucose tolerance by the two-step method had any worse neonatal outcomes than those determined to have normal glucose tolerance by the one-step method [26].

Women diagnosed with GDM by either process were treated according to the local management protocol, including endocrinology review, glucose monitoring, dietary advice and medication if required. The one-step method gave a GDM prevalence rate of 14.5% and the two-step method a prevalence of 6%. Women determined as having normal glucose tolerance in the two-step method had a greater risk of pre-eclampsia and macrosomia compared with the women defined as having normal glucose tolerance in the one-step method. While this study was small, the authors propose that this adds support to the arguments for the elimination of the two-step process.

Cost-effectiveness of diagnosing GDM

A life course approach to managing GDM (diagnosis using IADPSG criteria, treatment during pregnancy and intervention for the mother after pregnancy to reduce risk of maternal progression to T2DM) has been evaluated in cost-modeling studies, which concluded that this approach is cost effective [27,28] or cost saving [29].

Prevention of T2DM and its chronic complications in women who have GDM in pregnancy is one of the major predicted cost savings. With the rise in morbidity and mortality associated with T2DM, the ability to identify this at-risk population and to target them with interventions to prevent T2DM is very attractive. A recent study has confirmed the ability to reduce

the incidence of T2DM in this patient group by up to 50% with intense lifestyle modifications [30]. There are no data on the prevention of T2DM in the offspring of mothers with GDM. A potential benefit in this area is often inferred from available epidemiologic data, but remains both unconfirmed and very difficult to evaluate in a controlled trial.

A cost-effectiveness comparison of GDM screening/treatment between using the ACOG guidelines (screening using 1-h GCT followed by the 3-h OGTT) and the new IADPSG guidelines (screening using 2-h OGTT) has been reported [27]. An analytic model was used to compare total costs and total maternal and neonatal quality-adjusted life years. This was a theoretical model involving a notional cohort of 100,000 women. The probabilities and cost of maternal and neonatal outcomes were determined from the literature. The incremental cost-effectiveness ratio (ICER), the ratio of healthcare dollars spent to health outcomes obtained, was measured in 2012 as US\$/quality-adjusted life years gained (ICER is the amount we are willing to pay for each unit of improved quality of life).

The cost of diagnosing and treating GDM included the following elements: direct cost of test materials and analysis; indirect costs of travel; opportunity costs for the patient; costs of pharmacotherapy; cost of additional antenatal visits; costs of additional ancillary diabetes-related visits; and costs of antepartum fetal surveillance. Cost-effectiveness analysis results showed that testing for GDM with the 2-h OGTT is more expensive than the 1-h GCT screening. However, screening, diagnosis and management of women with GDM diagnosed with the 2-h OGTT following IADPSG guidelines resulted in a decrease in all measured adverse maternal outcomes and neonatal outcomes (and reduced ICER), making this screening method more effective.

A second study aimed to determine whether adopting the IADPSG criteria would be cost effective by comparing three groups: no screening; current ACOG screening practice (1-h 50-g GCT at 24–28 weeks followed by 3-h 100-g OGTT when indicated); or the screening guidelines proposed by the IADPSG (first prenatal visit FPG, followed by a 2-h 75-g OGTT at 24–28 weeks when indicated) [28].

The results of this simulation study revealed that using the IADPSG approach to GDM

screening and diagnosis, compared with the current ACOG screening practice and no screening, is cost effective only if a GDM diagnosis creates the opportunity for early and intensive interventions to prevent future T2DM. It did recognize that there were benefits in terms of perinatal outcomes with the IADPSG criteria, but these did not reach the predefined threshold for cost-effectiveness.

A third cost-effectiveness analysis used a computer simulation model (GD Model) developed to estimate the potential health impact, net cost and cost-effectiveness of various GDM screening and management strategies [29]. The GD Model aims to compare alternative screening algorithms, prenatal interventions and postpartum preventive lifestyle interventions. It is designed to estimate the cost/year of screening and interventions, perinatal complications and cases of T2DM. It also calculates averted disability-adjusted life-years (DALY). The early results from pilot analyses estimating the effect of long-term T2DM reductions in India and Israel showed that GDM screening and postpartum lifestyle management either result in a cost saving, or have a net cost but a positive cost-effectiveness ratio.

