Can J Diabetes 43 (2019) 547–548

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Note From the Editors

Diagnosis of Gestational Diabetes: More Questions Than Answers

The entity of gestational diabetes (GDM) has been acknowledged since the 1950s, but the role of screening and the criteria for diagnosis of GDM continue to be controversial to the present day. Several very basic questions remain regarding the screening and diagnosis of GDM that have yet to be fully resolved. What criteria should we use to diagnose GDM? Do we need a screening test? When in pregnancy should we diagnose and treat GDM? How do we differentiate GDM from newly discovered pre-existing type 2 diabetes (T2D) in pregnancy and how important is it to do so?

What criteria should we use to diagnose GDM? The diagnosis of GDM has evolved from the initial use of criteria developed to predict the development of T2D within 8 years postpartum (1) to the use of criteria based on adverse neonatal outcomes, as defined by the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (2). The HAPO study demonstrated that there is no definite glucose inflection point above which the incidence of adverse outcomes increases, but rather it is a continuum of risk. More recent data have suggested differential outcomes in offspring exposed throughout gestation to pre-existing T2D compared to GDM with respect to child-onset obesity and dysglycemia (3). Therefore, there continues to be great controversy regarding how to diagnose GDM and where to place that diagnostic cutpoint. Should we diagnose GDM using the criteria of the International Association of Diabetes in Pregnancy Study Group (IADPSG) (4,5)? These criteria define GDM as one or more: fasting and 1- and 2-hour glucose values during a standard 75-g oral glucose tolerance test at which the odds for adverse outcomes in offspring (including birthweight, percent body fat and cord blood C peptide) were 1.75-fold higher than those whose blood sugars were at or below the mean for those timepoints. Alternatively, should the cutpoints that reflect 2.0 times the risk be adopted, as the Diabetes Canada recommendations prefer (Diabetes Canada Clinical Practice Guidelines)? Given that both were derived by consensus, either seems justified. Several countries were early adopters of the criteria established by the IADPSG. However, evidence for use of these criteria is still insufficient.

First, although adverse outcomes were associated with the IADPSG criteria, there was no demonstration that their application would lead to improved outcomes compared with other criteria. Second, one should be fairly certain of the evidence for their use since adoption of these criteria leads to a significant increase in the incidence of GDM. In the HAPO trial, utilizing these criteria resulted in an incidence of GDM of 18% compared with the current incidence of 5.6% in Ontario (6). In this issue, Pouliot and colleagues report a retrospective cohort study comparing the incidence of GDM and pregnancy outcomes using 2 different diagnostic criteria (7). Before 2015, they used the current preferred diagnostic cutpoints (at least 1 of the following: fasting, $\geq$5.3 mmol/L; 1 hour, $\geq$10.6 mmol/L; 2 hours, $\geq$9.0 mmol/L) after a 75-g glucose tolerance test. After 2015, the criteria were changed, and clinicians used the 1-step IADPSG criteria (fasting, $\geq$5.1 mmol/L; 1 hour, $\geq$10.0 mmol/L; 2 hours, $\geq$8.5 mmol/L). Pouliot et al found that changing to the new criteria led to a significant rise in GDM incidence, from 10.8% to 17.6%. Although women diagnosed using the IADPSG criteria had a higher early pregnancy body mass index (26.3 vs 25.5, $p=0.01$), and higher rates of chronic hypertension (3.7% vs 1.2%, $p<0.0001$), they had lower rates of pre-eclampsia, labour induction and offspring admission to the neonatal intensive care unit. Does this mean the new criteria are better? One may wonder whether these improved outcomes were due to the inclusion of women with milder disease, who may or may not need to be treated. This point was illustrated in a study by Sacks et al (8). In their work, the authors compared pregnancy outcomes in women who were untreated but met the criteria for GDM only by the IADPSG criteria, but not the Diabetes Canada criteria, to those who were untreated but met the Diabetes Canada preferred criteria. Women with more severe GDM were treated and excluded. When compared to women without GDM, the authors found that women who met the criteria for GDM according to Diabetes Canada had a significantly higher risk of pre-eclampsia, preterm birth, shoulder dystocia and infants who were large for gestational age or had transient tachypnea or neonatal hypoglycemia. Women who met the IADPSG criteria had an increased risk of large-for-gestational-age infants, but had none of the other more serious adverse outcomes. Given these results, one must decide whether it is worth treating the many additional women who would be diagnosed using the IADPSG criteria, given their milder disease. A large randomized trial comparing treatment of women meeting both of these criteria would help to answer this question, preferably with an accompanying cost-effectiveness analysis.

