

Fetal Programming of Diabetes: Still So Much to Learn!

In the preinsulin era, pregnancy in a diabetic mother had a bleak outcome for both the mother and the baby. Availability of insulin and modern methods of treatment improved the survival of these babies, but they appear to be at increased risk of obesity and diabetes (1–3). Spread of the diabetes pandemic to the young means there is now a growing epidemic of gestational diabetes mellitus (GDM). This label encompasses all varieties of diabetes that happen to be diagnosed during pregnancy, but the majority of GDM cases have type 2 pathology and metabolic syndrome–like features. There is a tacit assumption that glucose intolerance may have arisen *de novo*, but this is unlikely. The majority of women have risk factors dating back before pregnancy, sometimes traceable to early life growth and development (4,5), and many continue to be diabetic after delivery or develop diabetes soon after (6). The degree of glucose intolerance qualifying for the diagnosis of GDM is still being debated, and there is little consideration of other metabolic parameters, such as lipids, in the diagnosis. There is a growing realization that even a mild change in the intrauterine environment influences the baby's prospects not only in the perinatal period but over the entire length of its life (7). These ideas are at the core of the emerging specialty of Developmental Origins of Health and Disease (DOHaD) (8). The process influencing long-term fetal outcomes is called fetal programming (9).

The conceptus begins its life as a bag of genes that directs the development of a new individual. The new and important realization is that the intrauterine environment dictates how these genes function. A small change in this environment has the potential to permanently alter the working of genes and therefore the structure and function of the developing system. These processes, which govern evolution of an individual phenotype from the genome, are called “epigenetic” (10) and involve chemical modifications in the structure of chromatin, through either methylation of DNA or acetylation of histones, that influence gene expression. Noncoding RNAs (iRNA) also play a part in regulation of gene expression. In animals, such chemical modifications alter

the phenotype despite the inheritance of the same genotype (11). This is distinct from the change in the sequence of base pairs (polymorphisms or mutations) that form the basis of genetic influence.

Our knowledge of the role of maternal diabetes in fetal programming owes itself to Jorgen Pedersen from Copenhagen and Norbert Freinkel and colleagues from Chicago. A combination of their ideas saw the birth of the concept of fuel-mediated teratogenesis (12) and extended the use of this term from disfiguring birth defects to a wide range of changes in the body habitus of the developing fetus. Fuels included glucose, fatty acids, and amino acids and were components of the culture medium bathing the fetus. Non-glucose metabolites have been forgotten in clinical practice, and the importance of micronutrients was realized only recently (13).

Pedersen highlighted the striking adiposity of an infant of a diabetic mother (IDM): “Most conspicuous is obesity, the round cherub's cheeks, buried eyes, and short neck” (14). He ascribed this to fetal hyperglycemia and hyperinsulinemia stimulating excess growth of insulin-sensitive tissues to cause macrosomia. Clinicians are aware of the mechanical and metabolic problems for a macrosomic baby at birth. However, the most intriguing aspect of the story unfolded during their follow-up in Chicago (15) and in Arizona Pima Indians (1–3), which demonstrated that IDMs had an increased risk of obesity and glucose intolerance, usually demonstrable by late childhood and independent of maternal genetic influence. Over half the cases of diabetes in young Pima Indians were estimated to be attributable to maternal diabetes. The relative role of genetics and epigenetic programming in the etiology of diabetes pandemic awaits further investigation.

Against this background, when Hales and Barker described an association between low birth weight and type 2 diabetes (16), it was met with some skepticism. They suggested that intrauterine undernutrition programmed the fetus for diabetes. Subsequent studies revealed that the real shape of this relationship was U shaped, i.e., both low and high birth weight increased risk of type 2 di-

abetes (17,18). It is important to understand that the story is not about birth weight but about fetal programming, and that intergenerational prevention of type 2 diabetes (primordial prevention) will need to target maternal nutrition and metabolism.

