

Diagnosing gestational diabetes

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Abstract The newly proposed criteria for diagnosing gestational diabetes will result in a gestational diabetes prevalence of 17.8%, doubling the numbers of pregnant women currently diagnosed. These new diagnostic criteria are based primarily on the levels of glucose associated with a 1.75-fold increased risk of giving birth to large-for-gestational age infants (LGA) in the Hyperglycemia Adverse Pregnancy Outcome (HAPO) study; they use a single OGTT. Thus, of 23,316 pregnancies, gestational diabetes would be diagnosed in 4,150 women rather than in 2,448 women if a twofold increased risk of LGA were used. It should be recognised that the majority of women with LGA have normal glucose levels during pregnancy by these proposed criteria and that maternal obesity is a stronger predictor of LGA. The expected benefit of a diagnosis of gestational diabetes in these 1,702 additional women would

be the prevention of 140 cases of LGA, 21 cases of shoulder dystocia and 16 cases of birth injury. The reproducibility of an OGTT for diagnosing mild hyperglycaemia is poor. Given that (1) glucose is a weak predictor of LGA, (2) treating these extra numbers has a modest outcome benefit and (3) the diagnosis may be based on a single raised OGTT value, further debate should occur before resources are allocated to implementing this change.

Keywords Diagnosis · Gestational diabetes · Large-for-gestational age · Pregnancy

Abbreviations

ACHOIS	Australian Carbohydrate Intolerance Study in Pregnant Women
GDS	Gestational diabetes screen
HAPO	Hyperglycemia Adverse Pregnancy Outcome
IADPSG	International Association of Diabetes in Pregnancy Study Groups
LGA	Large-for-gestational age infants
MFMU	Maternal–Fetal Medicine Units Network
RCT	Randomised control trial

The author was involved in the Consensus Panel Pasadena meeting of the International Association of Diabetes in Pregnancy Study Groups (IADPSG) as a Canadian representative but did not join the authorship of the final recommendation [1]. The opinions in this paper are the author's own and should not be taken to represent those of either the Canadian Diabetes in Pregnancy Study Group or the Canadian Diabetes Association. The author was not a member of the Hyperglycemia Adverse Pregnancy Outcome (HAPO) Study Cooperative Research Group.

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Introduction

Agreeing on the diagnostic cut-offs for gestational diabetes remains problematic. The International Association of Diabetes in Pregnancy Study Groups (IADPSG) recently published a consensus derived from the Hyperglycemia Adverse Pregnancy Outcome (HAPO) study data, suggesting that all pregnant women without known diabetes should have a 75 g OGTT at 24–28 weeks gestation [1].

Gestational diabetes would be diagnosed if one or more values met or exceeded the following levels of glucose: fasting 5.1 mmol/l, 1 h post glucose 10.0 mmol/l and 2 h post glucose 8.5 mmol/l. Use of these criteria will result in 17.8% of the pregnant population being diagnosed with gestational diabetes. A detailed analysis of the same HAPO study information and other recent related publications raises issues that are worthy of further debate in the wider diabetes community.

Observational data

HAPO was an international prospective observational study of 23,316 pregnant women directed to answer the question: ‘Is hyperglycaemia during pregnancy, at a level below that for overt diabetes, associated with increased risk of maternal or fetal complications?’ [2]. The participating women had an OGTT and were divided into seven glucose categories. The category 3 group encompassed the mean glucose values, i.e. fasting 4.5 mmol/l, 1 h post OGTT 7.4 mmol/l and 2 h post OGTT 6.2 mmol/l, while the new proposed cut-offs from IADPSG fall in category 5. The primary endpoints were large-for-gestational age infants (LGA), primary Caesarean section rate, neonatal hypoglycaemia and cord C-peptide. The study demonstrated a continuous relationship between glycaemia (fasting, and 1 or 2 h post glucose load) and each of the primary outcomes, having adjusted for field centre and ethnicity. While supporting the Pedersen hypothesis [3], the results did not show any inflection point indicating clearly increased risk of any of these outcomes with a particular glucose category; rather, risk increased gradually over the glucose range.

