COMMENTARY

It's All About Fat, Baby: Is Infant Adiposity Associated With Later Adverse Metabolic Health?

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Excessive neonatal adiposity is a risk factor for adverse cardiometabolic health including child obesity and insulin resistance (1,2). Fetal fat deposition occurs in late pregnancy and provides the neonate with energy stores postdelivery. Of all mammals, humans have the highest neonatal fat mass, although its role continues to be under investigation (3). Both too little and excessive neonatal adiposity have been demonstrated to lead to adverse cardiometabolic health (4). This commentary focuses on excessive neonatal adiposity, its causes and implications.

States of maternal overnutrition including gestational diabetes mellitus (GDM), obesity, and excessive gestational weight gain are associated with excessive neonatal adiposity (5–7). Maternal hyperglycemia, even below GDM diagnostic thresholds, is also associated with excessive neonatal adiposity (8). Recently, neonatal adiposity was identified as a mediator in the association between maternal hyperglycemia and childhood adiposity (1). Adiposity in childhood tracks into adulthood; once present it is difficult to reverse (9). However, the trajectory of adiposity from infancy through childhood is less understood due to lack of longitudinal studies. Measurement of adiposity during infancy is challenging, as nonbiased methods such as DEXA or air displacement plethysmography (ADP) use hospital-based expensive equipment (10). Portable anthropometry methods, including calipers to measure skinfold thicknesses, require significant training, and there is potential for poor reproducibility.

Reducing hyperglycemia in pregnancy may normalize neonatal adiposity and potentially decrease childhood obesity rates. However, much debate surrounds diagnostic testing for GDM (11). Universal screening for GDM at 24–28 weeks of pregnancy is standard practice in developed countries. The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) recommends a fasting 2-h 75-g oral glucose tolerance test for all pregnant women (12). Other professional organizations recommend glucose diagnostic thresholds higher than that recommended by IADPSG (13) or two-step testing (14), with a screening nonfasting glucose challenge test, and if threshold is exceeded, a fasting 3-h 100-g oral glucose tolerance test. In several recent randomized trials (15–17), investigators compared these diagnostic thresholds and came to similar conclusions: lower diagnostic glucose thresholds resulted in diagnosis and treatment of more women with GDM, with no significant differences in adverse perinatal outcomes between groups. Thus, due to increased health care use and costs without commensurate improvement in perinatal outcomes, the trial researchers endorse higher glucose thresholds for GDM diagnosis.

The debate over diagnostic testing strategies often centers on perinatal outcomes. Absent from these considerations, and from the conclusions drawn by investigators of the above-mentioned randomized studies, is discussion of the documented adverse long-term outcomes in children exposed to untreated gestational hyperglycemia (8,18).

The BabyGEMS study in this issue of *Diabetes Care* by Manerkar et al. (19) fills a major research gap in reporting infant adiposity at 5–6 months following exposure to GDM. The investigators conducted a prospective, nested cohort study in infants of individuals in the Gestational Diabetes Mellitus Trial of Diagnostic Detection Thresholds (GEMS), a randomized trial conducted in New Zealand in which the lower detection criteria for GDM as recommended by the IADPSG (12) was compared with the higher criteria in use for over 20 years (13). A control group not exposed to GDM was also enrolled. Four groups of infants (n = 760) were studied: *1*) control infants (with mothers without GDM according to the lower detection criteria), *2*) infants of mothers with GDM diagnosed according to the lower IADPSG criteria and treated, *3*) infants of mothers with GDM diagnosed according to the lower IADPSG criteria and untreated, and *4*) infants of mothers with GDM diagnosed according to the higher criteria and treated. This was a robustly designed study in which the investigators hypothesized that fat mass at 5–6 months would be higher in infants exposed to GDM as detected according to higher criteria (group 4) or detected according to lower criteria but untreated (group 3) compared with infants unexposed to GDM

