Translating the HAPO Study into New Diagnostic Criteria for GDM? From HAPO to IADPSG and Back to O’Sullivan

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Abstract: The various strategies to diagnose gestational diabetes mellitus (GDM), starting from O’sullivan, followed by numerous opinions and recommendations and up to the recently published International association of diabetes and pregnancy study groups criteria, have been and still are the subject of extensive and ongoing debate, since the 1960s, and holding, fiercely than ever, nowadays. In this review we shall provide an overlook on the history of GDM diagnosis, concentrating on the interpretation of the hyperglycemia and adverse pregnancy outcome results into clinical guidelines, and the pros and cons for changing the criteria for GDM diagnosis.

Key words: HAPO, IADPSG, pregnancy, diabetes

Introduction
Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance first diagnosed during pregnancy.1 It is associated with adverse outcome not only for the mother, but also for the fetus, neonate, child, and adult offspring of the diabetic mother. Maternal consequences include increased rate of operative and cesarean delivery, preeclampsia, and future risk for type 2 diabetes mellitus (T2DM). Fetal complications include macrosomia, shoulder dystocia, and birth trauma. The neonate is at risk for respiratory distress syndrome, neonatal intensive care (NICU) admission, hypoglycemia, hyperbilirubinemia, polycythemia, and other electrolyte imbalances. Later in life, as the result of in utero
exposure to glucose and insulin, the child and adult are prone to develop obesity, T2DM, and GDM.

The worldwide incidence of GDM varies widely, and is on the rise, paralleling the pandemic proportions of obesity and T2DM. GDM prevalence ranges between 1% and 28%, with a median of 5% to 8%, depending upon race, ethnicity, obesity, family history, and other comorbidities. In light of the increasing incidence of all of these factors, mainly obesity and T2DM, it seems probable that the rate of GDM is on the rise.

The various strategies to diagnose GDM, starting from O’Sullivan, followed by numerous opinions and recommendations and up to the recently published International association of diabetes and pregnancy study groups (IADPSG) criteria, have been and still are the subject of extensive and ongoing debate, since the 1960s, and holding, fiercely than ever, nowadays. In this review, we shall provide an overlook on the history of GDM diagnosis, concentrating on the interpretation of the hyperglycemia and adverse pregnancy outcome (HAPO) results into clinical guidelines, and the pros and cons for changing the criteria for GDM diagnosis.

How Did It Come To Be?

FIRST CAME O’SULLIVAN
The foundation for GDM diagnosis was laid down by O’Sullivan and Mahan in the early 1960s. Thresholds for diagnosis were based on 2 SD above the mean blood glucose values for 752 pregnant women. The definition of an abnormal 100 g oral glucose tolerance test (OGTT) was selected to identify women at risk for subsequent T2DM. Many follow-up studies have confirmed that the diagnosis of GDM, based on those designations, indeed categorizes women at high risk for future postpartum diabetes.

THE PRE-HAPO ERA
Current guidelines for GDM diagnosis were last presented in the fourth and fifth international Workshops and are based on O’Sullivan’s work with some modifications. They were endorsed by the American College of Obstetricians and Gynecologist (ACOG) and the American Diabetes Association (ADA). The World Health Organization has published other criteria, derived from classification of impaired glucose tolerance in a nonpregnant population using a universal 75 g OGTT in which only fasting and 2-hour measurements are used. Nevertheless, other organizations have modified these criteria or abandoned GDM screening all together.

Current strategy for screening and diagnosis of GDM is summarized in Tables 1 and 2. Screening may be universal (for all pregnant women) or selective (depending upon risk factors). Screening is usually achieved by a 50 g glucose challenge test (GCT). The cutoff for a positive screening test is typically set at 130 to 140 mg/dL (7.2 to 7.8 mmol/L), at which 14% to 23% of women will be screen positive. As the precise cost-benefit ratio for diagnosing GDM remains unresolved, both thresholds are acceptable, and are decided locally. In regions with a high prevalence of GDM/T2DM it is reasonable to use the lower threshold, for increased sensitivity, and in low prevalence regions, cost-effectiveness may favor the choice of a higher threshold. If screening is positive, a diagnostic OGTT is preformed, measuring glucose while fasting and 1, 2, and 3 hours following 100 g of glucose load. At least 2 of the 4 OGTT values should be abnormal to diagnose GDM either using the Carpenter and Coustan criteria or the National Diabetes Data Group thresholds. Alternatively, one of 2 values if a 75 g OGTT is used as suggested by the World Health Organization (Table 2).

