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Why Do Exercise and Dietary Restriction During Pregnancy Affect Glucose Tolerance in Opposite Ways?

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The prevalence of type 2 diabetes (T2D) or adult-onset diabetes has significantly increased in the U.S. during the past several decades not only in adults (1) but also in adolescents (2) and children (3). In view of the health, personal, and financial burdens of T2D (2,4), the high interest and effort toward its prevention or reversal is understandable. A new approach to the study of the etiology and potential prevention of T2D is the analysis of epigenetic and adaptive changes in glucose clearance and insulin action by dietary and exercise manipulations during pregnancy and the perinatal periods. As there have been historical (5,6) and epidemiological (7) opportunities to observe the consequences of dietary energy deficiency during pregnancy or the early postnatal period to glucose tolerance, insulin sensitivity, and other metabolic functions of the offspring, a substantial new body of knowledge has emerged and implicated intrauterine growth retardation because of severe food restriction in late pregnancy in the reduced size of the endocrine pancreas and its capacity to secrete insulin (8,9). Semistarvation during pregnancy reduced fasting insulin and glucose tolerance (10) and insulin resistance in the liver (11). Unexpectedly, exposure to the opposite extreme of energy balance during pregnancy such as maternal obesity (12) is also associated with increased risk of glucose intolerance, insulin resistance, and T2D.

More recently, the research interest has shifted to the examination of the effects of exercise during pregnancy on the risk of insulin resistance, glucose intolerance, and diabetes in the offspring. Despite the lower resolution of their short gestation, pregnant rodents provide a useful model of the effects of exercise on human pregnancy. In 2012, two reports from the same research group revealed that voluntary energy-expending exercise during rodent pregnancy (in contrast to dietary energy restriction) increases glucose tolerance and insulin sensitivity in male and female offspring (13,14). The key findings were that male and female mice born to exercising dams presented higher glucose tolerance between 31 and 72 weeks of life, cleared glucose more rapidly during insulin tolerance testing at 37 weeks, and had enhanced insulin-stimulated glucose uptake in their soleus muscle and retroperitoneal fat pad compared with the offspring of sedentary dams (13). They also showed improvements in systemic glucose tolerance at 15 months and insulin sensitivity tested with hyperinsulinemic-euglycemic clamp at 17 months, and their gastrocnemius and extensor digitorum longus (EDL)—but not the soleus or white adipose tissue—displayed increased insulin-stimulated glucose uptake (14).

The recent study in this issue of *Diabetes* by Stanford et al. (15) from Dr. L.J. Goodyear's research group adds to this important knowledge base by showing that systemic glucose tolerance can be enhanced in the male offspring of exercising dams compared with the offspring of sedentary dams at 8–36 weeks of age before any measurable increases in body fat are recorded at the age of 52 weeks. Importantly, the improvements were present regardless of whether the exercising dams were fed low-fat, high-carbohydrate chow or a high-fat, low-carbohydrate diet. Unlike the previous study (13), the skeletal muscles (tibialis anterior, soleus, gastrocnemius, and EDL) of the offspring of exercising dams fed either diet did not show increased insulin-stimulated glucose uptake at 52 weeks, the age at which systemic glucose tolerance and insulin-stimulated glucose clearance were increased.

The data presented in the study by Stanford et al. raise several interesting questions with implications to exercise during human pregnancy (Fig. 1) that would benefit from

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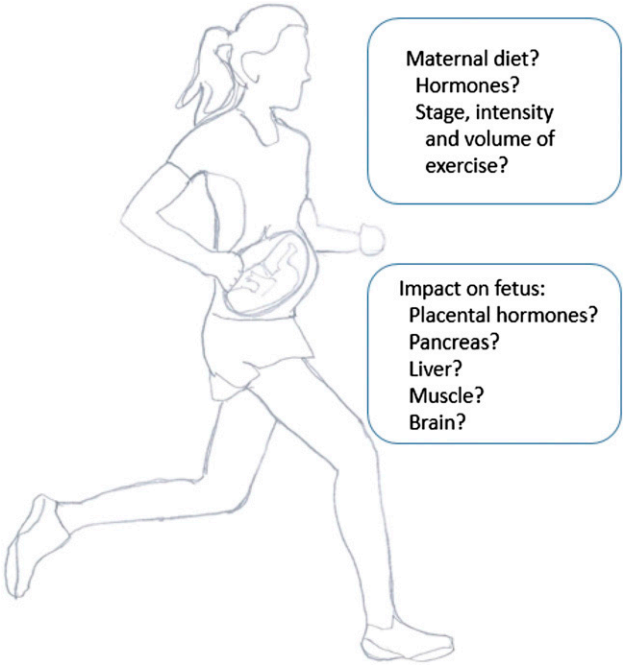

Figure 1—Knowledge gap regarding the mechanisms through which maternal exercise may exert adaptive and epigenetic effects on fetal glucose tolerance and insulin sensitivity.

additional research. Does the timing of exercise during a particular perinatal period account for the study outcome as the title of the study by Stanford et al. could be interpreted to imply? The male offspring of pregnant dams exposed to 8 weeks of exercise that included 3-week prepregnancy and 5-week gestational periods displayed increased glucose tolerance over a period of 52 weeks. Exercise confined to the gestational period increased glucose tolerance in the offspring only during the first 12 weeks of their life. Thus, without the appropriate controls, the difference in the outcome may reflect a dose-response effect of different exposures to exercise rather than a particular stage of fetal development.

The key knowledge gap in the area of prenatal influences on glucose tolerance and insulin sensitivity of the offspring is in our lack of understanding of how the different levels of energy supply during pregnancy, consisting of energy drain of exercise and food restriction on one hand and overnutrition on the other, produce opposite transgenerational effects on glucose tolerance and insulin sensitivity. Fragmentary and often contradictory information implicates exercise during pregnancy in changes in placental size and vascularization, fetal body mass, and the rate of organ growth (16), while the exposure to dietary restriction or overnutrition during pregnancy can affect the rate of fetal growth (8–10) and individual organ size (17). This topic would benefit from systematic research and the integration of findings.

An additional area in need of further exploration is the role of specific dietary macronutrients during pregnancy with or without simultaneous exercise. The two diets provided in the study by Stanford et al. (15) exposed pregnant dams to a low-fat, high-carbohydrate diet (21–60%) or a high-fat, low-carbohydrate diet (60–35%). High-fat, low-carbohydrate feeding of exercising dams tended to produce better glucose tolerance (significant at week 24) in the offspring than the low-fat, high-carbohydrate diet. The trend was present (although not statistically significant) also at 8, 12, 36, and 52 weeks. That a high-fat, low-carbohydrate diet promotes greater glucose tolerance and insulin sensitivity than the high-carbohydrate, low-fat diet has been documented both in healthy adults (18) and in (19) adults with diabetes and may be particularly relevant during energy-dependent rapid fetal growth. The type of fat in the diet during pregnancy has also been implicated in a number of health outcomes of the offspring (20). Finally, in view of the evidence that dietary energy restriction during exercise suppresses growth of fetal endocrine pancreas (8,9), additional research on the effects of dietary supply and quality as well as exercise energy expenditure on the glucose-induced insulin release would help close these gaps in our knowledge and provide a better understanding of the mechanisms through which exercise and variable nutrition exert transgenerational and epigenetic effects.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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