A further publication from the group examined the role of maternal BMI with the same primary outcomes [4]. This report used an adjustment (Model 1) for many of the expected confounders (age, alcohol, smoking, sex etc.), and also a model (Model 2) that adjusted for fasting plasma

glucose and mean arterial pressure. The OR for LGA, primary Caesarean section and cord C-peptide increased significantly for increasing categories of BMI, this difference being maintained when adjusted for glucose and mean arterial pressure (reference group BMI <22.6 kg/m²; Fig. 1a). When the plot for LGA vs glucose is added (reference group category 1 glucose as used in the HAPO report; Fig. 1a), it is apparent that maternal BMI has a greater impact on OR than maternal glucose in all except the highest glucose category. This is also true for the primary Caesarean section rate (Electronic supplementary material [ESM] Fig. 1a), whereas the glucose level had more influence on the OR for cord C-peptide in glucose categories 5–7 (ESM Fig. 1b). Thus, maternal BMI and glucose both contribute to risk of LGA, but the role of BMI was more pronounced than that of glucose in determining LGA incidence, until the highest glucose category was reached. Using the category BMI 22.6–28.4 kg/m² (which includes overweight women) and category 3 for glucose as the reference groups (i.e. using reference groups that include the means) shows that BMI and glucose have a similar impact on the OR (ESM Fig. 2a–c).

The majority of women from the HAPO data had glucose levels ≤category 3, i.e. the category encompassing the mean glucose level (Fig. 1b). Moreover, the number of LGA increased proportionately with higher glucose levels (Fig. 1b), but when the numbers of mothers with LGA in given glucose categories are classed separately (Fig. 1c), the majority (63%) of women with LGA are seen to have glucose levels from the OGTT at or lower than category 3, the category incorporating the mean glucose level. This is also true for the 1 and 2 h post-load challenge (ESM Fig. 3). It is also noteworthy that at category 5 (equivalent to the IADPSG cut-off criteria, accepting that some cases in category 5 will lie above these cut-offs within category 5) women below these cut-offs who had LGA represented 78% of all women giving birth to LGA.

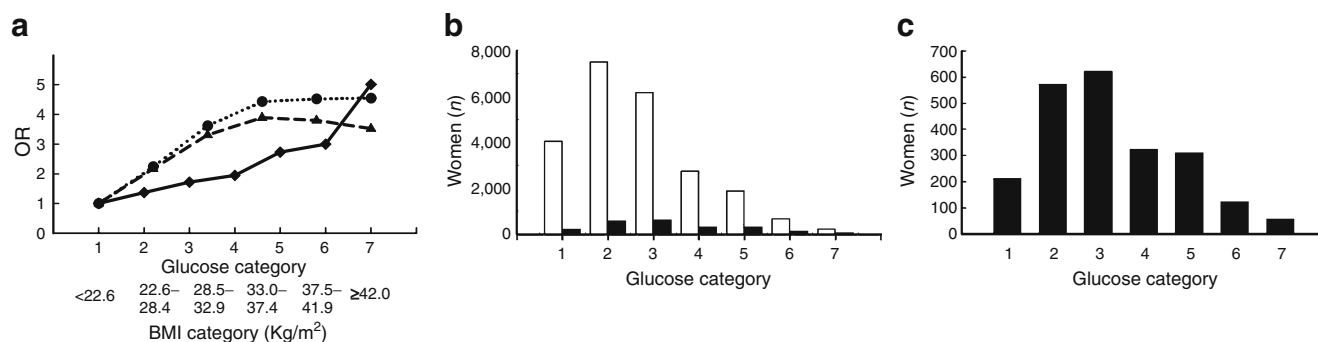


Fig. 1 a Relationship of the OR for an infant of birthweight >90th percentile vs the BMI in categories (reference group BMI <22.6 kg/m² [4]) or maternal fasting glucose in categories from HAPO (diamonds; reference group category 1 lowest glucose [2]). a The BMI relationship is adjusted for model 1 (circles) or model 2 (triangles)

(see text for details). The relationship for maternal fasting glucose categories is also shown (black diamonds). b Number of participants in each category of glucose in HAPO (white bars), with number of mothers with LGA infants (black bars). c Number of participants in each category of glucose who had LGA infants

Thus, the observational study showed that maternal weight and glucose predict LGA. However, BMI is more relevant at all but the highest glucose levels and most cases of LGA occur in the presence of normal maternal glycaemia. A large prospective study from Spain found that the upper quartile of maternal BMI was responsible for 23% of macrosomia, while gestational diabetes accounted for 3.8% [5]. Of course, an interrelation between BMI and glucose is not precluded.

