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Diagnosis of GDM - A suggested consensus

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Diagnosis of Gestational Diabetes Mellitus - A suggested consensus

Abstract:
Despite recent attempts at building consensus, an internationally consistent definition of gestational diabetes mellitus remains elusive. Within and between countries there is disagreement between obstetric, medical and endocrine groups as to the diagnosis and management of GDM. The current article aims to discuss the background to the controversy of GDM diagnosis and to address issues related to detection and treatment of GDM in low, middle and high resource settings. The criteria recommended by IADPSG, ADA and WHO are endorsed. We also wish to put into perspective the importance of GDM, both during and after pregnancy, in terms of its relationship to overall women's health.

Key words: Diabetes, gestational, pregnancy, diagnosis, definition
Background to the diagnosis of gestational diabetes mellitus (GDM):

The observation that diabetes could develop during pregnancy and resolve thereafter dates back at least to the nineteenth century. The first published case description of diabetes diagnosed in pregnancy with subsequent resolution post-partum was in 1828 by Heinrich Gottleib Bennewitz. [1] He described a patient with symptoms of severe hyperglycemia, exhibiting excess production of sugar who delivered a baby of “such robust and healthy character ... you would have thought Hercules had begotten”. The baby was macrosomic and stillborn and the mother’s symptoms resolved post-partum. Subsequently, the term “gestational diabetes” was coined in 1957 by ER Carrington [2]

The first systematic evaluation of the oral glucose tolerance test (OGTT) for the diagnosis of diabetes in pregnancy was in the 1950s in Boston. O’Sullivan et al used a four sample, 100g 3h OGTT and initially applied the US Public Health Service criteria, which were in common use at the time for OGTTs performed outside pregnancy [3]. These required 3/4 values to exceed threshold for diagnosis of diabetes. Women in this study were enrolled due to additional risk
factors for diabetes and were tested on several occasions during pregnancy if they had an initial normal result. GDM frequency was low at 0.9%.

The need to define OGTT criteria for the pregnant population was recognized and the Boston group conducted further studies. The most widely reported cohort study involving 752 women was published in 1964 by O'Sullivan and Mahan [4]. Given its iconic status in the world of GDM diagnosis, further description seems warranted. O'Sullivan and Mahan determined the 97th centile levels for whole blood glucose on 752 women who underwent a full (100g, four sample, 3 hour) OGTT. Initially they enrolled 986 women who underwent a 50 gram, non-fasting “glucose challenge test” (GCT) at their first antenatal visit. Of these, 752 returned for further testing and formed the basis of their cohort. Importantly, the GCT results were not used to triage women for the full OGTT. O'Sullivan and Mahan arbitrarily decided that two abnormal values would be needed for GDM diagnosis and rounded the 2 and 3 hour value for equally arbitrary reasons. The subsequent 97th centile whole blood glucose values (Fasting 90, one hour 165, two hour 145, three hour 125 mg/dL; [respectively 5.0, 9.2, 8.1, 6.9 mmol/L]) were then applied to a separate cohort of 1013 women who had been followed
up post-partum and the retrospective diagnosis of GDM was found to be predictive of subsequent diabetes in the mother. Importantly, this concept of “pre-diabetes” in the mother was of paramount interest, not the ability of OGTT results to predict adverse pregnancy outcomes.

These “O’Sullivan criteria” have since been adjusted to convert the original measurements of “whole blood sugar” (glucose and other non-glucose carbohydrate molecules using the Somogyi – Nelson method) to plasma glucose concentrations. Varying results have been obtained [5, 6], but the most methodologically correct and widely accepted criteria for GDM diagnosis using venous plasma glucose can be traced back to the original O’Sullivan cohort and are commonly referred to as the “Carpenter and Coustan criteria”. [7]

A growing body of evidence has since accumulated associating abnormal glucose tolerance in pregnancy with adverse perinatal outcomes.