The clinical significance of GDM is related first and foremost to the associated
pregnancy complications, rather than to future development of maternal diabetes. Thus, the diagnostic value of O’Sullivan’s criteria—and based upon guidelines—are of limited value. Multiple studies have suggested that the glucose values which have an impact on pregnancy outcome are indeed lower than those suggested.\textsuperscript{29–36} However, the true levels of hyperglycemia that have an impact on pregnancy outcome were not established in a properly designed trial. To establish the evidence base for the diagnosis of GDM, the HAPO study was initiated, aiming to provide the evidence for GDM diagnostic criteria, and to clarify relationship between maternal hyperglycemia and adverse pregnancy outcome.\textsuperscript{37}

### TABLE 1. Screening Strategy for Detecting GDM

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Blood glucose testing not routinely required</td>
</tr>
<tr>
<td></td>
<td>If all of the following characteristics are present:</td>
</tr>
<tr>
<td></td>
<td>Member of an ethnic group with a low prevalence of GDM</td>
</tr>
<tr>
<td></td>
<td>No known diabetes in first-degree relatives</td>
</tr>
<tr>
<td></td>
<td>Age ≥ 25 y</td>
</tr>
<tr>
<td></td>
<td>Normal weight before pregnancy</td>
</tr>
<tr>
<td></td>
<td>Normal weight at birth</td>
</tr>
<tr>
<td></td>
<td>History of abnormal glucose metabolism</td>
</tr>
<tr>
<td></td>
<td>No history of poor obstetric outcome</td>
</tr>
<tr>
<td>Average risk</td>
<td>Perform glucose testing at 24-28 wk using either:</td>
</tr>
<tr>
<td></td>
<td>2-step procedure: 50 g GCT followed by a diagnostic OGTT in those meeting the threshold value in the GCT</td>
</tr>
<tr>
<td></td>
<td>1-step procedure: diagnostic OGTT performed on all subjects</td>
</tr>
<tr>
<td></td>
<td>If none of the low-risk or high-risk criteria is fulfilled</td>
</tr>
<tr>
<td>High risk</td>
<td>Perform blood glucose testing as soon as feasible, using the procedures described above:</td>
</tr>
<tr>
<td></td>
<td>If GDM is not diagnosed, blood glucose testing should be repeated at 24-28 wk or at any time a patient has symptoms or signs suggestive of hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>If any one of the above, or one or more of these present:</td>
</tr>
<tr>
<td></td>
<td>Severe obesity</td>
</tr>
<tr>
<td></td>
<td>Strong family history of type 2 diabetes</td>
</tr>
<tr>
<td></td>
<td>Previous history of: GDM, impaired glucose metabolism, or glucosuria</td>
</tr>
</tbody>
</table>

GCT indicates glucose challenge test; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test.

### TABLE 2. Diagnosis of GDM by an Oral Glucose Tolerance Test (OGTT)

<table>
<thead>
<tr>
<th>Glucose</th>
<th>Carpenter and Coustan</th>
<th>NDDG</th>
<th>WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 g</td>
<td>100 g</td>
<td>75 g</td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>95 mg/dL 5.3 mmol/L</td>
<td>105 mg/dL 5.8 mmol/L</td>
<td>110 mg/dL 6.1 mmol/L</td>
</tr>
<tr>
<td>1 h</td>
<td>180 mg/dL 10.0 mmol/L</td>
<td>190 mg/dL 10.6 mmol/L</td>
<td>— —</td>
</tr>
<tr>
<td>2 h</td>
<td>155 mg/dL 8.6 mmol/L</td>
<td>165 mg/dL 9.2 mmol/L</td>
<td>140 mg/dL 7.8 mmol/L</td>
</tr>
<tr>
<td>3 h</td>
<td>140 mg/dL 7.8 mmol/L</td>
<td>145 mg/dL 8.0 mmol/L</td>
<td>— —</td>
</tr>
</tbody>
</table>

GDM indicates gestational diabetes mellitus; NDDG, National Diabetes Data Group; OGTT, oral glucose tolerance test; WHO, World Health Organization.