The contribution of maternal diabetes to offspring obesity and diabetes outside of the high-risk populations remains sparsely investigated. There are many unanswered questions: What is the role of maternal obesity? What is the contribution of glucose, lipids, and other metabolites (alone or in combination)? What are the differences by type of maternal diabetes (type 1, 2, GDM, and other)? What are the critical windows of exposure? How does maternal undernutrition interact with maternal diabetes? Does treatment of GDM reduce fetal programming? . . . and many more. A recent report from Copenhagen provided some answers (19). Clausen et al. followed 597 offspring of diabetic mothers at 22 years of age and compared them with a background population. They found that maternal hyperglycemia (GDM), maternal risk factors for diabetes even in absence of GDM (family history of diabetes, prepregnancy obesity, history of previous GDM, or a macrosomic baby), and type 1 diabetes all increased risk of type 2 diabetes and prediabetes in the child. Maternal GDM increased the risk by eight times, while type 1 diabetes increased the risk four times above the background population. Interestingly, mothers with risk factors but no GDM also increased the risk four times. The degree of maternal hyperglycemia in the third trimester in type 1 diabetic mothers was a significant predictor of the child's glucose tolerance. They interpreted this as meaning that genetic predisposition and maternal hyperglycemia had contributed similarly to the risk of diabetes in the offspring (19).

This issue of *Diabetes Care* includes articles that add further information (20–23). They address a variety of maternal exposures and offspring outcomes. All agree that maternal hyperglycemia (irrespective of type of diabetes) promotes macrosomia. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study showed that this relationship is continu-

ous, without any distinct threshold (24). In the Belfast center of the HAPO study, maternal glycemia had only a weak effect on overweight and obesity in the offspring at 2 years of age (20), while in Scotland type 1 diabetes had a significant effect on overweight and obesity at 7 years of age (21). These results could be viewed in relation to a previous observation that the macrosomic IDMs catch down during infancy, only to catch up at the time of adiposity, rebound, and become obese. Against this background, the report on the follow up of children in the ACHOIS trial is interesting (22). In this trial, GDM was diagnosed in the third trimester and randomly allocated to intensive or conventional treatment. Intensive treatment significantly reduced macrosomia and related problems at the time of delivery but had no effect on overweight and obesity at 5 years of age; both groups were more obese than the background population (22). Despite lower birth weight, at 5 years children in the intensive group had similar weight and BMI as those in the conventional treatment group, raising the possibility that these children had an earlier adiposity rebound. Did intensive treatment introduce an element of intrauterine growth restriction that promoted a childhood catch up? Only time will tell, but this issue has been raised before (25). Follow up of 16 year olds in the Northern Finnish Birth Cohort 1986 showed that maternal prepregnancy obesity is a more potent determinant of offspring overweight and obesity compared with maternal hyperglycemia (23). Maternal gestational hyperglycemia by itself had no effect, but in combination with obesity was very detrimental. These observations highlight a crucial role for the periconceptional environment in fetal programming of obesity, and indirectly raise the possibility that nonglucose metabolic abnormalities of obesity (fatty acids and lipids) may be important. Perhaps we gestational diabetologists have become too glucocentric? Together, these studies raise a concern that the current practice of diagnosing gestational hyperglycemia in late pregnancy might be bolting the door after the horse has fled. In our attempts to improve perinatal outcomes, we should not ignore the long-term outcomes that have a bearing on the diabetes pandemic.

Researchers in India, myself included, have focused their attention on maternal micronutrient nutrition and offspring body composition (8). Indian babies are “thin-fat,” i.e., have less lean mass

but more fat mass compared with British babies (26). At least part of this phenotype results from a maternal imbalance of vitamin B12 and folate nutrition. Maternal homocysteine concentrations predicted fetal growth restriction, and low maternal vitamin B12 and high folate predicted higher insulin resistance in the child (13), thus contributing to the concept of nutrient-mediated teratogenesis (27). In Mysore, vitamin B12 deficiency was associated with gestational glucose intolerance (28), and babies born to GDM mothers had heightened risk of adiposity and glucose intolerance at 5 years of age (29), suggesting that a dual teratogenesis (due to simultaneous occurrence of micronutrient deficiencies and hyperglycemia) could make a substantial contribution to the escalating epidemic of diabetes in India (27).

Prevention of fetal programming of diabetes will need to concentrate on the health of young girls. Definition of critical periods in fetal programming will guide us to the windows of opportunity, which may be pre- and periconceptional, gestational, and even lactational. These issues were highlighted at a meeting in the United Nations (Women, Development and Diabetes) (30) and form the core of the “Kathmandu Declaration” which offers a new interpretation of the blue circle of the International Diabetes Federation by recommending a “life-circle” approach to prevention and treatment of diabetes, (31).

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