**Association of hyperglycemia and adverse pregnancy outcomes**

In 1995, Sacks et al published an open observational study entitled: “Toward universal criteria for gestational diabetes: The 75-gram glucose tolerance test in pregnancy” [8]. They reported pregnancy outcomes in 3505 women who underwent a 75 gram OGTT without a
prior GCT. The OGTT results were not blinded, but women were
treated for GDM only if fasting glucose was ≥ 5.8 or 2-hour glucose ≥
11.1 mmol/L (105 or 200 mg/dl respectively).
Sacks et al demonstrated a continuous relationship between fasting,
1 hour and 2 hour OGTT glucose values and both birthweight centile
(adjusted for maternal race, parity, BMI and mean weight gain) and
macrosomia (defined as birthweight > 90th percentile). Detailed
analysis of the data failed to demonstrate any threshold or “inflection
point” above which macrosomia increased dramatically. The authors
commented that criteria for GDM “will probably be established by
consensus”.
Also in 1995, Sermer et al [9] published the findings of the “Toronto
Tri-Hospital Gestational Diabetes Project”. They recruited 3836
women, all of whom underwent both a 50 gram GCT and a 100 gram
OGTT, performed irrespective of GCT results. The glucose results
were blinded to caregivers unless NDDG criteria for GDM were met
[9], leaving a study cohort of 3637 women. They reported primary
outcomes of pre eclampsia, macrosomia (birthweight > 4000g) and
cesarean section, all of which increased progressively across
quartiles for each glucose measurement. As confirmed later in the
Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study [10],
these investigators noted that individual glucose measures on the OGTT were poorly inter-correlated, suggesting their independent associations with outcomes. They developed a variety of regression models and the overall report of their findings was “a clear graded relationship between values of the oral GTT, as well as glucose challenge results and a variety of adverse maternal – fetal outcomes”. As in the Sacks study, no threshold of maternal glycemia was associated with a marked increase in risks.

In 2001, Jensen et al reported the results of a Danish epidemiologic study of mild GDM [11]. Their diagnostic protocol was selective, involving a combination of historical risk factors and laboratory measurement of either plasma or blood glucose from a capillary sample, as well as repeated urine glucose testing. They did not utilize a GCT, but instead women underwent a 75gram OGTT if random plasma glucose exceeded 4.7 mmol/L (85 mg/dl) on two or more occasions. Their threshold for “abnormality” on the OGTT required two or more values to exceed the Mean+3 standard deviations for a separate, small group (n=40) of healthy, non-pregnant, non-obese women. In contrast with the other epidemiologic reports, all women in their final cohort of 2904 participants had either one or more risk factors for GDM or previously demonstrated mild hyperglycemia. The
prevalence of macrosomia rose significantly across quartiles of both fasting and 2 hour glucose, whilst hypertension, emergency cesarean section and shoulder dystocia were associated only with the 2 hour glucose values.

An epidemiologic study from Brazil, authored by Schmidt et al was also published in 2001[12]. This study included 4977 women who also underwent a primary 75 gram OGTT without prior GCT. The OGTT results were not blinded, but it was noted that women with mild GDM did not routinely receive treatment in Brazil at the time of the study. Rather than reporting overall relationships between OGTT values and pregnancy outcomes, this study used post hoc classification of OGTT results according to the divergent World Health Organization (WHO) and American Diabetes Association (ADA) thresholds in use at the time. Both sets of criteria identified women at risk of developing pre eclampsia or delivering a macrosomic infant. The more stringent ADA criteria also identified a group of babies at higher risk of perinatal death.

Despite the overall congruence of results from the four studies described above, controversy continued regarding GDM diagnosis, with a worldwide impetus towards a fully powered, blinded
epidemiologic study of hyperglycemia in pregnancy. This was the motivation for the HAPO study.

HAPO has been described in detail elsewhere [10, 13-15]. It was a large, multicenter, multinational, epidemiologic study of 23,316 women (over 30 times larger than the O’Sullivan cohort) who underwent blinded 2 hour, 3 sample, 75 gram OGTTs at 24 – 32 weeks’ gestation. The key finding of HAPO was a linear relationship between each of the glucose values (fasting, 1 hour, 2 hour) on the OGTT and a broad range of pre-defined, carefully ascertained and adjudicated adverse clinical and biochemical pregnancy outcomes. Primary HAPO outcomes were the frequency of large for gestational age (LGA, > 90th centile) babies, primary 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 each of the maternal OGTT glucose results in a continuous fashion. Further, the independent associations of hyperglycemia with pregnancy outcomes persisted after extensive adjustment for potential confounders including maternal BMI, age, height, mean arterial pressure and parity.