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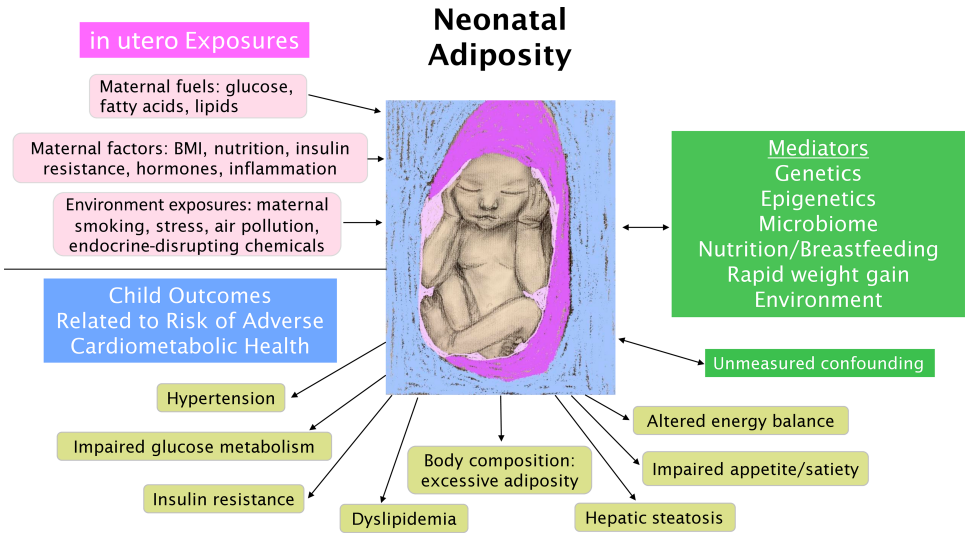

Figure 1—Neonatal adiposity: in utero exposures, child outcomes related to risk of adverse cardiometabolic health, and potential mediators in the associations.

(group 1) and those exposed to mild yet treated GDM (group 2).

The primary outcome of this study was infant fat mass measured with ADP (PEA POD, COSMED) at 5–6 months. Along with birth measurements, secondary outcomes at 5–6 months, considered by the investigators to be infant risk factors for later metabolic disease, are also reported: skinfold thickness, lean mass, rapid weight gain from birth to 5–6 months, breastfeeding, early introduction to solid foods, energy intake, and information on feeding behavior from parent surveys.

No difference in fat mass was identified between the four groups at mean age 5.2 months among infants exposed to GDM compared with control infants, and regardless of maternal treatment. While ADP measures of fat mass were only available for 57% of the infants, adiposity assessed according to skinfold thicknesses in 87% of infants demonstrated findings consistent with those of ADP measures, without differences between the four groups. However, adiposity outcomes at birth demonstrated thicker skinfolds and increased fat mass in group 3, those infants whose mothers had GDM detected by lower criteria and were not treated, compared to control infants in group 1. Group 3 also had higher rates of large-for-gestational-age birth weight. At birth, infants exposed to treated GDM (groups 2 and 4) had significantly lower lean mass and overall reduced body size compared with control infants. At 5–6 months, there were no differences between groups for secondary outcomes of energy intake, feeding behaviors, breastfeeding predominance, or early introduction to solid foods.

The finding of increased neonatal adiposity in infants exposed to untreated, albeit mild, GDM is consistent with findings of previous studies. The results of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) epidemiological study demonstrated increased neonatal adiposity as measured by skinfold thicknesses along the continuum of maternal glucose levels below diagnostic thresholds of GDM (20). The primary finding in BabyGEMS that fat mass at age 5.2 months was not different among groups was contrary to the study hypothesis. The lack of difference in infancy fat mass was not unexpected, as in the limited studies among infants exposed to GDM reporting on body composition differences, there are conflicting findings (21–23). Evidence from a number of longitudinal studies of offspring exposed to GDM indicates that adiposity differences emerge in the peri-pubertal years (8,24,25). Results of the BabyGEMS Study demonstrate a "regression to the mean" in body composition soon after birth in infants exposed to maternal hyperglycemia. While a mechanism for this finding has not been identified, potential interventions to maintain normal body composition from childhood onward require exploration.

Strengths of the study include the blinded detection and treatment group allocation, diversity of the cohort, and multiple measures of infant adiposity. A limitation was the lack of primary outcome data (ADP fat mass) on 40% of the cohort, largely due to nonportability for ADP. However, home visits were conducted to obtain infant anthropometrics, which corroborated the findings. Other limitations included lack of data on maternal glycemic control and potential residual confounding of GDM pharmacologic treatment type. The results of the BabyGEMS Study were not influenced by metformin exposure, yet in neonates of individuals with type 2 diabetes, metformin is associated with reduced adiposity and lower birth weight (26).

Longitudinal follow-up of this cohort with direct measures of adiposity is imperative as researchers disentangle the contributions of in utero and postnatal environments to adiposity development over the life course (Fig. 1). The BabyGEMS Study reports that untreated, mild GDM is associated with increased adiposity in neonates in comparisons with treated GDM and unexposed neonates, but an unanswered question is whether treatment of mild GDM as detected by lower glucose thresholds leads to improved cardiometabolic health in adolescence. The increase in child obesity and prevalence of type 2 diabetes diagnoses in youth is disconcerting. Reducing hyperglycemia in pregnancy and subsequent excessive neonatal adiposity is one strategy with the potential to reduce these rates.

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