COMMENT ON SCHOLTENS ET AL.

Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): Maternal Glycemia and Childhood Glucose Metabolism. Diabetes Care 2019;42:381–392

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Scholtens et al. (1) conducted an important study on the association between maternal glycemia and childhood glucose metabolism. In a subanalysis, the authors applied latent class trajectory modeling to assess the shape of maternal glucose response curves during the oral glucose tolerance test (OGTT). Even though I am in favor of this approach because it focuses on the shape of glucose curves rather than just individual time points, I have some concerns regarding how the analysis was conducted and reported.

The model is described as having random effects for linear, quadratic, and cubic terms for time. However, readers can only assume that the same terms were included and tested as fixed effects. Glucose values were available only at three time points (0, 60, and 120 min), which makes it statistically infeasible to fit cubic curves. This approach is similar to trying to fit a straight line when having data from only one time point. The authors also tested a quadratic model (and found it to be the best), which is also problematic but for a different reason. During the 2-h OGTT, most individuals have an initial rise in their glucose level followed by a decline (2). However, the rate of decline has to slow down at some point to reach a rather constant level again (which usually happens within 2 h in the general population). Quadratic curves do not have inflection points by definition and therefore cannot capture such dynamics. To develop a feasible latent class trajectory model (with cubic polynomial or rather spline specification for time), a minimum of four time points is necessary at least in the development data set. Once such a model is developed, studies with certain combinations of time points (also less than four) can apply it with confidence due to the relatively good agreement between class membership probability estimates based on different combinations (3). Therefore, I partly agree with the authors' conclusion that the inclusion of the 60-min measurement offers new opportunities, but the clinical relevance of glucose response patterns has to be further investigated before changing current guidelines.

Another analytical issue is with regard to the comparison of impaired glucose tolerance risk between groups B and C. The authors elaborate on a "possible trend of higher risk" in class C compared with B, even though they could have easily calculated an odds ratio for this association by defining class B as the reference category or by using an appropriate contrast matrix in their original model. Furthermore, it is not clear how the curves in Fig. 3 were estimated. They seem to have break points at 60 min and therefore cannot be based on the latent class model, which had a quadratic time specification. Latent class trajectory modeling is a complex method that needs just as rigorous reporting as conduct. Recent publications by Lennon et al. (4) and van de Schoot et al. (5) provide excellent guidance on the challenges and potential solutions within the field.

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