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The HAPO study was a prospective, observational, multinational, blinded study, encompassing approximately 25,000 women, each performing a 2-hour 75 g OGTT during 24 to 28 weeks of gestation. The caregivers and the participating women were blinded to the results, unless, hypoglycemia or overt diabetes were detected. HAPO results demonstrate a linear association between increasing levels of fasting, 1- and 2-hour plasma glucose post a 75 g OGTT, to all 4 primary endpoints of the study: birth weight above the 90th percentile, cord blood C-peptide level above the 90th percentile, primary cesarean delivery, and clinical neonatal hypoglycemia. Positive correlations were also found to the 5 secondary outcomes: premature delivery, preeclampsia, shoulder dystocia or birth injury, NICU admission, and hyperbilirubinemia. The associated morbidity was demonstrated at minimal levels of maternal hyperglycemia, and did not occur at a specific threshold, rather, a linear continuum of growing risk with increasing hyperglycemia.

The results of the HAPO study are supported by previously published studies that also reported a continuous association between different measures of hyperglycemia to large-for-gestational-age (LGA) newborns, cesarean section rate, preterm delivery, shoulder dystocia or birth injury, NICU admission, and hyperbilirubinemia. Secondary analyses of the HAPO cohort demonstrated several key findings: (1) maternal hyperglycemia, C-peptide, and body mass index (BMI) are associated with preeclampsia. (2) There is correlation between maternal hyperglycemia, on all OGTT values, and cord C-peptide to neonatal adiposity. (3) BMI, independent of maternal glycemia, is strongly associated with adverse pregnancy outcome, particularly, LGA, adiposity, and preeclampsia. GDM and obesity are independently associated with adverse pregnancy outcomes and their combination has a greater impact than either one alone. (4) Biochemical and clinical neonatal hypoglycemia are weakly related to OGTT glucose measurements, but strongly associated with cord C-peptide. Other than ancillary and secondary analysis of the HAPO, multiple commentaries, views, and opinions were published.

Into this atmosphere came the IADPSG, aiming to convert the results of the HAPO into practical guidelines, as was done only once, more than 50 years earlier, with O’Sullivan’s data. The IADPSG criteria attempt to solve to long-standing controversy on the diagnosis of GDM, and were for sure assumed to do so, as they are based on a solid base of evidence—but this was not the case, and as will be discussed later, the debate lives.

The overall strategy recommended by the IADPSG Consensus Panel for detection and diagnosis of hyperglycemic disorders in pregnancy is summarized in Table 3. Thresholds for diagnosis of overt diabetes during pregnancy are summarized in Table 4, and for GDM diagnosis in Table 5. Shortly, at the first prenatal visit, all (universal) or only high-risk (selective) women should be tested for either fasting plasma glucose (FPG), glycosylated hemoglobin, or random plasma glucose. The choice for screening is based on the background frequency of abnormal glucose metabolism and on local circumstances. Criteria for low-risk women for GDM include all of the following: absence of diabetes in first-degree relatives, age of less than 25 years, normal prepregnancy weight, no history of poor carbohydrate metabolism, and no history of adverse pregnancy outcome. High-risk criteria include one of the following: pre-pregnancy obesity, family history T2DM, GDM in a prior pregnancy, and known
carbohydrate intolerance or glucosuria. To diagnose GDM at 24 to 28 weeks of gestation, a 2-hour 75 g OGTT is recommended to be performed after overnight fasting, for all women not previously found to have overt diabetes or GDM during earlier testing.

CANNOT DO WITHOUT CROWTHER AND LANDON
Alongside the HAPO study, 2 other trials were being conducted—published in 2005 and 2009—concerning the choice of threshold values for GDM treatment, rather than diagnosis.60,61 These were randomized control trials (RCTs), comparing active treatment versus standard care for women with mild hyperglycemia in pregnancy, at glucose levels lower than those commonly used. The definition for mild hyperglycemia in the ACHOIS trial by Crowther et al60 was a GCT over 140 mg/dL (7.8 mmol/L) and a 75 g OGTT fasting glucose <140 mg/dL (7.8 mmol/L) and 140 to 198 mgdL (7.8 to 11.0 mmol/L) at 2 hours. In the NICHD-MFMU trial by Landon et al,61 GCT-positive women with at least 2 of 3 abnormal OGTT, were included, but with FPG <95 mg/dL (5.3 mmol/L). In both the trials, treatment of mild GDM reduced birth weight, LGA, and preeclampsia with cesarean rate reduced in 1

TABLE 3. Strategy for the Detection and Diagnosis of Hyperglycaemia Disorder in Pregnancy