Interventional studies

There are two major randomised control trials (RCTs) and a meta-analysis addressing whether controlling glucose in gestational diabetes is of value [6–8]. The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) [6] had a composite endpoint of fetal death, bone fracture, shoulder dystocia and nerve palsy. The Maternal–Fetal Medicine Units network (MFMU) [7] study also had a composite, albeit slightly different endpoint, namely fetal death, birth trauma, hyperbilirubinaemia, neonatal hypoglycaemia or hyperinsulinaemia. Both studies randomised approximately 1,000 patients to therapy or observation, were well conducted and formed the backbone of the meta-analysis. Both studies also had a two step approach to diagnosis with risk factors/gestational diabetes screen (GDS) in ACHOIS or GDS alone in the MFMU. The ACHOIS showed a significant decreased risk in the composite outcome, whereas the MFMU study composite outcome was not significantly altered. However, in both studies the incidence of LGA was decreased significantly, while shoulder dystocia was significantly decreased in the MFMU, but not in the ACHOIS study, and birth injury was not significantly decreased in either study. In both of the RCTs, maternal weight gain from diagnosis to term was significantly lower in the interventional groups (mean 1.7 kg less in ACHOIS, 2.2 kg less in the MFMU study).

A recent meta-analysis assessed the benefits from interventions for gestational diabetes in terms of perinatal and long-term outcomes [8]. In the primary intervention studies, of all perinatal issues only LGA/macrosomia and shoulder dystocia were significantly reduced by intervention, with a trend for decreased birth trauma (OR 0.39, 95% CI 0.13–1.15). In the comparison of intensive vs less intense care, only shoulder dystocia was significantly diminished by intervention, with no significant change in LGA/macrosomia or birth trauma.

At this juncture the evidence indicates that treating gestational diabetes decreases LGA and shoulder dystocia, which provides a trend towards a decrease in birth injury.

IADPSG process and outcomes

The IADPSG convened in Pasadena (CA, USA) to develop a consensus as to what level of less severe hyperglycaemia

is important and at what level of glucose gestational diabetes should be diagnosed. This was in the context of the US Preventative Services Task Force and a UK report questioning the value of screening for gestational diabetes [9, 10]. The HAPO results were reviewed, and other studies and long-term outcomes were noted, followed by recent publication of the consensus panel recommendations [1]. Important outcomes were deemed to be birthweight, cord C-peptide and per cent body fat in the neonate >90th percentile. The reference point taken was the outcome for the group associated with mean glucose in the OGTT (4.5 mmol/l fasting, 7.4 mmol/l 1 h post challenge, and 6.2 mmol/l 2 h post challenge). There was prolonged discussion about the OR relative to the mean that was considered to be important: for example, was a 1.5-, 1.75- or twofold increased risk of these outcomes damaging enough to warrant the diagnosis of gestational diabetes? The consensus group decided on a 1.75-fold increased risk threshold, giving cut-offs of 5.1, 10.0 and 8.5 mmol/l for fasting, and 1 and 2 h post-challenge glucose respectively, with a diagnosis of gestational diabetes being made if one of these values was met or exceeded. These values fell within category 5 of the original HAPO groupings. A twofold increased risk gave values of 5.3, 10.6 and 9.0 mmol/l for fasting, and 1 and 2 h post-challenge glucose respectively (data provided at Pasadena meeting), and fell in category 6 of the original HAPO study data for the fasting and 2 h values, and close to the upper boundary of category 5 for the 1 h value (9.6–10.7 mmol/l).

