The Vicious Cycle of Maternal Diabetes and Obesity: Moving From “What” to “How” and “Why”

The prevalence of childhood obesity has risen dramatically, bringing with it serious health consequences including diabetes, cardiovascular disease, and lifelong obesity. Although a number of factors contribute to childhood obesity, there is strong evidence supporting a significant role of exposure to maternal diabetes in utero. The most compelling human evidence comes from studies in the Pima Indians, which have shown that offspring exposed to maternal diabetes in utero have a 10-fold higher rate of childhood obesity, independent of maternal obesity and birth weight. Their findings suggest that the level of fetal hyperglycemic exposure might be an important determinant in the risk for childhood obesity, confirming the level of maternal glycemia during pregnancy and the risk of obesity in offspring in some, but not all, studies showing increased adiposity in offspring not exposed to maternal diabetes. Importantly, the risk for obesity was shown to be higher in siblings born after their mothers developed diabetes than in those born before their mothers developed diabetes, providing strong evidence that in addition to genetics, there is an independent effect of the intrauterine environment on the risk for developing early-onset obesity. Studies in populations other than Pima Indians have demonstrated mixed results, with some, but not all, studies showing increased adiposity in offspring exposed to maternal diabetes in utero.

One potential explanation for the lack of association between maternal diabetes and obesity in offspring in some studies is the inclusion of mothers who achieved optimal glucose control during pregnancy. Hillier et al examined the relationship between the level of maternal glycaemia during pregnancy and the risk of obesity in a multiethnic cohort of 5-to-7-year-old offspring of women with glucose levels ranging from normal to gestational diabetes, and found a continuous relationship between rising maternal glucose level and increased risk of obesity in offspring. They concluded that the level of fetal hyperglycemic exposure might be an important determinant in the risk for childhood obesity, confirming results from other groups. Their findings suggest that the risk of obesity in offspring could be mitigated by good glucose control. However, in a recent follow-up of children whose mothers participated in a randomized trial of treatment versus nontreatment of mild gestational diabetes mellitus, Gillman et al found that body mass index (BMI) at age 4 to 5 years was not lower in their treated group compared with their untreated group despite a lower mean birth weight and macrosomia rate in the treated group.

The specific age at which height and weight are measured also may influence the results of relevant studies. In this issue of The Journal, Crume et al investigated the influence of in utero diabetes exposure on average BMI and BMI growth trajectory from infancy through childhood. Data were from a multiethnic population of offspring exposed to maternal gestational and preexisting diabetes compared with nonexposed peers from the Kaiser Permanente of Colorado Health Plan. By examining growth trajectories rather than relying on data from one time point, the authors aimed to improve our understanding of how and when intrauterine exposure to maternal diabetes influences postnatal growth. They used mixed linear effects models to assess differences in average BMI and BMI growth velocity from birth through age 13 years. They developed 2 separate growth curves to account for the change in use of recumbent length to standing height that occurred around 2 years of age. They found that neither average BMI nor overall BMI growth trajectory differed significantly between exposed and unexposed offspring from birth through 26 months of age. Therefore, intrauterine exposure to maternal diabetes was associated with significantly higher average BMI and accelerated BMI growth velocity. The effect was particularly prominent at age 10 to 13 years.

This study of Crume et al corroborates earlier reports suggesting that the increased risk of obesity associated with intrauterine diabetes exposure might not manifest until after the first 1 to 2 years of life. The findings are important for 3 reasons. First, they suggest a mechanism that creates a chronic imbalance between energy intake and expenditure. Alterations in appetite regulation that create long-term overeating could account for such a pattern, as could alterations in energy expenditure. Second, as Crume et al point out, their findings identify the early childhood years as a window of opportunity for targeted interventions aimed at preventing the obesity associated with intrauterine exposure to diabetes before it develops. Third, the findings indicate that follow-up beyond age 4 to 5 years, as reported by Gillman et al, may be required to fully test the impact of antepartum maternal glycemic control on long-term obesity risk in offspring.

The study of Crume et al was performed in a multiethnic population. Thus, it provides evidence of an association between intrauterine exposure to diabetes and increased BMI in several racial and ethnic groups. However, to date no direct comparisons to determine whether such risks are greater in particular ethnic/racial groups have been reported. Further studies are needed to address this question. In addition, longitudinal studies that continue through adolescence are needed to identify whether exposure to maternal diabetes influences body fat accumulation during puberty, when large

**BMI** Body mass index
and important changes in body composition normally occur. Finally, there is a need to evaluate whether intrauterine exposure to diabetes influences the distribution and biology of the excess fat, characteristics that may in large part determine the associated risks, such as diabetes and cardiovascular disease. In that regard, a concurrent report by Crume et al\textsuperscript{12} from the EPOCH Study found that intrauterine exposure to diabetes is associated with a more centralized fat distribution in 6- to 13-year-old offspring. This important finding may encourage further investigation into how body fat distribution and adipocyte biology are affected by intrauterine exposure to maternal diabetes.

The study of Crume et al adds to our knowledge of what happens when human fetuses are exposed to diabetes in utero. We are still far from understanding how and why it happens. Current theories include fetal overnutrition, resulting in fuel excess and increased fat accumulation. Animal studies suggest that fetal hyperinsulinemia, a direct consequence of maternal hyperglycemia, results in a malprogramming of the neuroendocrine systems that regulate appetite and body weight, thereby increasing the risk of obesity in extrauterine life.\textsuperscript{13,14} Human studies are needed to determine whether intrauterine exposure to maternal diabetes alters appetite, energy expenditure, and/or feeding behavior, which may increase the risk of developing obesity throughout life. Epigenetic studies hold promise for identifying how such effects could occur.\textsuperscript{15} Understanding the underlying mechanisms will aid the development of targeted interventions aimed at reducing the risk for obesity in children exposed to maternal diabetes. For now, potential interventions could include the aggressive treatment of hyperglycemia during pregnancy; promotion of breastfeeding, which appears to reduce obesity risk;\textsuperscript{16} and implementation of lifestyle interventions early in life.

As proposed by Freinkel\textsuperscript{17} more than 30 years ago, exposure to maternal diabetes during critical periods of development can have long-lasting consequences on health. Mounting evidence indicates that obesity is one such consequence that may be contributing in a feed-forward fashion to the epidemics of obesity and diabetes that are sweeping developed and developing countries. Understanding this effect in ways that will allow us to mitigate it should be a priority for research that can add weapons to our relatively weak armamentarium in the battle against obesity.

\textbf{References}