In summary, the epidemiologic association of mild pregnancy hyperglycemia with adverse pregnancy outcomes is now well
understood. The major studies have generally been performed with a 75 gram OGTT, without prior GCT. The results, in particular the associations with excess fetal growth and its complications and the risk of pregnancy hypertension, remain consistent despite varying methods of analysis and some variations in reported statistical significance (most likely due to sample size in the smaller cohorts). No study found a clear diagnostic threshold or “inflection point” for any glucose measure above which risk increased sharply. In addressing the challenges of GDM or “hyperglycemia in pregnancy” we need to be mindful of these consistent findings. It is clear that no set of glycemic criteria will ever be able to identify all pregnancies at risk of complications and that any set of criteria proposed will need to evolve from a consensus approach, balancing risks and benefits in particular social, economic and clinical contexts.

**The randomized controlled trials**

The randomized trials performed by Crowther et al (ACHOIS) [16] and Landon et al (MFMU) [17] were also very influential in determining recommendations for GDM diagnosis. It is worthwhile to summarize the similarities and differences between these major trials, both in terms of the cohorts studied and the relevant outcomes.
Crowther et al followed the prevailing WHO criteria for GDM in recruiting women for their trial. Although recruitment of women on the basis of risk factors without a prior glucose challenge test (GCT) was allowed under their protocol, 93% of included participants did undergo an initial GCT, followed by a two sample (fasting and 2 hour) 75 gram OGTT. Women with a 2 hour glucose of 7.8 – 11.0 mmol/L (140 – 198 mg/dL) were eligible for inclusion. The fasting venous plasma glucose (VPG) value was used only to exclude women, initially using fasting VPG ≥ 7.8 mmol/L (later changed to 7.0 mmol/L after a change in WHO recommendations). Thus, it would have been possible for women with marked fasting hyperglycemia to be included in this trial. However, since this degree of fasting hyperglycemia is very uncommon in pregnancy when the 2-hour plasma glucose is <11.1 mmol/L (200 mg/dL), this criterion was rarely invoked. The mean fasting plasma glucose of 4.8 mmol/L (86 mg/dL) in ACHOIS is the same as the mean FPG in the MFMU RCT.

Landon et al also performed a 50 gram GCT, followed in their study by a 100 gram, four sample OGTT. They also used the fasting glucose value solely for exclusion, but applied a much more stringent criterion, excluding women with fasting VPG ≥ 5.3 mmol/L (95 mg/dL). Presumably this was done because they believed that
fasting glucose values above this level definitely required treatment. They followed the US convention of requiring two (by definition “post load”) values ≥ threshold (1 hour - 10.0 mmol/L [180 mg/dL]; 2 hours - 8.6 mmol/L [155 mg/dL]; 3 hours - 7.8 mmol/L [140 mg/dL]) for inclusion.

Some authors have attempted to paint the results of the ACHOIS and MFMU trials as divergent [18]. In fact there is a high degree of congruence in the results of these two studies and given the substantial effort required to conduct such trials and the fact that they took respectively 10 [16] and 6 [17] years to perform, it seems worthwhile to further examine their outcomes.

Both studies showed a reduction in excess fetal growth and related complications with identification and active treatment of mild GDM. This was seen both in terms of mean birthweight, frequency of LGA [16, 17] and reduction in fat mass [17] and in reduction of less common complications such as shoulder dystocia [17]. Hypertensive disorders of pregnancy (gestational hypertension and pre eclampsia) were also substantially reduced by active GDM treatment [16, 17]. Maternal weight gain was lessened by active therapy [16, 17]. Induction of labor was increased by active treatment in the Crowther study [16], but not in the Landon study [17]. Caesarean section
frequency was unchanged in the Crowther study [16] and reduced in the Landon report [17]. A subsequent systematic review has concluded that the observed reductions in LGA, shoulder dystocia and pre eclampsia are consistent across these and other available reports [19].