A fourth trial conducted in the United Arab Emirates also attempted to assess the cost and workload involved in a switch from the current two-step ACOG criteria to the one-step IADPSG criteria [31]. The costs involved in using the FPG on the 2-h OGTT alone to make the diagnosis of GDM were also investigated. If the FPG was $>7\text{mmol/l}$, overt diabetes was diagnosed. If the FPG was $5.1\text{--}6.9\text{mmol/l}$, the patient was diagnosed as having GDM. If the FPG was between 4.4 and 5.1mmol/l , the result was considered indeterminate and the full 2-h OGTT was completed.

In this specific patient group (predominantly of Arabic origin), there is a very high estimated prevalence of GDM, varying from 8 to 25% depending on the criteria used, and it is estimated to increase to 37.7% with the IADPSG criteria. In this population, previous trials have shown that the use of the result from the initial FPG in the 2-h OGTT can avoid 50% of full OGTTs [32].

This United Arab Emirates study reported that the use of the new IADPSG criteria was the most costly of the three strategies. However, if the FPG (using the IADPSG criterion of 5.1mmol/l) was used to determine the need

to progress to a full OGTT then this was the most cost-effective strategy for this patient population [31].

These four trials provide suggestive evidence that adopting the new IADPSG criteria will allow cost-effective diagnosis and management of GDM, especially for preventing T2DM in this at-risk patient group. Each health system should assess their own costs for implementing the new IADPSG criteria and also the outcome of preventative measures in the women identified with GDM to prevent the later development of T2DM.

Resource-poor settings

The situation of resource-poor settings must be considered in the discussion of implementing internationally acceptable criteria for the diagnosis of GDM. The formal 2-h OGTT is an expensive and resource-intensive test [14]. The IADPSG criteria recommend the universal screening of women with a 2-h OGTT, which has major cost implications for resource-poor settings. The investigation of simpler investigations such as FPG only or finger-stick capillary glucose is important.

With IADPSG criteria, the FPG alone is diagnostic for GDM in between 24 and 74% of women depending on ethnicity [22]. The lowest rates of diagnosis on the FPG alone are in women of southeast Asian origin (Thai and Hong Kong cohorts in the HAPO trial) and highest ($>70\%$) in the Barbados and the US HAPO cohorts, with groups in the UK and Australia falling in between. In the HAPO cohorts, 55% of women with GDM had FPG meeting the criteria for an IADPSG GDM diagnosis ($>5.1\text{mmol/l}$).

The low-cost algorithm proposed by the United Arab Emirates group, discussed in the 'Cost-effectiveness of diagnosing GDM' section, may suit settings where the diagnosis of GDM is more likely to be made based on the FPG alone [33]. Although the United Arab Emirates is not a resource-poor setting, there are still difficulties in arranging for all women to attend clinics for the full 2-h OGTT.

It is important to recognize that there is a balance between 'ideal' recommendations and pragmatism in the choice of testing strategies for GDM. Poorer countries may not be able to test widely for GDM if a 2-h OGTT is the only recommended test. Furthermore, wealthier nations will need to deal with the logistics of arranging for all women to have a 2-h OGTT.

An alternative approach to this has been to use the finger-stick capillary glucose measure [34]. It has been suggested that this can prevent the need for a full OGTT in up to 50% of women, and rule in/out GDM with some accuracy. The major concerns about this approach revolve around the limited accuracy of standard hand-held glucose meters, commonly employed for home glucose testing. The use of fasting capillary glucose is clearly a major compromise in terms of diagnostic accuracy. It may be appropriate for pragmatic reasons to include this approach in the GDM diagnostic process in some resource-poor settings, although further studies assessing its utility in populations with a lower GDM prevalence are needed. Another potential approach might involve the use of fasting or post-glucose-load fingerstick capillary glucose measurements with a (yet to be determined) lowered threshold to compensate for the intrinsic inaccuracy of the methodology. Such an approach could be adapted to 'rule out' GDM in a large number of women, with the proviso that women testing above such thresholds would require formal laboratory glucose testing. This approach may potentially prove valuable in resource-poor settings, but would require formal evaluation of the specificity and sensitivity of such a testing protocol, as well as a cost-benefit analysis.

Conclusion & future perspective

The acceptance of uniform criteria for the diagnosis of GDM and subsequent treatment and follow-up of this group of women is needed. Recent endorsement of the IADPSG criteria by the WHO [104] may assist with international acceptance of these diagnostic thresholds. International use of the same criteria for GDM diagnosis will allow useful comparisons regarding treatment and longer-term outcomes for this population. The diagnosis and appropriate management of GDM provides the ideal opportunity for healthy interventions in a large group of women, potentially improving outcomes for their current pregnancy, offspring and future health.

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