As published, the IADPSG criteria cut-offs give rise to an overall gestational diabetes prevalence of 17.8% (with some regional variation). As a result, 8.3% of women would be diagnosed on the basis of fasting glucose ≥ 5.1 mmol/l, a further 5.7% would be diagnosed on the basis of 1 h post-challenge glucose ≥ 10.0 mmol/l and 2.1% would be diagnosed on the basis of a 2 h post-challenge value ≥ 8.5 mmol/l. A further 1.7% of the women in HAPO were excluded at the start because their glucose values were markedly elevated, i.e. fasting values > 5.8 mmol/l or 2 h levels > 11.1 mmol/l. If the twofold increased risk cut-offs were used, 8.8% would be diagnosed by OGTT for a total of 10.5% including the markedly hyperglycaemic group.

The IADPSG consensus suggested a single 75 g OGTT at weeks 24–28 of gestation. Testing in earlier pregnancy for overt diabetes was recommended in populations with a high prevalence of diabetes, with determination of fasting plasma glucose, HbA_{1c} or random glucose. Overt diabetes may be diagnosed in pregnancy at fasting glucose values of ≥ 7.0 mmol/l, HbA_{1c} $\geq 6.5\%$ or random glucose ≥ 11.1 mmol/l, the latter needing to be confirmed by one of the former. If fasting glucose in early pregnancy is ≥ 5.1 mmol/l, the woman is diagnosed with gestational diabetes.

Impact of criteria

The two major intervention RCT studies [6, 7] showed a mean occurrence of 18.25% LGA in controls, reduced to 10.05% with therapy, with a corresponding occurrence of 3.5% shoulder dystocia (reduced to 1.25% with therapy) and birth injury reduced from 1.03% to 0.3%. Applying this information to HAPO data gives some indication of the impact of intervention given the different cut-offs for diagnosis.

In HAPO there were 2,221 cases of LGA. If category 5 had been used as a cut-off for diagnosing gestational diabetes (approximating the IADPSG cut-offs), then 491 potential cases of LGA would have been identified, treatment of which would have been expected to prevent 221 cases. If category 6 had been used as cut-off, fewer potential cases of LGA overall would have been diagnosed (181), with proportionally fewer cases prevented (81) (Table 1).

Translating this to the more important outcomes of shoulder dystocia [11] and birth injury, in HAPO 212 cases of shoulder dystocia and 139 cases of birth injury occurred. Using the adjusted OR of 1.18 for fasting maternal glycaemia and the risk of shoulder dystocia/birth injury [2], 108 cases of shoulder dystocia would have been identified at category 5 diagnostic cut-offs, of which 69 would have been prevented by intervention. At category 6, some 75 cases of shoulder dystocia would have been found and 48 cases prevented. Using category 5 diagnostic cut-offs, 70 cases of birth injury would be identified, of which 50 would be prevented, while at category 6 the numbers would be 48 and 34, respectively (Table 1).

Thus using the IADPSG report based on HAPO data of 23,316 pregnant women, 4,150 cases of gestational diabetes would be diagnosed with the new criteria based on an OR risk for adverse outcomes of 1.75 and equivalent to category 5 cut-offs vs 2,448 cases based on an OR risk for adverse outcomes of 2.0, equivalent to category 6 cut-offs. This would result in prevention of 221 vs 81 cases of LGA, 69 vs 48 cases of shoulder dystocia and 50 vs 34 cases of birth injury. Thus at a cost of diagnosing and

treating an extra 1,702 cases of gestational diabetes, one might expect to avoid 140 cases of LGA, 21 cases of shoulder dystocia and 16 cases of birth injury. It should be debated whether diagnosing this many extra women with gestational diabetes is worth this benefit.

Long-term risks to the offspring of gestational diabetes

Hyperglycaemia in utero is associated with increased insulin resistance and hyperglycaemia in offspring as described in animal studies [12–14]. Some human studies suggest similar outcomes, a risk cited as an additional argument for diagnosing more gestational diabetes, since diagnosing and treating gestational diabetes may decrease obesity and diabetes in the long-term. Hillier et al. demonstrated that excess obesity in the offspring of women with gestational diabetes was ameliorated by therapy [15]. However, maternal weight was not available to assess the role of maternal obesity. Previous studies have shown increased obesity in teenage offspring of women exposed to hyperglycaemia vs siblings of the same women who were not exposed to hyperglycaemia [16], but other studies in Pima Indians showed that this impact on offspring weight was lost in older offspring aged 20–24 years [17]. A prospective longitudinal study showed that the occurrence of gestational diabetes had no impact on obesity rates in 16-year-old offspring in the absence of maternal obesity [18]. HAPO data for offspring at age 2 showed no relationship between offspring weight and maternal glycaemia level during pregnancy [19]. Follow-up of children at 4–5 years old from the ACHOIS trial failed to show a difference in BMI z scores between offspring of intervention and control gestational diabetes mothers, despite the former having a reduced macrosomic rate at birth [20], although it may be too early to see any epigenetic effects. Most offspring of women with type 1 diabetes are exposed to much more severe hyperglycaemia in utero than offspring of women with gestational diabetes, yet the increased risk of glucose intolerance in the offspring of women with type 1 diabetes