In an attempt to achieve consensus on uniform diagnostic criteria from this diversity and in response to the HAPO data [10] and the randomized controlled trial data [16, 17], the International Association of Diabetes in Pregnancy Study Groups (IADPSG) convened a workshop conference in June 2008 [20]. Following this conference an IADPSG consensus panel was convened and over the next two years this group developed outcome based criteria for the diagnosis of GDM, which were published in 2010. [20]

The IADPSG consensus panel of 50 people 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 (LGA, excess fetal adiposity and fetal hyperinsulinemia) as compared to the mean of the HAPO study cohort. Potential cut points representing Odds ratios of
1.5, 1.75 and 2.0 were specifically evaluated. In the end, the IADPSG consensus panel recommended that cut off points for the OGTT fasting, 1 hour and 2 hour plasma glucose levels associated with fully adjusted odds ratios of 1.75 for adverse outcomes compared to the rates seen at mean glucose levels of the HAPO cohort should be designated the diagnostic levels for GDM. [20] Translating these numbers from odds ratios to unadjusted hazard ratios (HRs), these thresholds correspond to HRs of approximately 2.0 (two-fold) for the major outcomes considered. [21]

These “IADPSG criteria” have been accepted by a variety of professional and other health care bodies including: The Endocrine Society[22], American Diabetes Association [23], Australasian Diabetes in Pregnancy Society [24] and World Health Organization [25], but challenged by others including the National Institute of Health consensus panel [26] and the American College of Obstetricians and Gynecologists [27]. The Canadian Diabetes Association has been either broad minded or indecisive in allowing two divergent approaches to GDM diagnosis [28]. A summary of known acceptance / rejection or decision pending regarding the IADPSG criteria is presented in Table 1.
“The real world” - testing for hyperglycemia in pregnancy around the world

Consensus between countries and even within countries regarding GDM diagnostic strategies is lacking. Subsequently, GDM prevalence remains difficult to define and compare between countries and development and implementation of management strategies is challenging.

A recent multicenter report from Jiwani et al [29] presents 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. They received and collated data from 47 countries. 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 minimal evidence that these guidelines were being followed. In some countries it was estimated that only 10% of pregnant women received active management after a GDM diagnosis. Most non-responding countries were of low income and it appears likely that GDM is 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. In the USA, the NHANES survey data reports an estimated prevalence of impaired glucose metabolism in women aged 18-44 years outside of pregnancy (Impaired fasting glucose [IFG], Impaired glucose tolerance [IGT] and T2DM) of 30.7%. [30]. Therefore it is not surprising that GDM may also be prevalent in women of 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 prevalence of GDM in different countries and subsequently on the outcome of differing 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, 1h or 2h glucose measurements). [31] HAPO used a 75g OGTT performed between 24-32 weeks 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 California (25.5%), closely followed by Singapore (25.1%), Manchester UK (24.3%) and Bangkok Thailand (23%). The lower prevalence countries included Australia (15.5% in Newcastle and 12.4% in Brisbane) and only 9.3% in Israel. [31]

There was also center to center variation in which glucose measurement(s) met the threshold for the diagnosis of GDM. Across the entire HAPO cohort, 55% of those diagnosed post hoc with GDM by the IADPSG criteria qualified solely on the fasting glucose, 33% solely on the 1 hour glucose and 13% solely on the 2 hour glucose. This has clear implications for the use of the IADPSG criteria in different population groups. It may be possible in some areas to use
an alternative “two step algorithm” or simply target the most common glucose abnormalities in a particular population. For example, in a population with a high frequency of elevations in fasting glucose, an initial measurement of the fasting glucose could potentially detect most cases of GDM. This approach has been evaluated by Agarwal et al in the United Arab Emirates [32]. In such populations, glucose tolerance testing could then either be reserved for those not already diagnosed on the fasting test or eliminated if considered to be of low yield in the local context. By contrast, certain countries, such as India, which have reported predominant abnormalities in post load glucose, might choose to use an approach primarily aimed at detecting such alterations. Such an approach, emphasizing a single glucose estimation 2 hours after a (potentially non fasting) 75 gram load, has been recommended by the Diabetes in Pregnancy Study Group India (DIPSI) [33]. However, in another series from India, fasting glucose was elevated in 87% of women diagnosed with GDM [34]. Therefore selective testing approaches need to be considered in their specific context (even within countries) as all assume a relatively ethnically homogenous population.
Timing of testing for hyperglycemia in pregnancy

