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COMMENTARY

Diagnosing gestational diabetes: can expert opinions replace scientific evidence?

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Abstract Preventive medical interventions should be based on the highest level of scientific evidence. Actual criteria for diagnosing gestational diabetes mellitus (GDM) are neither uniform nor based on pregnancy outcomes. An expert panel from the International Association of Diabetes in Pregnancy Study Groups recently proposed that all pregnant women undergo a one-step 75 g OGTT, and defined new lower cut-off points to diagnose GDM (Metzger BE et al. *Diabetes Care* 33: 676–682). These criteria will double the prevalence of GDM, as 18% of all pregnant women will be labelled as abnormal. A recent article in *Diabetologia* (Ryan EA 54:480–486) claimed that maternal glucose is a weak predictor of big babies, that a single OGTT is poorly reproducible, and that expected benefits from intervention would be, at best, modest. This Commentary discusses other objections and argues that guidelines on any new GDM diagnostic strategy should be based on the results of randomised controlled trials rather than on disputable expert opinions.

Keywords Diagnostic controversy · Diagnostic criteria · Evidence-based medicine · Experts consensus · Gestational diabetes · Macrosomia · Medicalisation · Observational studies · Pregnancy · Preventive medicine

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Abbreviations

aOR	Adjusted OR
GDM	Gestational diabetes mellitus
HAPO	Hyperglycemia and Adverse Pregnancy Outcomes
IADPSG	International Association of Diabetes and Pregnancy Study Groups
LGA	Large-for-gestational age babies
MFMU	Maternal-Fetal Medicine Units network
RCT	Randomised control trial

Pregnancy is a time when women are particularly receptive to advice on good lifestyle choices, but it is also a time when women are vulnerable to stress, anxiety and guilt. During this very special time in women's lives, medicine should respectfully limit its intrusions to those that have been proven to be necessary and beneficial.

The lack of uniform criteria to diagnose and manage gestational diabetes mellitus (GDM) has perpetuated diverging practices and hampered research. A consensus would surely be welcome. Existing criteria are either the same as those used in non-pregnant individuals, like those of the World Health Organization [1], or have been derived from ancillary studies [2] designed to identify women at high risk of developing diabetes after pregnancy, like those proposed by Carpenter and Coustan [3]. In March 2010, a consensus panel from the International Association of Diabetes and Pregnancy Study Groups (IADPSG) published new recommendations for the diagnosis of GDM [4]. These suggested that all pregnant women who have not previously been diagnosed with diabetes should undergo a one-step 75 g OGTT at 24 to 28 weeks' gestation and that GDM should be diagnosed if any glucose result meets or exceeds the recommended value at the following time points: fasting, 5.1 mmol/l; 1 h,

10.0 mmol/l; and 2 h, 8.5 mmol/l. Adoption of these criteria would almost double the number of women who are diagnosed with GDM.

The recommendations were largely based on the results of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study [5], a large multicentre international study that attempted to clarify the association between maternal glucose and adverse pregnancy outcomes. The data remained blinded and pregnant women untreated unless their plasma glucose level after a 75 g OGTT at 24–32 weeks' gestation exceeded a fasting value of 5.8 mmol/l or a 2 h value of 11.1 mmol/l. The main conclusion of the HAPO study was that, after adjustment for confounders, the relationship between maternal glucose levels and markers of fetal hyperinsulinaemia at birth was continuous, without any inflexion point.

In a recent article in *Diabetologia* [6], Dr E. Ryan criticises the IADPSG recommendations, arguing three major points. He shows that maternal glucose is a weak predictor of big babies, so even if lower IADPSG GDM threshold values had been used in the HAPO cohort, 78% of large-for-gestational-age (LGA) babies would have been born to women with normal plasma glucose levels. He also demonstrates that, if we infer modest treatment benefits from previous randomised controlled trials (RCTs) to women with GDM diagnosed according to the new suggested criteria, this mean that an extra 1,702 cases of GDM would have to be diagnosed and treated to avoid 140 cases of LGA babies, 21 cases of shoulder dystocia and 16 cases of birth injury. Finally, Dr Ryan questions the reproducibility of a single 75 g OGTT to diagnose GDM.

As a number of diabetic and healthcare associations around the world are now contemplating the adoption of these recommendations, other important dimensions have to be considered in this debate.

The medicalisation of pregnancies currently deemed healthy

Diagnosing 18% of all pregnant women with GDM will lead to the medicalisation of hitherto healthy pregnancies. Some individuals outside the field go even further, evoking potential financial ties and/or intellectual conflicts of interests of experts and suggesting that panels should be broadened to include non-medical representatives [7]. The public and caregivers are increasingly sceptical of preventive medical interventions and are concerned about the appropriate allocation of resources. Lowering the glycaemic bar and prescribing questionable interventions to a large number of asymptomatic individuals can seriously affect the credibility of any association and decrease compliance to their recommendations, even for those with less disputable levels of glycaemic dysfunction during pregnancy. In addition, what are the potential long-term effects of labelling one out of five women as having GDM? Concerns include maternal anxiety, pernicious effects on future insurance costs, and medical follow-up, to name but a few.

