Much to HAPO FUS About: Increasing Maternal Glycemia in Pregnancy Is Associated With Worsening Childhood Glucose Metabolism

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The initial purpose of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study was to examine the associations of increasing degrees of untreated maternal glycemia, less severe than overt diabetes, with adverse pregnancy and neonatal outcomes and bring a unified approach to the diagnosis of gestational diabetes mellitus (GDM).

The HAPO study (1) demonstrated linear increases in the risk of the primary outcomes of neonatal birth weight, cord C-peptide >90th percentile, neonatal hypoglycemia, and primary cesarean delivery with increasing maternal glycemia on a one-step 75-g 2-h oral glucose tolerance test (OGTT). The secondary outcomes including neonatal skinfold thicknesses >90th percentile, preterm delivery, preeclampsia, and shoulder dystocia had similar associations. In two long-term offspring follow-up studies published in this issue of *Diabetes Care* (2,3), risks of adverse outcomes related to this continuum of maternal glycemia in pregnancy are now demonstrated to persist into early adolescence.

The long-term risk of maternal hyperglycemia to the offspring exposed in utero has been an ongoing concern for decades. In 1954, Pedersen (4) proposed that excessive glucose in mothers with diabetes is available for trans-placental passage, resulting in fetal hyperinsulinemia and excess fat accretion. In his Banting lecture, Norbert Freinkel (5) proposed the concept that fetal exposures to altered levels of maternal fuels, after organogenesis, may result in long-range adverse anatomical and metabolic changes in the offspring, which he called "fuel-mediated teratogenesis." A related "fetal programming" hypothesis proposed by Barker and Osmond (6) holds that nutritional (and other environmental) exposures during critical developmental windows may induce changes in tissue development and function that contribute to long-term chronic disease risk. Based on studies in animal models and in human tissues, such long-term effects may be mediated through epigenetic changes in the β-cells, liver, and insulin target tissues, along with hypothalamic appetite signaling, the gut microbiome, plasma metabolites, and other factors (7,8). However, reviews and systematic analyses of human data (9–12) have demonstrated inconsistent long-term offspring outcomes, which may be due to variable adjustment for important confounders such as maternal and paternal BMI and glycemia (9,13), the inability to ascertain effects of GDM treatment (12), and the study of special populations with high prevalence of type 2 diabetes and GDM, which might not be generalizable (14). Thus, there is a critical knowledge gap regarding long-term health outcomes in the offspring of women with gradations of glucose intolerance in pregnancy.

The two articles herein examine the associations of untreated maternal plasma glucose on the one-step 75-g OGTT at 24–32 weeks of gestation with markers of glucose metabolism in 4,160 racially/ethnically diverse offspring at 10–14 years of age (2,3). The article by Lowe et al. (2) focuses on untreated maternal GDM (based on post hoc International Association of the Diabetes and Pregnancy Study Groups/World Health Organization criteria) (15,16) as the primary exposure, with comprehensive markers of offspring metabolic outcomes including impaired fasting glucose (IFG); impaired glucose tolerance (IGT); 75-g OGTT glucose values at 0, 30 min, 1 h, and 2 h; A1C; type 2 diabetes; insulin sensitivity (Matsuda index [IS]) and secretion (insulinogenic index); and the oral disposition index (oDI), a measure

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of β-cell compensation for insulin resistance and a strong predictor of type 2 diabetes (17). The article by Scholtens et al. (3) examines associations between in utero exposure to maternal glucose across the spectrum, both continuous associations of maternal glucose and categorical associations across five maternal ranges for glucose, and offspring markers of glucose metabolism.

In the article by Lowe et al. (2), offspring of mothers with GDM had higher prevalence of IGT; higher 30-min, 1-h, and 2-h glucose during OGTT; and reduced IS and oDI compared with children of mothers without GDM. GDM in mothers was not associated with IFG or type 2 diabetes in offspring. In the article by Scholtens et al. (3), the authors demonstrate strong positive associations between maternal continuous and categorical glycemia status with offspring 75-g OGTT glucose, A1C, IGT, and IFG, along with inverse associations with IS and oDI. Maternal fasting plasma glucose (FPG) was positively associated with offspring FPG, IFG, and A1C and inversely associated with offspring IS. Moreover, maternal 1-h and 2-h glucose levels were positively associated with offspring IGT, A1C, and glucose levels during OGTT and inversely related to offspring IS and oDI. Strengthening the findings, multiple models were presented to address potential confounders, including field center (a proxy for race/ethnicity); child age, sex, pubertal status, and family history of diabetes in a first-degree relative; maternal factors (e.g., age, height, blood pressure, parity, smoking, and drinking); and both maternal BMI and child BMI *z* score. Notably, adjustments for maternal BMI, child BMI, and family history of diabetes did not alter the associations. Recognizing that associations may differ by pubertal status (18), the authors stratified by Tanner stage. While many of the continuous associations of maternal and child outcome were significant upon stratification by Tanner 1, Tanner 2–3, and Tanner 4–5, the authors note that statistical models were not powered for all of the associations.

These studies indicate strong continuous associations between maternal glycemia in pregnancy and long-term effects on offspring glycemia, insulin sensitivity, and β-cell function. As a note of caution, the studies found effects on offspring risk of IGT and in some analyses IFG but did not show a significant increase in risk of type 2 diabetes with increasing maternal hyperglycemia. However, type 2 diabetes is rare in children, and the study was likely underpowered to look at this outcome. Still, in youth, these diagnostic categories are fluid. A recent study from Galderisi et al. (19) showed that 65% of adolescents (mean age 12.7 years) with IGT at baseline reverted to normal glucose tolerance at follow-up (mean 2.9 years), but notably 8% did progress to type 2 diabetes during this short time period. While these associations do not prove causality, they do give cause for concern. In the search for markers that identify children at risk for abnormal glucose metabolism, maternal glycemia in utero may be among the earliest. Of importance, the nature of these associations shows that risks are continuous and may argue for broader use of the one-step 75-g OGTT to diagnose GDM to identify children with higher risks of abnormal glucose metabolism in early adolescence.

Further studies are needed to evaluate whether treatment of women with higher glucose levels in pregnancy will reduce or reverse abnormal glucose metabolism in offspring. The optimal time period(s) to intervene to reduce offspring metabolic risk needs further study (i.e., treatment of pregnant mothers, treatment of affected infants, children, or youth, or a multifaceted approach). Other possible mechanisms should be studied to assess their possible contribution to offspring metabolic outcomes in relation to maternal hyperglycemia, including shared genetics, shared environment—similar diets and exercise patterns as well as chemical exposures (20)—and paternal effects (21,22). Still, with childhood obesity, metabolic disease, and type 2 diabetes being challenging conditions to treat successfully, any interventions that may prevent their emergence should be strongly considered by professional societies and clinicians. Finally, the continuum of increasing offspring metabolic risk associated with maternal hyperglycemia raises the question: What maternal glucose thresholds on the one-step 75-g OGTT should we use to identify offspring who are at greatest risk? Studies of cost-benefit and health economic impact will be necessary to answer this question.

The HAPO Follow-up Study (HAPO FUS) data presented in this issue of *Diabetes Care* (2,3) provides an additional strong argument for the need to derive and use diagnostic glucose levels in pregnancy based on the available science rather than history or common usage.

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