Fetal adiposity epidemic in the modern world: a thrifty phenotype aggravated by maternal obesity and diabetes

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Along with the ongoing struggle to overcome undernutrition, infectious disease, and low birth weight in many countries, we are facing a rising epidemic of obesity, diabetes, and big babies (1). The large infants have excess fat in the body (adiposity) which is thought to be the harbinger of the obesity and diabetes epidemics. Controlling fetal adiposity may be the only solution to the vicious intergenerational cycle of obesity and diabetes. We now have a double duty to solve this double burden of malnutrition.

Fetal growth and body composition are driven by genetics and epigenetics, the latter being the route for the intrauterine environment to exert its influence. Study of rare monogenic conditions has helped us understand the role of genes and environment in fetal growth but the major influences are polygenic and epigenetic (2, 3). The intrauterine environment thus becomes the major modifiable influence on fetal growth. It is composed of maternal nutrition (including dietary requirements, dietary intake, and nutritional status), metabolism, disease, pollutants, and other factors. Maternal diabetes has long been known to influence fetal adiposity, vividly described by Pedersen in the 1950s: "Most conspicuous is obesity, the round cherub's cheeks, buried eyes, and short neck…" (4). This visual description misses the fat in the intra-abdominal (visceral) tissue.

In this issue of *The American Journal of Clinical Nutrition*, Mya-Thway et al. (5) report associations of maternal glycemia with MRI measurements of abdominal fat (subcutaneous and intra-abdominal) in ∼300 South Asian newborns in the GUSTO (Growing Up in Singapore Towards healthy Outcomes) birth cohort in Singapore, and again at 4.5 y of age. They make important and interesting observations: *1*) maternal glycemia is positively *and continuously* associated with both compartments of neonatal abdominal fat, *2*) fasting glucose is more strongly associated than the 120-min oral-glucose-tolerance test (OGTT) glucose, *3*) the effects are larger in female than in male infants, and *4*) maternal glycemia continued to be associated with offspring abdominal adiposity at 4.5 y of age, although weakly and only with subcutaneous fat in females. There are of course limitations that affect the study's interpretation, including its reporting no information on prepregnancy and early pregnancy glycemia of the mother, no analysis of nonglucose nutrients (lipids, amino acids, and micronutrients), and no information on fathers.

Notwithstanding these limitations, this study expands our knowledge of determinants of fetal adiposity and highlights the limitations of current clinical practices in pregnancy diabetes. The multinational HAPO (Hyperglycemia and Adverse Pregnancy Outcome) study also showed a continuous and graded association without any threshold between maternal glycemia and clinical correlates of fetal adiposity [large-for-gestational-age (LGA) infants, cesarean delivery rates, and others], which was strongest for fasting glucose (6). An arbitrary statistical consensus led to the current International Association for Diabetes and Pregnancy Study Groups (IADPSG) criteria for gestational "diabetes," subsequently legitimized by the American Diabetes Association and WHO/International Diabetes Federation. In the primary analysis, the HAPO study validated Pedersen and Osler's (4) glucose-hyperinsulinemia hypothesis which suggested that excess transfer of glucose from the mother to the fetus stimulates fetal pancreatic islets to secrete more insulin which promotes fetal overgrowth. Freinkel (7) expanded the concept to include maternal nonglucose metabolites (lipids, amino acids) and included risk of later adiposity and diabetes in the offspring ("fuel mediated teratogenesis"). The IADPSG criteria were based on "short-term" pregnancy outcomes but not the long-term risk of obesity and diabetes in the offspring. A follow-up study confirmed the continuous and graded association of maternal pregnancy glycemia with offspring adiposity and glycemia, confirming the lack of a "diabetes" threshold (8). Confusion is compounded because many countries soon declared different criteria for abnormal maternal glycemia in pregnancy, for a variety of reasons.