<table>
<thead>
<tr>
<th>First prenatal visit</th>
<th>Measure one of the following, on all or only high-risk women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose (FPG)</td>
<td>If results indicate overt diabetes as per Table 4</td>
<td>Preexisting diabetes</td>
</tr>
<tr>
<td>Hemoglobin A1C</td>
<td>If results not diagnostic of overt diabetes as per Table 4 and FPG is 92-126 mg/dL (5.1-7.0 mmol/L)</td>
<td>GDM</td>
</tr>
<tr>
<td>Random plasma glucose</td>
<td>If results not diagnostic of overt diabetes as per Table 4 and FPG &lt;92 mg/dL (5.1 mmol/L)</td>
<td>Test for GDM from 24 to 28 wk with a 75 g OGTT</td>
</tr>
<tr>
<td>24-28 wk</td>
<td>Perform 75 g OGTT on all women not previously diagnosed with overt diabetes or GDM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L)</td>
<td>Preexisting diabetes</td>
</tr>
<tr>
<td></td>
<td>If one or more values ≥ thresholds as per Table 5</td>
<td>GDM</td>
</tr>
<tr>
<td></td>
<td>If all values &lt; thresholds as per Table 5</td>
<td>Normal</td>
</tr>
</tbody>
</table>

GDM indicates gestational diabetes mellitus; OGTT, oral glucose tolerance test.

TABLE 4. Threshold Values for Diagnosis of Overt Diabetes in Pregnancy

<table>
<thead>
<tr>
<th>Measures of Glycemia</th>
<th>Threshold</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose</td>
<td>≥ 7.0 mmol/L</td>
<td>≥ 126 mg/dL</td>
</tr>
<tr>
<td>Hemoglobin A1C</td>
<td>≥ 6.5%</td>
<td></td>
</tr>
<tr>
<td>Random plasma glucose</td>
<td>≥ 11.1 mmol/L</td>
<td>≥ 200 mg/dL</td>
</tr>
</tbody>
</table>

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of the RCTs. The result of both studies demonstrated that intervention, by lifestyle modification, diet, and insulin resulted in improved pregnancy outcome.

Because of significant overlap between glucose values used for inclusion in the RCTs and those recommended by the IADPSG, it was used as backing for the IADPSG consensus. However, the extrapolation of conclusion from any of these 2 trials to support the IADPSG criteria may be misplaced as the methodology of the trials versus the HAPO, were not similar in many aspects. First, a 2-stage screening (GCT) and diagnosis (75 or 100 g OGTT) was used to select the women to participate in the RCTs, and not a single-step diagnostic 75 g OGTT, as in the HAPO. Also, the inclusion criteria, as well as the level of glyce- mia considered eligible were different.

**Frequently Asked Questions for Adopting the IADPSG Recommendations**

Current guidelines are related to outcomes such as postpartum T2DM or non-pregnant thresholds. The HAPO study, for the first time, provided the evidence base for perinatal outcomes, to allow for a clinically relevant diagnosis of GDM. As the results showed a continuous relationship between glucose values to perinatal adverse outcome, no cutoff exist. Determining it is therefore arbitrary, and is not a pure medical issue. This is what the IADPSG did, and that set the debate in the literature, for or against adopting the recommendations.

The key point in this debate is considering the prevalence of GDM. Implementing the IADPSG criteria on the HAPO study population sets the prevalence of GDM at approximately 18%, ranging from 10% to 25%, in the HAPO participating center. Other reports set the prevalence of GDM at 12.4% to 37.7%, using the newly proposed criteria. This point has been a major weak point in the IADPSG recommendation, as it seems that the prevalence of GDM using the new criteria appears to exceed the anticipated eventual increase in the prevalence of T2DM.

In the following sections we shall explore the arguments against and in favor for the suggested criteria.

**TABLE 5. Threshold Values for Diagnosis of GDM**

<table>
<thead>
<tr>
<th>Glucose Measure</th>
<th>Glucose Threshold mmol/L</th>
<th>mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose</td>
<td>5.1</td>
<td>92</td>
</tr>
<tr>
<td>1 h after 75 g OGTT</td>
<td>10.0</td>
<td>180</td>
</tr>
<tr>
<td>2 h after 75 g OGTT</td>
<td>8.5</td>
<td>153</td>
</tr>
</tbody>
</table>

GDM indicates gestational diabetes mellitus; OGTT, oral glucose tolerance test.