The IADPSG thresholds are arbitrary

The IADPSG Expert Panel chose to redefine GDM using glucose values corresponding to 1.75 times the adjusted OR (aOR) to give birth to LGA and hyper-insulinemic babies in the HAPO cohort study. Defining a 'disease' (in this case, GDM) as a maternal risk factor for giving birth to babies over the 90th percentile for birthweight, percentage body fat or cord blood C-peptide is disputable: by definition, it will label 10% of any cohort as 'abnormal'. Furthermore, macrosomia is not a clinical event, but a surrogate marker for difficult delivery and future maternal and offspring metabolic anomalies. The proposed expert thresholds correspond to more modest aORs for other clinical perinatal endpoints, such as neonatal hypoglycaemia (1.18 for the 2 h plasma glucose to 1.24 for the fasting), shoulder dystocia and/or birth injury (1.3 for the fasting to 1.43 for the 2 h) or pre-eclampsia (1.4 for the fasting to 1.57 for the 2 h) [4]. ORs of this magnitude are far from being useful to discriminate high-risk pregnancies, where interventions could help, from lower risk ones, where iatrogenia becomes a concern. As for those who believe that changes in the diagnostic criteria for GDM are needed to fight the worldwide epidemics of obesity and diabetes [8], we must remind them we have yet to demonstrate that acting to reduce macrosomia will result in reduced long-term obesity and glucose intolerance in children of mothers with GDM.

Observational research is subject to limitations

The debate raises numerous issues regarding observational research. Observational studies can only show associations and cannot predict the effects of interventions. If experts have a duty of 'translation', it is first and foremost to prevent caregivers jumping from experimental findings to clinical applications. Clinicians do not treat OGTTs, they treat specific women, with a given BMI, blood pressure and past obstetric history. As Dr Ryan points out in his article [6], in the HAPO study, maternal BMI was a more powerful risk factor than maternal glycaemia, not only for macrosomia and fetal hyperinsulinism [9], but also for pre-eclampsia [10]. Clinicians know that a 'glucocentric' approach to GDM is too reductive because the outcomes we are trying to prevent are multifactorial.

The IADPSG diagnostic thresholds are not evidence-based

The IADPSG panel evades the necessity for a new trial. However, the two available RCTs, the Australian Carbohydrate Intolerance Study in pregnant women (ACHOIS) [11] and the Maternal-Fetal Medicine Units network (MFMU) [12] studies used different definitions of GDM plus a two step diagnostic strategy, as opposed to the one step, poorly reproducible OGTT proposed by the IADPSG Expert Panel. The MFMU study randomised women with at least two post-100 g load abnormal glucose values and although a secondary analysis found similar frequencies of adverse outcomes among non-randomised untreated women with only one abnormal OGTT value [13], one cannot validly infer treatment benefits to them. Treating a larger number of 'less hyperglycaemic' women may very well reach a tipping point where therapy may turn out to be useless, or worse, harmful. Realistic concerns include maternal hypoglycaemia, poor fetal growth, and earlier and more frequent induced deliveries.

Dr Ryan [6] proposes that we should continue using a two-step diagnostic approach with a 1 h 50 g glucose screen confirmed by a 75 g OGTT using criteria derived from a twofold (rather than a 1.75-fold) increased risk of LGA babies in HAPO. This proposal is more reasonable as it is closer to the GDM definitions used in the RCTs and closer to the current prevalence of GDM but, unfortunately, it is still a glucocentric approach. In future, any new proposed diagnostic or treatment strategy should be based on an RCT comparing it to standard care. Hopefully, this strategy will not rely solely on any new glucose diagnostic values but on a prognostic model built on HAPO results that would combine the most pertinent risk factors such as maternal glycaemia (left as a continuous variable), BMI, age, blood pressure, previous adverse obstetrical outcome, and so on. Some have argued that a trial designed to show the benefits (and lack of harm) of any new GDM thresholds would be costly and time consuming. But what could be more costly and time consuming than definitively adopting more strict thresholds without sufficient evidence? Arbitrary recommendations could also severely obstruct the conduct of any future trial by sending the message that doctors know what to do when in fact they do not. Furthermore, endorsement of these new recommendations by medical associations as 'practice guidelines' could be considered 'standards of care', so that departure from them puts individuals or centres in a defensive position. Medical experts should discipline themselves to limit their recommendations to high-level RCT evidence. We can no longer ignore that changing the definition of a medical condition can have a significant impact on patient care.

Preventive medicine concerns all women. It must consequently be proved to be safe and effective in all of them. While therapeutic medicine only has an obligation of means, prevention has an obligation of results. As Dr Sackett eloquently wrote following the first publication of the Women Health Initiative trial [14]: 'the presumption that justifies the aggressive assertiveness with which we go after the unsuspecting healthy must be based on the highest level of randomized evidence that our preventive manoeuvre will, in fact, do more good than harm…There are simply too many examples of the disastrous inadequacy of lesser evidence as a basis for individual interventions among the well'. If the necessary trial to test a new GDM diagnostic strategy is not even considered worth undertaking, then changing the way we care for pregnant women is not only unjustified, but unsafe.

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