Another, sometimes overlooked, recommendation of the IADPSG panel [20] was to develop strategies for early detection of pre-existing diabetes through testing in early pregnancy.

It is important to identify pre-existing diabetes as early as possible in pregnancy, or ideally prior to pregnancy. Pre-existing diabetes is associated with diabetes complications such as retinopathy as well as an increased risk of congenital anomalies and other serious pregnancy complications including gestational hypertension and pre-eclampsia [35]. Early treatment may help to reduce these risks. Recognition of pre-existing diabetes also has implications for the need for monitoring and treatment in the early post-partum period.

IADPSG recommends that pre-existing diabetes should be screened for opportunistically at the first antenatal visit either universally or in high risk women (this decision is left to local discretion) or in all women. The Endocrine Society Guidelines [22]) recommend testing all pregnant women, using the same diagnostic cut-offs which are
recommended in the non-pregnant population. WHO did not issue recommendations on when to test for hyperglycemia in pregnancy.

**One abnormal versus two abnormal values**

The GDM diagnostic criteria initially developed by O'Sullivan [4] required two elevated OGTT values for a diagnosis of GDM. This was an empirical decision and has not gained general acceptance in the diagnosis of diabetes outside of pregnancy. The arguments advanced in favor of this centered largely around poor reproducibility of whole blood glucose measurements in the late 1950s using the whole blood Somogyi – Nelson technique. 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 similar to those found with two or more abnormal values. [36] The requirement for two abnormal values limits the number of women classified as having GDM, but not in any logical way. It essentially represents another (rough) expression of “glucose dose” [37] but does not identify a group of women who are at a uniquely higher risk of complications than those with a single value exceeding
threshold. Although its familiarity gives face validity in the USA, it has never gained prominence in other parts of the world.

Single-step process, elimination of the GCT

In the USA, the American College of Obstetricians and Gynecologists (ACOG) still promotes a two-step process with initial 50g non-fasting glucose challenge test (GCT), with progression to a formal OGTT if the venous plasma glucose one hour after this glucose load exceeds a (variable) threshold. A recent systematic review compares the 50g GCT and the OGTT (either 75g or 100g) to estimate the sensitivity and specificity of the GCT for GDM. [38] 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 around 26% of potential GDM diagnoses.

We would recommend against the widespread use of the GCT in diagnostic algorithms (except perhaps in low resource settings) due to its lack of sensitivity and specificity and the inevitable delay in diagnosis and subsequent initiation of appropriate treatment.

A recent prospective observational study randomized 786 pregnant women to either screen for GDM with a one-step method using a 75g
OGTT using IADPSG criteria (n=386) or a two-step method with 50g GCT and 100g OGTT using the Carpenter and Coustan criteria (n=400) and then analyzed the prevalence of GDM using the one and two step methods. This study also aimed to determine if women diagnosed as having normal glucose tolerance by the two - step method had any worse neonatal outcome than those determined to have normal glucose tolerance by the one - step method[39].

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 had a GDM prevalence of 14.5% and the two step method a prevalence of 6%. Women determined to have normal glucose tolerance in the two - step method had a greater risk of pre-eclampsia and macrosomia compared to the women defined as normal glucose tolerance in the one step method. While this study was small (n-400), the authors propose that this adds support to the arguments for the elimination of the two - step process.
Cost effectiveness of diagnosing GDM

A number of authors have attempted to perform cost benefit analyses regarding alternative strategies of testing and treatment for GDM. These publications are largely theoretical and the results depend heavily on the assumptions used in formulating the specific model employed. In particular, models vary as to whether pregnancy events alone are “costed” or whether costs and benefits are allocated to post pregnancy events, including potential prevention / delay of onset of diabetes in mother and offspring.