**HOW TO DIAGNOSE EARLY GDM AND OVERT DIABETES IN PREGNANCY?**

Before the suggested IADPSG guidelines, it was that per definition, any carbohydrate intolerance discovered during pregnancy is GDM. However, this is not truly the case, as women may have overt diabetes, simply not tested or not diagnosed before pregnancy. As the epidemic of obesity and T2DM grows, such cases become more prevalent. Moreover, others may have GDM diagnosed early in pregnancy, not preexisting before pregnancy. The possibility to diagnose overt diabetes during pregnancy is important as it has practical implications on prenatal care and postpartum management. The importance of recognizing these women involves: higher prevalence of major congenital malformations, possibility of diabetic nephropathy and retinopathy during pregnancy, and continued treatment of diabetes after delivery.

The novel approach presented in the IADPSG criteria allows for the diagnosis of...
early GDM and overt diabetes, to be made during early pregnancy. However, these recommendations have few drawbacks: (1) guidelines for early diagnosis of overt diabetes and GDM are supported mainly by expert opinion; (2) it has not been determined whether universal or selective testing should be done, and the IADPSG has left it to be decided by local preferences; (3) there is no recommendation as of the timing of such screening and is vaguely defined to be done “during the first prenatal visit”; (4) there are no data to support that treatment of early GDM, will improve outcome.

Recently, in the ADA’s standards of medical care in diabetes, the definition has been revised to “GDM diagnosed during pregnancy and not definitively overt diabetes.” This is in concordance with IADPSG recommendations, which gives practical methods on how to accomplishing this new definition.

HOW TO CHOOSE PREGNANCY OUTCOME?
To determine diagnostic thresholds, the primary preparatory step is to select the related outcome to be associated with the cutoff. The HAPO study explored endpoints related to adverse pregnancy outcome, including 4 primary and 5 secondary outcomes: (1) birth weight above the 90th percentile; (2) cord blood serum C-peptide level above the 90th percentile; (3) primary cesarean delivery; (4) clinical neonatal hypoglycemia; (5) premature delivery; (6) preeclampsia; (7) shoulder dystocia or birth injury; (8) NICU admission; and (9) hyperbilirubinemia. The HAPO results demonstrated strong linear associations between LGA babies, cord C-peptide, and neonatal adiposity with each of the 75 g OGTT values. Therefore, as O’Sullivan chose postpartum T2DM, the IAPPSC consensus panel chose the associations with these 3 outcomes. These outcomes, and primarily LGA, were chosen because they showed the strongest associations to glucose values, and considered to be important constituents of diabetic fetopathy.

This approach was supported not only by the HAPO results, but also by previous publications that have established that LGA and fetal macrosomia are correlated to gestational hyperglycemia. In the HAPO Study, LGA babies were at an increased risk of a cesarean delivery and clinical neonatal hypoglycemia. Others have shown that LGA is independently associated with other adverse pregnancy outcome, such as: neonatal adiposity, fetal hyperinsulinemia, and birth trauma.

Nevertheless, the choice of these outcomes sustained major criticism. The selected outcomes are not the true clinically important outcome that should guide the diagnosis. Rather, LGA is a surrogate marker to difficult delivery and future maternal and offspring metabolic anomalies. Also, there is no long-term follow-up to determine if these LGA babies are at an increased risk for metabolic complications and no proof that reducing macrosomia will result in long-term benefits. The more relevant outcomes and the ones that should have been chosen are: cesarean section rate, shoulder dystocia, and preeclampsia. However, these outcomes and other endpoints that have been explored in the HAPO study produced much more modest risk ratio: neonatal hypoglycemia, (1.18 for the 2-h plasma glucose to 1.24 for the FPG), shoulder dystocia and/or birth injury (1.3 for the FPG to 1.43 for the 2 h), or preeclampsia (1.4 for the FPG to 1.57 for the 2 h). Such risk ratio’s are far from being useful to discriminate between the healthy and the sick with GDM.

Therefore, it is questionable whether the choice of LGA as an outcome is an adequate and clinically relevant endpoint, upon which to base the diagnosis of GDM. If GDM, diagnosed accordingly to IADPSG, has no long-term effect than the need to diagnose mild cases is negated.
This fact emphasizes the need for a long-term follow-up of the HAPO population.