One of the other reasons given for choosing the IADPSG criteria is based on the finding from the HAPO follow-up study (9) showing that GDM, as diagnosed by the IADPSG criteria and left untreated, leads to an increase in childhood obesity in offspring compared with offspring of women with normal glucose levels, even after controlling for many confounders, including maternal body mass index. Although this shows that untreated hyperglycemia is harmful to offspring, questions persist. It remains unknown whether a difference in childhood outcomes would be apparent at different cutpoints and if treatment would reduce these outcomes. It is known, however, that identification and treatment of women with mild GDM during pregnancy has no discernible impact on subsequent maternal diabetes, metabolic syndrome or obesity at 7 years after delivery (10). These are important issues for future research.

Using a completely different approach to diagnosis, in this issue of the Journal, Ardilouze et al (11) compare use of the Canadian "preferred" approach to simply doing self blood glucose monitoring

https://doi.org/10.1016/j.jcjd.2019.09.006

(fasting and 2-hour postprandial) for 7 days without modifying the maternal diet or lifestyle. GDM was diagnosed if at least 4 of 7 glucose values were out of the target range before breakfast or after any meal. The authors found that approximately half the women with an abnormal OGTT had normal values on testing, and 12% of women with hyperglycemia on testing had a normal OGTT. Both groups had more neonatal complications than those with normal values on both tests. They also suggest that the use of both methods may identify women in need of treatment, and thus improve care. Other groups are exploring the use of continuous glucose monitoring for the diagnosis of GDM. This has already been advocated for the diagnosis of GDM in women with prior bariatric surgery who have reactive hypoglycemia. Future studies will inform the clinical utility of these approaches.

Another controversial aspect is the inclusion of an initial screening test. The IADPSG has suggested abandoning the glucose challenge test (GCT), whereas, in Canada, the "preferred" approach recommends continued use of the 50-g GCT. However, there are pros and cons to this approach. The 50-g GCT has a 98% negative predictive value and is both convenient and cost-effective (Diabetes Canada Clinical Practice Guidelines), and one could argue that it is reassuring to diagnose a woman on 2 positive tests (i.e. GCT and OGTT), thus yielding fewer false positives. On the other hand, the GCT results may vary day to day; the sensitivity for diagnosing women with GDM is only 76% and it misses almost 20% of women with only fasting hyperglycemia (12). In addition, treatment is often delayed because women must return for a second confirmatory test before diagnosis.

When is the best time to screen and diagnose GDM? Should GDM be diagnosed early in those at risk? If so, what criteria should be used? Is it worth treating from the first trimester? These questions remain unanswered. There are problems using the same criteria for GDM early in pregnancy as those used at 24 to 28 weeks gestation. Studies have shown that fasting glucose levels are higher during the first 10 weeks of pregnancy than later in gestation. Furthermore, because of the normal insulin resistance that occurs later in pregnancy, post-GCT results are higher in the second and third trimester than earlier in the pregnancy. Given that the IADPSG criteria were derived from women tested between 24 and 32 weeks, the prevalence of GDM in the first trimester may be systematically overestimated using fasting glucose and underestimated using post-GCT results after applying these criteria in the first trimester (13). Perhaps we should use a glycated hemoglobin cut-point of $\geq$5.9% to treat early "GDM," as these women have been shown to have worse outcomes (14). Given the lack of data surrounding this issue, Diabetes Canada has not made any recommendations for diagnosing GDM early on, which in itself can lead to confusion. Many researchers have tried to use predictive models (15) or biomarkers (16) to predict the development of GDM in order to treat early in the first trimester. It makes sense that treatment earlier than the usual 24 to 28 weeks gestation may improve outcomes but this has yet to be proven. Currently, a randomized study in Australia is underway to determine whether early treatment would be beneficial (17).

In summary, a unified approach to the diagnosis of GDM, which takes into account both short- and long-term outcomes, has yet to be determined. Getting this diagnosis right is essential in view of the issues of labelling, the cost of diagnosis and treatment, the absence of evidence of long-term maternal or child benefit of treatment during pregnancy to date and the many short- and long-term risks of diabetes in pregnancy on mothers and their offspring.

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Author Disclosures

Conflicts of interest: none.

Acknowledgments

The authors thank Dr David Sacks for his insightful comments.

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