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 type 2 diabetes (T2DM)) has been evaluated in cost modeling studies, which concluded that this approach is cost-effective [40, 41] or cost-saving [42]. However, such conclusions may be overly optimistic as although there is some evidence that the onset of diabetes may be delayed by intensive lifestyle interventions [43], no diabetes prevention study has shown substantial overall benefit in terms of prevention of chronic diabetes complications.

There is 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 1 hour GCT followed by the 3 hour OGTT) and the new 2h OGTT with IADPSG guidelines has been reported. [40] This simulation suggested that testing for GDM with the 2h OGTT is more expensive than the 1h GCT screening but that it is more effective as screening, diagnosis and management of women with GDM diagnosed with the 2h OGTT and IADPSG guidelines resulted in a decrease in all measured adverse maternal outcomes and neonatal outcomes.

A second simulation [41] aimed to determine whether adopting the IADPSG criteria would be cost-effective by comparing 3 groups, 1) no screening, 2) current ACOG screening practice (1h 50g glucose challenge test between 24 and 28 weeks followed by 3h 100g glucose tolerance test when indicated), or 3) the screening guidelines proposed by the IADPSG (first prenatal visit fasting glucose, followed by a 2h 75g GTT between 24 and 28 weeks when indicated).

This study reported that using the IADPSG approach to GDM screening and diagnosis compared to the current ACOG screening
practice and a no-screening practice is cost-effective only if a GDM diagnosis helps prevent future T2DM.

A third cost computer simulation model (GDModel) was developed to estimate the potential health impact, net cost, and the cost-effectiveness of various GDM screening and management strategies.[42] The GDModel aims to compare alternative screening algorithms, prenatal interventions, and postpartum preventive lifestyle interventions. The early results this model as applied to health care in India and Israel showed that GDM screening and postpartum lifestyle management are either cost-saving or have a net cost but a positive cost-effectiveness ratio.

A fourth trial conducted in United Arab Emirates (UAE) also attempted to assess the cost and workload involved in a switch from the current 2 step ACOG criteria to the IADPSG criteria. [44] The costs involved in using the fasting plasma glucose (FPG) on the 2 hour OGTT alone to make the diagnosis of GDM were also investigated. If the FPG was > 7 mmol/l, overt diabetes was diagnosed. If the FPG was 5.1 – 6.9 mmol/l the patient was diagnosed as having GDM. If the FPG was between 4.4 and 5.1 mmol/L, the result was considered indeterminate and the full 2h OGTT was completed. In this specific patient group (predominantly Arabic
origin) there is a very high estimated prevalence of GDM, varying from 8-25% 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 hour OGTT can avoid 50% of full OGTTs. [45]

This UAE study reported that the use of the new IADPSG criteria was the most costly of the 3 strategies. However, if the FPG (using the IADPSG criterion of 5.1mmol/L) was used to determine the need to progress to the full OGTT then this was the most cost effective strategy for this particular patient population and pathology system. [44]

These 4 trials provide some support for cost effectiveness in the diagnosis and treatment of GDM. However, all findings are heavily model dependent and need to be considered in the context of specific health systems. 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.

Low resource settings
The situation of low resource settings must be considered in the discussion of implementing internationally acceptable criteria for the diagnosis of GDM (REF Colagiuri 2014 DRCP). The formal 2 h OGTT is an expensive and resource intensive test. [46] The IADPSG recommends the universal testing of women with a 2h OGTT which has major cost implications for low resource settings. Further, the place of diabetes and GDM among the causes of maternal and perinatal morbidity and mortality in low resource settings is presently unknown. The investigation of the use of simpler investigations such as using only FPG 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. [31] The lowest rates of diagnosis on the FPG alone are in women of South East Asian origin (Thai and Hong Kong cohorts in the HAPO trial) and highest (>70%) in Barbados and the US HAPO cohorts, with groups in UK and Australia falling in between. In the HAPO cohorts overall 55% of women with GDM had FPG meeting the criteria for IADPSG GDM diagnosis (>5.1mmol/L). Despite its large cohort size, the HAPO study was not population based and is unlikely to be representative.
of all world populations. Data on the local population of women of child bearing potential are desirable.