Table 1 Frequency of women with LGA whose infants experienced shoulder dystocia or birth injury

Condition	All cases <i>n</i>	Category 5 ^a		Category 6 ^b	
		Identified (<i>n</i>)	Prevented (<i>n</i>) ^c	Identified (<i>n</i>)	Prevented (<i>n</i>) ^c
LGA	2,221	491	221	181	81
Shoulder dystocia	212	108	69	75	48
Birth injury	139	70	50	48	34

Data are based on 23,316 participants in HAPO [2]

^a Numbers equate with proposed criteria for gestational diabetes by IADPSG [1]

^b Numbers equate with those from using glucose criteria associated with a twofold increased risk of adverse fetal outcome

^c Derived from the mean expected benefit from the two major prospective outcome studies in the treatment of gestational diabetes [6, 7]

was half that of offspring whose mothers had treated gestational diabetes, with no associated difference in offspring BMI [21]. Offspring of type 1 diabetic women were less overweight than those of mothers who had gestational diabetes [22]. These studies indicate that hyperglycaemia in utero plays some role in adult offspring glucose tolerance and obesity, but that other factors are more important.

Long-term risks of gestational diabetes for the mother

Since gestational diabetes is associated with insulin resistance and a beta cell defect, features that are evident in the postpartum state [23], identifying gestational diabetes allows recognition of a group at increased risk in the long term of developing diabetes [24]. Such labelling opens the possibility that these women may be targeted for intervention to prevent diabetes in the future. While high rates of diabetes are common in women with a history of gestational diabetes, these studies used criteria with higher historical glucose thresholds for the diagnosis of gestational diabetes, and extrapolating the same frequency for the development of diabetes using the newer proposed values is likely to lead to an overestimation.

Negative outcomes

Diagnosing gestational diabetes has cost implications. While some diabetes organisations specifically exclude a cost–benefit analysis when determining guidelines [25], major expenses occur when diagnosing more cases, especially when they may translate into decreased opportunity costs for other aspects of diabetes, e.g. type 2 diabetes in pregnancy. Increased costs include those associated with care from nurses, dietitians and physicians, as well as with glucose monitoring and therapy of the diabetes [26]. Although the Caesarean section rate decreased in the MFMU study [7], treatment of gestational diabetes does not always decrease the Caesarean section rate [6, 27]. Several centres have developed policies that dictate delivery protocols for women diagnosed with gestational diabetes, particularly those who have been started on insulin regardless of glycaemic control achieved or fetal size. Finally, and perhaps most importantly, there are labelling costs for the individual diagnosed with gestational diabetes in terms of their care and future insurability.

Other considerations

Other issues that the IADPSG proposals raise include the concern that the OGTT itself is poorly reproducible [28, 29], particularly in this intermediate zone of impaired glucose tolerance [30, 31]. Thus, diagnosing individuals

on the basis of one test, with a single abnormal value that on repeat could well be normal, needs to be debated. The criteria proposed are derived from HAPO data collected at 24–28 weeks of gestation, yet the consensus panel proposed that the fasting criteria should be used for diagnosing gestational diabetes in early pregnancy, before fetal and hormonal changes of pregnancy have had an impact. Thus a woman with fasting glucose of 5.1 mmol/l at 7 weeks gestation would be diagnosed as having gestational diabetes, but in the non-pregnant state this value would be considered perfectly normal!