**HOW TO SET THE ODDS RATIO (OR)?**

The IADPSG consensus panel acknowledged that the choice of thresholds for associations that are continuous and linear is arbitrary, and an OR of 1.75 was recommended for the diagnosis of GDM. The IADPSG recommended thresholds that are the average glucose values at which odds for birth weight above the 90th percentile, cord C-peptide above 90th percentile, and percent body fat above 90th percentile reached 1.75 times the estimated odds of these outcomes at mean glucose values. The glucose values at a 1.75 OR are: 5.1 mmol/L (92 mg/dL), 10.0 mmol/L (180 mg/dL) and 8.5 mmol/L (153 mg/dL) for FPG, 1- and 2-hour OGTT plasma glucose concentrations, respectively (Table 5). OR of 1.75 identifies 17.8% of the HAPO population as diabetic—16.1% with one or more glucose values that meet or exceed the threshold and 1.7% of the cohort with overt diabetes. Accordingly, at this OR, adverse pregnancy outcome is increased, including: preeclampsia [risk ratio (RR) = 2.02, \(P < 0.001\)], LGA (RR = 1.95, \(P < 0.001\)), cord C-peptide (RR = 2.62, \(P < 0.001\)), newborn adiposity (RR = 1.96, \(P < 0.001\)), preterm delivery (RR = 1.47, \(P < 0.001\)), shoulder dystocia or birth injury (RR = 1.44, \(P < 0.01\)), and cesarean delivery (RR = 1.45, \(P < 0.001\)).

The value of 1.75 is arbitrary, and as such has been debated and questioned extensively, in multiple aspects: increased prevalence, not easy to remember cutoffs, lack of evidence to support treatment, and more. Ryan concluded that an OR of a 1.75 would lead to GDM diagnosis in 4150 women of the HAPO cohort (with 296 LGA babies) rather than in 2448 women (with 181 LGA babies) if an OR of 2.0 would have been applied. The expected benefit in these 1702 additional women would be the prevention of 140 cases of LGA, 21 cases of shoulder dystocia, and 16 cases of birth injury. At an OR of 2.0, the incidence of GDM in the HAPO cohort is reduced from 16.1% to 8.8%, meaning that the higher thresholds will not label many cases with GDM, while keeping a comparable risk of adverse outcomes.

**IS IT THE GLUCOSE OR OBESITY?**

Obesity, as GDM, is associated with adverse pregnancy outcome. The rates of obesity have more than doubled in the last decade all over the world, reaching a 30% epidemic in the United States. Women with a BMI over 30 kg/m² are 3.5 to 4 times at risk for GDM. It has been suggested that obesity, rather than glucose, may have a greater risk ratio for adverse perinatal complications than hyperglycemia.

However, the risk of hyperglycemia is underestimated in the HAPO population as with FPG > 5.8 mmol/L (105 mg/dL) or those with 2-hour 75-g values > 11.1 mmol/L (200 mg/dL), were excluded from the study population, and this was not done for extreme BMI classes. Also, secondary analysis of HAPO data demonstrated that maternal BMI is independently associated with pregnancy complications and the combination of both is the riskiest.

An interesting use of BMI was suggested by Kalter-Leibovici et al. They analyzed the 3345 Israeli HAPO participants, in 3 subgroups: GDM according to IADPSG criteria; GDM according to IADPSG criteria with risk stratification or screening with BMI or FPG. They found that one third of IADPSG-positive women were at low risk for adverse outcomes and could be managed less intensively, and this subpopulation can be identified by means of risk stratification with BMI (< 33.5 kg/m²) or FPG (< 88 mg/dL at 28 to 32 wk), so as to
prevent overtreatment and reducing the number of women requiring treatment.

Both entities—diabetes and obesity—are of importance, they are not mutually exclusive, and should be dealt as such and not competed.

HOW TO MEASURE GLUCOSE?
During the HAPO trial, emphasis was made on the laboratory measurements of glucose, to achieve reliable diagnosis and classification of hyperglycemia in pregnancy. Venous plasma or serum glucose using an enzymatic method with high accuracy and precision was used by a central reference laboratory. Strict criteria were kept to insure proper sample collection and processing to minimize preanalytic glycolysis and proper laboratory analysis. Although highly accurate, this may hinder problems, because keeping such rigorous laboratory standard for glucose is impractical in the day to day practice outside of clinical research.

Also, as the OGTT has a poor reproducibility of 24% to 34%, and even lower when glucose values are lower. Thus, any minute change in the glucose threshold will be lost, and many women will be diagnosed as GDM, by laboratory limitations. Similarly, as the minor changes in OGTT glucose values are smaller than the usual coefficient of variation for glucose testing of 3%, the change will be lost with the laboratory.

IS THERE A BENEFIT FOR ALL THE NEWLY DIAGNOSED?
Other than all the practical issues for implementing the IADPSG criteria, the single most important question—is it indeed better for the women and their offspring?