On this background of fetal overnutrition, it is intriguing that adiposity is also a characteristic of the small infants born to undernourished mothers in India (9). The average "thin-fat" infant born in the Pune Maternal Nutrition Study was 800 g lighter (2.7 compared with 3.5 kg) but had higher subscapular skinfold, cord blood leptin concentrations, and MRI abdominal fat than an average English infant. The mothers were short (1.52 m) and thin (BMI: 18.1 kg/m^2), and had low glycemia (fasting plasma glucose: 4.0 mmol/L; and 2-h plasma glucose during an OGTT: 4.1 mmol/L). Despite this, maternal glycemia, cholesterol (total and HDL), and triglyceride concentrations predicted infants' size and adiposity in a continuous manner. Deficiencies of vitamins (folate, vitamin B-12, and vitamin D) and deranged one-carbon metabolism (higher homocysteine) predicted smaller infant size, and adiposity and insulin resistance during childhood, which we called a "nutrient-mediated teratogenesis." Thus,

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fetal undernutrition and overnutrition are both linked with fetal adiposity and can combine to cause "dual teratogenesis." This undernutrition scenario is embedded in the "thrifty phenotype" hypothesis of Hales and Barker (10).

It is perhaps not without reason that the relatively tiny human infant invests in depositing the highest body fat percentage among the mammals; much more than a piglet, sea lion, or an elephant (11). Fat is a ready store of energy and vital thermal insulation after birth. Social scientists also tell us that baby fat lures the mother into feeding the infant. The molecular and cellular mechanisms in human developmental adipogenesis are still being understood. Adipocytes are derived from a mesenchymal precursor shared with muscle cells, differentiating through intermediate preadipocytes (12). Postmortem light microscopy studies suggest that adipocyte differentiation is active between 19 and 23 weeks of gestation, and proliferation and expansion between 23 and 29 weeks of gestation (13). The number of fat cells is largely fixed at this time. A recent article reported a larger weight gain (a surrogate for adiposity) from 20 weeks of gestation onwards in infants whose mothers were subsequently diagnosed with gestational diabetes mellitus (GDM), than in infants of glucose-tolerant mothers (14). The accompanying comment "timing is everything" suggests it will be important to intervene in early pregnancy to reduce fetal adiposity (15). We will have to decide: are feasible interventions effective? Safe? How early is early?

Trials targeting maternal diet and weight, physical activity, and diabetes have helped reduce LGA but not childhood adiposity and glucose intolerance (16, 17). These disappointing results could at least partially be attributed to missing the periconceptional window of epigenetic programming which decides allocation of cells to different lineages (18). Many trials are started in the second or third trimester. The majority of risk factors for diabetes (genetic and epigenetic susceptibility, stunting, obesity) and even hyperglycemia (measured in only a few studies) are present well before pregnancy. Catalano et al. (19) showed that GDM mothers had lower insulin secretion and insulin sensitivity from before pregnancy. In the Pune Maternal Nutrition Study, we found that high glycemia during pregnancy was traceable to higher glycemia from age 6 y (20). The ova of these mothers would thus be exposed to an abnormal milieu from long before pregnancy, and susceptible to epigenetic changes (18). The current convenient practice of diagnosing and treating "gestational" diabetes in pregnancy is like closing the door after the horse has bolted. John Jarrett (21) reminded us that "gestational diabetes is no more than a special case of impaired glucose tolerance, temporally associated with pregnancy." Thus, short-term pregnancy outcomes dependent on third-trimester exaggeration of fetal growth may be helped in these and other intervention trials, but the pre- and periconceptional molecular and cellular imprinting which program long-term risk of obesity and diabetes are left untouched, and the epidemics continue to grow.

It is time to think how we can influence fetal adiposity to control the obesity-diabetes epidemic. Fetal adiposity is a relic of multigenerational undernutrition, amplified by the relative overnutrition of modern times. A balanced life-course approach to nutrition and lifestyle is a possible solution. The window of opportunity is before, and in very early, pregnancy. This should spur clinicians and policy makers to shift the focus from clinics to the community. It will need substantial efforts, given the giant sickness industry that has developed around this specialty. Wolpert's reminder: "it's not birth, marriage or death but gastrulation that is truly the most important time in your life" should give us, combined with these recent data, more than enough inspiration (22).

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