On the positive side it must be acknowledged that diagnosing and treating gestational diabetes, in addition to the benefits outlined above, is also associated with less preeclampsia, gestational hypertension, obstetrical interventions and maternal health issues [6, 7]. However, the question of whether these positive outcomes relate to treatment of glycaemia or less weight gain remains unanswered. The proposed IADPSG diagnostic criteria are not based on a composite of these benefits, they are based on LGA, cord C-peptide and fetal adiposity, and for LGA the BMI level may be a better predictor than glucose alone [5, 32].

Where does this leave us?

The increased diagnostic rate of 17.8% using the IADPSG criteria would only prevent 140 cases of LGA and 16 cases of birth injury out of a total denominator group of 23,316 pregnancies. Yet 78% of cases of LGA will be born to women not diagnosed according to these criteria, as maternal obesity is a stronger predictor of LGA than maternal glycaemia in HAPO glucose categories 1–6 and the reduced LGA rates with treatment of gestational diabetes could be due to the lower weight gain in the interventional groups; moreover, a single abnormality in an OGTT may not be reproducible.

Serious hyperglycaemia during pregnancy requires identification and therapy. For women with milder hyperglycaemia the benefits of therapy are so modest that the cost–benefit relation of proposed diagnostic cut-offs have to be considered. Identifying women with increased risk of later diabetes has an undetermined benefit. At the same time, the value of treating gestational diabetes, independently of maternal weight, with a view to the long-term well-being of the offspring has not been established. The cut-offs associated with a twofold increased risk of LGA deserve consideration. They would give a prevalence of 10.5% for gestational diabetes, similar to the prevalence of diabetes in the general population [33], and are close to the values currently used for gestational diabetes diagnosis in Canada. Thus 75 g OGTT criteria derived from a twofold increased risk of LGA in HAPO, i.e. fasting glucose ≥ 5.3 mmol/l, 1 h

post-challenge glucose ≥ 10.6 mmol/l and 2 h post-challenge glucose ≥ 9.0 mmol/l, may be a reasonable starting point. Since in the HAPO study each glucose cut-off level from the OGTT was associated with adverse outcomes, one elevated value should be sufficient for diagnosis. A diagnosis of diabetes typically requires the test be confirmed, unless elevation of glucose level is unequivocal. Continued use of the GDS 50 g screen may satisfy this need, and a two-step procedure was more cost-effective than the universal OGTT approach in the analysis by the National Institute for Health and Clinical Excellence [26]. Furthermore, setting upper limits for the GDS to diagnose gestational diabetes simplifies the approach [34] with proven cost-effectiveness [35]. In time, the use of the 50 g test in this manner would have to be validated.

Thus a proposal for the diagnosis of gestational diabetes could be that all pregnant women without a diagnosis of diabetes should have a 50 g glucose load between 24 and 28 weeks of gestation, without regard to fasting and with determination of plasma glucose 1 h later. The findings should then be interpreted as follows: (1) a value of ≥ 11.1 mmol/l would merit a diagnosis of gestational diabetes; (2) values of 7.8–11.0 mmol/l would warrant conducting a 75 g OGTT, with OGTT cut-offs at 5.3 mmol/l fasting, 10.6 mmol/l 1 h post-challenge and 9.0 mmol/l 2 h post challenge, one of which would be sufficient for diagnosis if equalled or exceeded; and (3) a value of < 7.8 mmol/l would indicate that gestational diabetes is not present.

Using such criteria would diagnose the more severe forms of gestational diabetes and give a diagnosis of gestational diabetes in about 10% of the pregnant population, with gestational diabetes associated with a twofold increased risk of adverse outcomes for the baby; it would also involve two steps to help overcome the reproducibility issues of a one-off OGTT.

While LGA and associated birth injury are related to hyperglycaemia, it appears probable that maternal weight or weight gain plays a more important role for most women. Markedly increasing the number of women diagnosed with gestational diabetes is likely to be an inefficient way of dealing with the problem of LGA. The resources saved by not having an extra 8% of the population diagnosed with gestational diabetes would be better spent on women with pre-existing diabetes in pregnancy. Future research, hopefully, will lead us to what really causes unexplained LGA. Glucose contributes, but with three quarters of LGA infants born to women with normal glucose tolerance, it is clearly not the whole story.

Duality of interest The author declares that there is no duality of interest associated with this manuscript.

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