The 2 previously mentioned treatment trials do indeed show an improvement in perinatal outcome when treating lower glucose values. As such, their results were used to support treatment according to IADPSG thresholds. However, the definitions for mild GDM diagnosis in those RCTs were not similar to those suggested by the IADPSG, and were likely to include more severe cases of GDM.

Treating GDM is usually straightforward and uncomplicated, mostly by diet, with 8% to 20% failing to achieve glycemic control, switching to pharmacological treatment. This may be interpreted in favor for adopting low thresholds, so all will be diagnosed and treated. However, this does not take into account overdiagnosis and overtreatment that may occur resulting in breaking the primary directive of rule of primum non nocere. Iatrogenic outcomes of GDM management may include: frequency of visits and monitoring, labor induction, cesarean section, and more. Other nonbeneficiary aspects include patient’s discomfort of self-monitoring blood glucose, frequent prenatal care appointments, and last but not least the psychological burden on those diagnosed.

Bodmer-Roy et al compared 186 women with IADPSG-defined GDM versus 372 women with classically defined GDM, and found that the rate of adverse pregnancy outcome is similar. Therefore, treating minor glucose abnormalities does not seem to be beneficiary to the patient, and may indeed be harmful. Currently, there is no evidence to support that those diagnosed with GDM according to the IADPSG scheme will benefit from treatment. Also, treating early GDM, before 24 to 28 weeks, has yet to be proved as beneficial.

IS THE IADPSG CRITERIA TOO CUMBERSOME?
The IADPSG approach suggested a universal 75 g OGTT, which means that each and every pregnant woman would need to undergo the OGTT—this is very demanding, both clinically and economically. Prior ADA recommendation were that low-risk populations should use risk-based or GCT screening to avoid the demanding OGTT, and the OGTT was
used only in high-risk women. In contrast, some have suggested that by performing a single-step methodology, the diagnosis of GDM will be easier for both the patients and caregivers, with better compliance, and earlier diagnosis of GDM.

Data support the first notion that the OGTT is a costly and cumbersome test. Agarwal and colleagues studied the UAE population which has the second highest T2DM prevalence (approximately 20%) and a GDM prevalence of 8% to 25%. They have learned that universal OGTT in a nearly impossible logistic task even in affluent medical systems and that for poorer countries it may be an incentive to abandon GDM diagnosis all together.

Alternatively, Agarwal and colleagues has suggested a 2-threshold approach based on FPG as a screening procedure. A high FPG rules in the diagnosis of GDM, a low FPG rules out GDM, and in both the cases circumvents the need for an universal OGTT. Any value in between mandates an OGTT. The decision to do or not to do an OGTT is made on-site, once the FPG results have turned in. In the HAPO population $F_{PG} \geq 5.1 \text{ mmol/L}$, as suggested by the IADPSG, rules in the diagnosis of GDM, and if $F_{PG} \leq 4.4 \text{ mmol/L}$ that GDM is effectively ruled out (although discussed by the IADPSG, this cutoff as not endorsed in the recommendations).95 Agarwal and colleagues studied 10,283 women using the IADPSG criteria and the 2-threshold approach—29% had $F_{PG} \geq 5.1 \text{ mmol/L}$ and 22% had $F_{PG} \leq 4.4 \text{ mmol/L}$. The 2-threshold approach would save 50.6% of the OGTTs, and missed GDM in only 4.6% of the cases.95 However, in the same approach for the HAPO population, 57% of the women are spared from the OGTT; however, nearly one quarter of the GDM cases are missed.71

The 2-threshold approach in of course limited by laboratory timing, as the woman has to wait in the fasting state before the decision is made to proceed or not with the OGTT. This can be shortened by using a venous blood sample on a glucometer96 or even a capillary sample with a glucometer.97

**IS IT COST-EFFECTIVE OR JUST COSTLY?**

Concern has been raised regarding the cost and cost-effectiveness of detecting and treating GDM, even before the IADPSG. The United States preventive services task force, the UK National Health Service, and the Canadian Task Force on the Periodic Health Examination have asserted that there is insufficient good-quality evidence to recommend for or against screening for GDM.26–28 This concern has been raised again, following the IADPSG publication, suggesting that adopting IADPSG recommendations will result in more GDM than the health resources can cope with.63–65

