Gestational Diabetes Mellitus and the Offspring—Jack and Jill Are Different Still

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Hyperglycemia is the most common metabolic disorder complicating pregnancies across the globe. With rising maternal age, obesity, physical inactivity (1), and increasingly stringent diagnostic criteria, about one in seven women now has a pregnancy complicated by hyperglycemia (2). The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) confirmed that treating women with gestational diabetes mellitus (GDM) reduces serious perinatal complications (infant death, shoulder dystocia, fracture and nerve palsy) (3). Likewise, a trial by Landon et al. (4) showed that treating women with hyperglycemia reduces maternal weight gain, gestational hypertension, preeclampsia, cesarean delivery, infant adiposity, and birth weight. Of note, the degree of glycemia in the Landon et al. trial was comparatively less than that in ACHOIS, as suggested by only 8% of women in the intervention arm requiring insulin therapy compared with 20% in ACHOIS. A secondary analysis in a subgroup of offspring in the original Landon et al. trial showed that male offspring had a lower birth weight percentile and fat mass and gained greater benefit from the maternal GDM intervention compared with female offspring (5). These landmark trials have changed the clinical practice of GDM, placing greater emphasis on glucose-lowering interventions to reduce obstetric and perinatal complications.

Emerging evidence suggests that the intrauterine and early postnatal environment can influence cardiovascular and metabolic health in later life. Maternal hyperglycemia in GDM is thought to confer a greater risk of diabetes and obesity in exposed offspring via fetal programming. Animal models suggest similar associations but are hampered by a lack of replication (6), exposure to severe hyperglycemia (7,8), and unclear relevance to human pathophysiology (9). Most human studies in this area are observational and therefore cannot control for transmission of risk from parent to child by shared genetic and environmental susceptibility.

Randomized trials of GDM treatment offer an opportunity to examine whether maternal GDM does "program" obesity and diabetes in exposed offspring: attenuation of this association with GDM treatment would identify a causal relationship. To date, only one randomized trial (ACHOIS) has followed this approach, finding no difference between obesity (BMI *z*-score) in children born to mothers from intervention (n = 94) or control (n = 105) arms (3). The study had substantial limitations, notably insufficient power (only 200 offspring were included), childhood follow-up occurring at preschool age before the expected emergence of diabetes and obesity, and lack of detailed anthropometry. In this issue of *Diabetes Care*, a follow-up study performed by Landon et al. (10) presents a welcome addition to the field with its larger size including 500 children born to mothers with mild hyperglycemia enrolled in their original GDM treatment trial (4).

In their original trial, Landon et al. (4) recruited 958 pregnant women with mild GDM defined by established diagnostic thresholds (11) and randomized them to treatment (92% diet, 8% insulin) or no treatment. Treatment was associated with reductions in gestational weight gain (2.8 vs. 5.0 kg), hypertensive disorders, cesarean delivery, fetal overgrowth, and shoulder dystocia. Surprisingly, secondary analysis suggests a differential impact of GDM treatment according to offspring sex, with greater reductions in birth weight and neonatal fat mass in males than in females (5). In this unplanned follow-up study, only 55% of the original study offspring (n = 500) at age 5–10 years were included (10). By 7 years of age, prevalence of childhood obesity and impaired fasting glucose were 21.8% and 6.4%, respectively. No differences in measures of obesity (BMI >95th centile) or hyperglycemia (fasting glucose, impaired fasting glucose, diabetes, HOMA-IR) were found in children born to mothers

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from either treatment arm. Female children of mothers in the treatment arm had lower fasting glucose, log HOMA-IR, and rates of impaired fasting glucose, suggesting a sex-specific impact. Girls from the treatment arm with highest neonatal adiposity had a lower BMI *z*-score at follow-up, an interaction that may suggest beneficial effect of treatment among higher-risk GDM-exposed female offspring.

This study brings additional uncertainty regarding the risks of GDM exposure and extent to which they are mitigated by treatment. First, even with 500 offspring, the study (as acknowledged) was underpowered to detect differences in childhood obesity. Second, the treatment effect size (a one-third reduction in childhood obesity from 30 to 20%) was optimistic in a population where 400 (80%) infants had a birth weight appropriate for gestational age. Third, BMI was used despite wide recognition of it being a poor marker of childhood adiposity due to its inability to reflect the complexity of body composition (fat versus lean mass). Fourth, the age of onset of programmed phenotypic differences in GDM-exposed offspring is not known and the absence of difference may be due to the young age (75% <Tanner stage 1) at which they were studied. Finally, a post hoc design with a recruitment rate of 55% could allow ascertainment bias and is indeed suggested by fewer Hispanic offspring participants at follow-up than in the original trial.

Landon et al. suggest that treatment of maternal hyperglycemia may reduce the immediate risk of adiposity in male neonates, whereas it may have an enduring impact on glucose metabolism in prepubertal girls. Additional sex-specificity is suggested as female offspring who were overweight at birth show reduced BMI in childhood associated with treatment of maternal GDM. These intriguing sex-specific differences in metabolic phenotype are previously described, with studies showing male neonates prone to greater adiposity and female neonates having higher cord blood C-peptide concentrations (12–14). Future studies investigating the causal relationship between maternal GDM and offspring phenotype must be sufficiently large to detect sex-specific differences and should include more detailed phenotypic assessment (using anthropometric or DXA measures of fat mass) to increase the precision with which differences are detected.

The study by Landon et al. (10) also highlights the need to quantify the overall risk reduction that a GDM intervention can achieve, including immediate maternal and fetal complications as well as future risk of metabolic disorders in offspring. While relative risk reductions associated with GDM treatment are large, the rate of GDM-associated maternal and immediate fetal complications is relatively low (compared with pregnancies complicated by pregestational diabetes), leading to a small absolute risk reduction. If it transpires that GDM exposure does not have a causal relationship with the development of childhood obesity and diabetes, the diagnosis and treatment of mild hyperglycemia in otherwise healthy pregnant women must be rebalanced alongside the risks and costs (15) associated with increased medicalization of a GDM pregnancy.

This study (10) is an important addition to a research area currently limited by multiple studies showing association without proof of causation. It provides an intriguing suggestion that maternal GDM may indeed have a beneficial effect on fasting glucose in female offspring but does not provide conclusive proof of this or its association with childhood obesity. The seemingly negative result overall leaves the field open to ongoing debate and necessitates future longitudinal studies that follow children through puberty and, ideally, that follow the females throughout their reproductive life span. This approach may allow the development of a "programmed" phenotype to become overt and provide the much-needed evidence to support or refute the hypothesis that GDM can have long-term adverse metabolic consequences on offspring. Follow-up of maternal cohorts is also needed to evaluate the impact of GDM treatment on future maternal outcomes, including GDM in subsequent pregnancy and progression to type 2 diabetes.

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