

## COMMENTARY

# This is the decade to find the solution for gestational diabetes mellitus screening and treatments

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The most common complication of pregnancy is diabetes. It is estimated that one in six pregnancies are affected (16.6%), with 84% of diabetic pregnancies being affected by gestational diabetes mellitus (GDM).<sup>1</sup> More than 15 years ago, the evidence was clear that treatment of even mild GDM had beneficial effects on both maternal and neonatal outcomes.<sup>2</sup> These findings were instrumental in encouraging clinicians to offer detection and intervention for GDM. The evidence is also accumulating linking maternal GDM with future disorders of maternal glucose metabolism and of increased childhood adiposity.<sup>3,4</sup> Identifying women with GDM is thus important for the health of the mother and infant in the index pregnancy but also for their future health to prevent non-communicable diseases.

The Hyperglycaemia and Adverse Pregnancy Outcomes study was a blinded observational study of 23,316 women from 15 centres in nine countries across five continents tested for glucose tolerance at 24–32 weeks. A continuous positive relationship was found between the fasting, 1- and 2-h glucose measurements and birth weight >90th percentile, cord C-peptide >90th percentile and percentage body fat >90th percentile.<sup>5</sup> The IADPSG criteria for GDM screening were calculated based on an adjusted odds ratio of 1.75 for these events.<sup>6</sup> These criteria are supported for use by many organizations including the WHO,<sup>7</sup> American Diabetes Association,<sup>8</sup> International Federation of Gynaecology and Obstetrics, European Board and College of Obstetrics and Gynaecology, European Association for Perinatal Medicine, Australasian Diabetes in Pregnancy Society and International

Diabetes Federation. The WHO recommends a one-step approach to screening as women with a positive glucose challenge test frequently do not attend for a glucose tolerance test. In addition, a GDM diagnosis is based on one abnormal value in contrast to two abnormal values required by the Carpenter and Coustan (CC) criteria. There is considerable evidence in the literature that when using the latter test, one abnormal value on the test confers an increased risk of adverse pregnancy outcomes when compared to a test where all values are normal. Nevertheless, considerable controversies remain for GDM diagnosis with some countries advising use of National Institute of Health and Care Excellence criteria or CC criteria<sup>9</sup> while others such as India and Canada devising their own population-based criteria.

The International Association of Diabetes and Pregnancy Study Groups (IADPSG) community was interested to read the recently conducted large pragmatic randomized controlled trial (RCT) by Hillier and colleagues of GDM screening, comparing a one-step approach using IADPSG criteria to a two-step approach using CC criteria. We congratulate the authors on this large pragmatic trial in a high-risk population and acknowledge the efforts required to complete such a trial. The trial concluded that there were no significant differences between approaches in the risks of the primary perinatal and maternal outcomes but importantly with a smaller proportion of women diagnosed as GDM.<sup>10</sup> We welcome additional RCTs in the field and note that this is the first large RCT to randomize between these strategies. Nevertheless, the results may be difficult to interpret and

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raise some questions: First, many women (33%) failed to proceed with their randomized one-step approach. The randomization component of an RCT is done in order to control for unmeasured variables and reduce bias. The authors acknowledge that this difference in randomization was not random, with different characteristics in patients/providers opting in and out of assigned randomization.<sup>11</sup> This may have influenced the final trial outcome. If provider bias was present at randomization, could it also have influenced treatment—particularly in those who fulfilled one-step but not the two-step approach? Second, first-trimester screening of obese and ‘high-risk’ women was implemented with over 3000 women in each study arm screened.<sup>11</sup> Agreement on whether or how risk for GDM can be diagnosed in first-trimester GDM is lacking<sup>12</sup> and this questions whether inclusion of this group may have influenced trial findings. Taken together we wonder whether, in a field where providers may hold strong views on the efficacy of one or other approach, blinding, as far as possible, would have been necessary to eliminate these possible biases. Finally, there was no black representation in this trial and just 15%–16% Medicaid recipients.

Another recently published article is also critical of current screening practices and argues that an international multicentre trial of treatment rather than screening is warranted using IADPSG criteria as a basis for patient selection.<sup>13</sup> The authors suggest that the trial should incorporate cost-benefit, cost-effectiveness and cost-utility analyses. We believe that with the correct trial design including blinding to eliminate bias, many questions regarding screening, treatment benefits and long-term maternal and offspring health could be examined simultaneously. In design of such studies, randomizing patients away from usual practice is often seen as an ethical issue. However, given the variety of practices internationally and the equipoise that exists we believe such blinded studies will be the only way to move forward. In addition, new technologies such as continuous glucose monitoring could be included to examine a more user-friendly approach to screening and a biobank could be incorporated to explore alternative biomarkers for GDM diagnosis. It would be important for the future applicability of any proposed trial that participants are multi-institutional and multinational. With the launch of the Horizon Europe Health Programme, now is the time to work collectively to design and deliver such a trial to address unanswered questions around GDM.

The IADPSG's interest in GDM has long been in promoting evidence-based practice for detection of metabolic disease in pregnancy. Ironically, while the controversy around criteria has raged, there has been worsening of underlying metabolic health in the pregnant population as measured in prevalent type 2 diabetes, newly discovered type 2 diabetes

and obesity during pregnancy. Add to this the concerns over intergenerational effects of maternal hyperglycaemia. Thus, there is no debate on the urgency of the problem. Promoting women's health in preparation for and during pregnancy should be our priority. This includes screening for and treating GDM. Rather than procrastinating further, let us work together to find the solutions.

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