Medicalising pregnancy with new diagnostic criteria for gestational diabetes mellitus: do we need more evidence?

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Abbreviations

2HG	2 h plasma glucose
FPG	Fasting plasma glucose
GDM	Gestational diabetes mellitus
HAPO	Hyperglycemia and Adverse Pregnancy Outcome (study)
LGA	Large for gestational age
NGT	Normal glucose tolerance

To the Editor: We read with interest the article by Koning et al [1]. The authors report that the additional women diagnosed with gestational diabetes mellitus (GDM) by the WHO 2013 definition (i.e. fasting plasma glucose [FPG] ≥ 5.1 mmol/l but ≤ 6.9 mmol/l) were more likely to be obese and have higher BMI and hypertension compared with women with normal glucose tolerance (NGT).

They also report, based on unadjusted analysis using χ^2 test and Fisher's exact tests, that the additional group of women diagnosed by the WHO 2013 FPG criteria (WHO 2013 only fasting glucose: GDM according to new WHO 2013 fasting glucose threshold, but do not meet WHO 1999 criteria) had higher rates of planned Caesarean section and induced labour despite similar unadjusted birthweight, macrosomia and large for gestational age (LGA) rates to the NGT group. The 'WHO

1999 only 2HG' group (GDM according to WHO 1999 2HG threshold, but do not meet WHO 2013 criteria), who received treatment for GDM had similar rates of LGA, but lower birthweight and lower rates of macrosomia than the NGT group. Interestingly the NGT group had higher birthweight (unadjusted for gestational age or offspring sex) than those diagnosed as GDM by either criterion but similar LGA rates. Based on these results the authors conclude that treating women with mild fasting hyperglycaemia (FPG 5.1–6.9 mmol/l) would improve outcomes, including LGA. This study has several important limitations that would make this conclusion difficult to make.

First, the authors reported differences in crude birthweight and not sex- and gestational-age-adjusted birthweight z scores. The crude birthweight (Table 3 in Koning et al [1]) in the additional women diagnosed by the WHO 2013 FPG criteria (WHO 2013 only fasting glucose group) was higher than those in the WHO 1999 only 2HG group. This 143 g lower birthweight in the WHO 1999 only 2HG group was most likely due to the early induction, and hence lower gestational age, because of a diagnostic label of GDM. It is likely that these differences would be insignificant if birthweight z scores for gestational age and sex were used. While the authors discuss that one of the key reasons to recommend a change to the new WHO 2013 criteria is the higher LGA rates in WHO 2013 only FPG group compared with the general population (21% vs 11%), this was not statistically different from the NGT group. In fact, the LGA rates were similar across NGT, WHO 1999 only 2HG and WHO 2013 only fasting glucose groups.

Second, this study did not account for the effect on birthweight of the significantly higher pre-pregnancy BMI and obesity rates in the WHO 2013 only fasting glucose group compared with the WHO 1999 only 2HG group. The statistical analysis was by unadjusted χ^2 test/Fisher's exact tests with no attempt to create a regression model to account for potential

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confounders such as BMI or obesity or even gestational age. It is also to be noted that the overall LGA rates in the population screened for GDM are higher than the general obstetric population. It is likely that the higher birthweight found in the WHO 2013 only fasting glucose group, as well as the increased LGA rates in the overall baseline cohort screened for GDM, was an effect of obesity rather than mild hyperglycaemia. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study clearly showed that maternal BMI had an independent effect on offspring outcomes especially LGA, fetal adiposity, Caesarean section rates, pre-eclampsia and cord C-peptide levels [2, 3]. The effects of maternal obesity on offspring outcomes are both independent and additive to blood glucose levels, with the highest risks in those with a combination of gestational diabetes and obesity [4]. Hence, presenting the data adjusted for the key confounder, BMI, would have helped to improve our understanding.

The higher rates of primary, emergency and repeat Caesarean section have been reported in obese women, with these women having difficulty completing the second stage of labour [5]. The HAPO post hoc analysis and other studies clearly show maternal obesity to be a more significant predictor of Caesarean rates than maternal glucose except in women with the highest degree of hyperglycaemia [2, 3, 6–8].

Third, pregnancy outcomes were reported only in a fraction, i.e. 4431 of 10,642 women who underwent screening for GDM. The baseline characteristics and pregnancy outcomes of the other half of the screened population are unknown. Missing data analysis is conspicuously absent.

Fourth, this study was on a retrospective selective screened population unlike the universally screened population that the WHO 2013 or International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria are based on. Most European countries (including the UK) used modified WHO 1999 criteria (FPG ≥ 6.0 mmol/l, 2HG ≥ 7.8) prior to the introduction of the WHO 2013 criteria. It would have been more relevant to see the data for this subpopulation.

Finally, despite detection of a higher risk cohort with more adverse offspring outcomes, the question of whether treatment of hyperglycaemia in the WHO 2013 only fasting glucose group would indeed improve outcomes such as LGA or Caesarean section still remains unanswered. Two non-randomised observational studies observed a reduction in LGA rates with treatment in this group, however only one study showed a reduction in Caesarean rates [9, 10]. Both these studies compared the WHO 2013 criteria (using universal screening) with the Carpenter–Coustan criteria, which uses a 50 g glucose challenge test screening strategy, hence making it difficult to make direct comparisons. In fact women in the above studies had far lower BMI than that seen in the Koning et al study, owing to the risk factor based selective screening used in the current study. Evidence from the Maternal–Fetal Medicine Units (MFMU) trial showed that women who benefited from intervention in GDM gained significantly less

weight in pregnancy than those in the control arm [11]. It is hence conceivable that the benefit of treatment came from the weight-lowering rather than glucose-lowering effects of the intervention. While it may be prudent to risk stratify and intervene in women with high BMI to reduce these risks, the available intervention trials among overweight and obese pregnant women have failed to show a benefit in reduction of perinatal risk, especially LGA [12, 13].

In summary, we believe that, contrary to the authors' conclusion, that although the newer criteria detect high-risk women with greater degrees of obesity, there is not enough evidence for treatment benefit to reduce adverse fetal outcomes in this group with mild hyperglycaemia. We also need to be acutely aware that, in a real life situation, labelling women as having GDM results in higher induction and Caesarean section rates resulting in lower gestational age at birth [7]. We therefore need to be confident that we are doing no harm by medicalising pregnancies with mild GDM, particularly given the potential long-term risk for women and their offspring with Caesarean section and early delivery [14].

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