Using current testing criteria in GDM prevalence in the United States is 5% to 6%, affecting approximately 240,000 of 4 million births annually, at a cost of 636 million dollars each year.98 The lower threshold in the newly suggested criteria will increase GDM prevalence by approximately 3-fold, consequently translating into dollars that will be drained from other priorities. The new IADPSG algorithm is expected to increase parameters such as: diagnostic workload, maternal-fetal specialist availability, diabetes nurses, and dieticians. It also means more fetal (although limited proof of efficacy) and maternal testing, more labor inductions (some causing iatrogenic prematurity), and more operative and cesarean deliveries (some being unnecessary). A problem still unsolved is how much workdays will be lost, when all pregnant women will spend a day when the 75 OGTT is preformed in all women.74

Several studies have attempted to address the question that whether implementing the IADPSG guidelines will be
cost-effective. Agarwal et al\textsuperscript{99} studied the cost and laboratory work loads of the IADPSG criteria versus the traditional 2-step approach, and calculated that it will increase costs by 42\% and decrease laboratory work load by 36\%. Werner et al\textsuperscript{100} found that the new criteria are cost-effective, but only if postdelivery consultation is provided to reduce the frequency of T2DM. For every 100,000 women, 6178 quality-adjusted life-years are gained at a cost of >125 million dollars. The incremental cost-effectiveness ratio for the IADPSG strategy compared with current standard was 20,336 dollars per a single quality-adjusted life-year gained. Ohno et al\textsuperscript{101} investigated the cost-effectiveness of treating mild GDM (as a secondary analysis of the MFMU-NICHD trial) and found it to be cost-effective for decreasing adverse perinatal outcome. In a follow-up study of IADPSG criteria, Mission et al\textsuperscript{102} concluded that the single 75 g OGTT is more expensive, more effective, and cost effective at 61,503 dollars per quality-adjusted life-year, and would remain such as long as it would reduce preeclampsia by 0.55% and cesarean section rate by 2.7\%. Although current evidence raise some economic benefit of single 75 g OGTT approach, this may only be true in affluent countries with a high rate of GDM in there population.\textsuperscript{74}

**WHO SHOULD MAKE THE RECOMMENDATIONS?**

The IADPSG is the assembly that published the new recommendations.\textsuperscript{57} This is a collaborative organization of various groups that focus on diabetes and pregnancy, and include representation from multiple worldwide organizations, groups, and associations. The suggested guidelines were developed during a 2008 International Workshop Conference on GDM diagnosis, with 225 conferees from 40 countries. The IADPSG consensus panel, with representation from the 10-member organizations, was the body of experts to finalize and publish the consensus guidelines. This group has received detrimental criticism as Langer et al\textsuperscript{74} noted that many of the IADPSG panelists were also HAPO investigators. Although being the best in their field, with extensive familiarity with the data, it still raises the question whether the consensus was unintended biased towards the HAPO, and if the experts were truly free of conflicting interests.

### Summary of Current Recommendations

The last ACOG recommendations, following the HAPO study and the published IADPSG criteria, were released as a committee opinion at September 2011.\textsuperscript{103} The committee continues to support the ACOG standing recommendation,\textsuperscript{23} in favor of a 2-step approach. The principal reason for maintaining the recommendation, not adopting the IADPSG criteria is the lack of evidence that treatment according to the IADPSG criteria will improve the outcome and the available evidence base for treatment by the current guidelines.

The opinion is: “There is no evidence that the identification and treatment of women based on the IADPSG criteria will lead to clinically significant improvements in maternal and neonatal outcomes and it would lead to a significant increase in health care costs.” In contrast, in January 2011, the approach suggested by the IADPSG was endorsed by the ADA.\textsuperscript{24} The standards of medical care by the ADA recommend the 75 g OGTT 1-step approach with the newly proposed IADPSG criteria.\textsuperscript{79} Finally, in the beginning of March 2013, the NIH published a draft summary with respect to the diagnosis of GDM. The single-step 75 g offers some advantage, mainly the ability to diagnose GDM within a day. The 2-step 100 g
approach is not used outside of pregnancy, and is preformed primarily in the United States. There would be value in a consistent diagnostic standard across the world, during and prior/after pregnancy. However, the single-step approach, as proposed by the IADPSG, is anticipated to increase the frequency of GDM, with a great impact on medical resources, without clear advantage to treatment. The NIH panel has concluded that: “...there is not sufficient evidence to adopt a one-step approach, such as that proposed by the IADPSG...the panel recommends that the two-step approach be continued.”

To conclude, it seems that by now, diagnosis of GDM will be established on 2-step approach and will be based on the Carpenter and Coustan’s criteria, unless new data will emerge proving the other.

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