The low cost algorithm proposed by the UAE group, discussed in the previous cost effectiveness section, may suit settings where the diagnosis of GDM is more likely to be made on the FPG alone. [47] Even though the UAE is not a resource poor setting there are still difficulties in arranging for all women to attend for the full 2h OGTT. Preliminary data from Cameroon also show that FPG ≥ 5.1 mmol/L diagnosed 90% of GDM, with a limited added value of the 2 hour OGTT measurement (E. Sobngwi, personal communication).

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 2h OGTT is the only recommended test. Further, more wealthy nations will also need to deal with the logistics of arranging for all women to have a 2h OGTT.

An alternative approach to this has been to use the finger stick capillary glucose measure. [48] It has been suggested that this can
prevent the need for a full OGTT in up to 50% 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 low resource settings, though further studies assessing its utility in populations with a lower GDM prevalence are needed. Another potential approach might involve 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 “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 low resource settings, but would require formal evaluation of the specificity and sensitivity of such a testing protocol, as well as a cost – benefit analysis.

**Conclusions and Future Perspectives**
The acceptance of uniform criteria for the diagnosis of GDM and subsequent treatment and follow up of this group of women is needed. WHO recently recommended adopting the IADPSG criteria in the interest of moving towards a universal standard recommendation for the diagnosis of GDM. [25] (also REF DRCP 2014) This may assist with international acceptance of these diagnostic thresholds. Table 1 shows the acceptance / rejection of the IADPSG criteria by a range of countries and societies. International use of the same criteria for GDM diagnosis would allow useful comparisons regarding treatment and longer term outcomes for this population group. The diagnosis and appropriate management of GDM provides the ideal opportunity for healthy interventions for a large group of women with potential for improved outcomes for their current pregnancy, offspring and future health. As part of its commitment to promoting comprehensive maternal health services along a continuum of care, the International Federation of Gynecology and Obstetrics (FIGO) recently embarked on an initiative to develop evidence based protocols on caring for women with gestational diabetes. In this way the document will be able to define the best, optimal and minimal care and individual
member associations of FIGO can choose which one they will promote as the most appropriate for their region. And even within regions and countries, individual clinics and doctors can decide which level they will adopt for their practice.

**Practice points**

The continuous epidemiologic relationship between maternal hyperglycemia and pregnancy complications including excess fetal growth and its consequences and the risk of pre eclampsia is well defined. Substantial, though not complete, consensus has been achieved regarding the use of the IADPSG diagnostic criteria for identification of a group of women at higher risk of pregnancy complications as meriting a diagnosis of “GDM”, but it is important to recognize that this description does not clearly separate “normal” from “abnormal” in terms of the risk of pregnancy complications related to hyperglycemia.

**Research agenda**

The implementation of widespread testing for GDM and delivery of appropriate therapy remains a major challenge on a worldwide basis. Individual countries and clinical settings will need to investigate the
contribution of GDM to pregnancy complications in their local context and develop appropriate policies for GDM detection and treatment.

Acknowledements:
“The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of WHO.”
Table 1. Uptake of IADPSG diagnostic criteria

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<td>European Association of Perinatal Medicine (EAPM) + (to be approved at the ECPM, June 2014)</td>
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<td>(FIGO GDM Initiative Expert Committee - work in progress)</td>
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<td>National Institutes of Health Panel (USA)</td>
<td>Israel (pending approval of Ministry of Health)</td>
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**Abbreviations used:**
GDM – Gestational diabetes
GCT – glucose challenge test
OGTT- oral glucose tolerance test
FPG – fasting plasma glucose
IFG – Impaired fasting glucose
IGT – Impaired glucose tolerance
T2DM – type 2 diabetes
IADPSG – International Association for Diabetes in Pregnancy Study Group
ADA – American Diabetes Association
NIH – National Institutes of Health
ACOG – American College of Obstetrics and Gynecology
ADIPS – Australian Diabetes in Pregnancy Society
WHO – World Health Organization
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