Time to reassess the optimal dietary prescription for women with gestational diabetes

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The article by Wijendran et al (1) in this issue of the Journal is the first to document alterations in maternal plasma phospholipids and amino acids in pregnancy complicated by gestational diabetes and managed by diet without requirement for insulin. The authors showed that glycated hemoglobin, a marker of hyperglycemia, was inversely related to plasma phospholipid arachidonic acid (20:4n–6; expressed as % by wt of total fatty acids) in control subjects but was positively associated with phospholipid 20:4n–6 in women with gestational diabetes that was managed with diet alone. In addition, pregravid body mass index (BMI; in kg/m²) was negatively associated with plasma phospholipid docosahexaenoic acid (22:6n–3; expressed as % by wt of total fatty acids) in pregnant women without (control) and with gestational diabetes who had a BMI < 30, but this relation did not apply to women who were more obese. Why were these relations different between these 2 groups of pregnant women? What does this mean and what implications does this article have on our dietary prescriptions for obese women with gestational diabetes?

Because long-chain polyunsaturated fatty acids are essential for optimal fetal growth and because the maternal supply of amino acids is essential for the developing nervous system (2, 3), the dietary supply of these nutrients must be ensured during pregnancy. Because other studies showed that insulin sensitivity and adiposity are independent factors in the regulation of essential fatty acid metabolism and amino acid concentrations (4), the dietary strategies we impose on women with gestational diabetes need to be reassessed.

In the study by Wijendran et al (1), the group with gestational diabetes had a higher intake of protein and a lower intake of carbohydrates than did the control group. Could this dietary difference have contributed to the differences in plasma fatty acids seen between the 2 groups? Although the higher protein intake in the women with gestational diabetes may have maintained their plasma amino acid concentrations at a level comparable with that of the control subjects, other dietary differences may have contributed to their abnormal fatty acid concentrations. The authors suggest that the degree of hyperglycemia and hyperinsulinemia played a major role in the resulting serum amino acid concentrations. Independent of the subjects’ dietary intakes, the glycated hemoglobin and fasting plasma insulin concentrations explained 58.2% of the variance in maternal plasma amino acid concentrations in the women with gestational diabetes. However, maternal plasma fatty acid concentrations were significantly lower in overweight than in normal-weight subjects regardless of glycemic status. Overall, the women with gestational diabetes had a significantly higher intake of polyunsaturated fatty acids, but the fatty acid content of the diet did not explain the difference in plasma fatty acid concentrations between the 2 groups.

Alternatively, the low-carbohydrate diet may explain the different relation between glycated hemoglobin and third-trimester fatty acid concentrations in women with gestational diabetes managed with diet alone and in normal pregnant control women. Perhaps the dietary restriction of carbohydrates caused an elevation of fatty acid concentrations and ketonemia, which accounted for the differences in fatty acid concentrations between the 2 groups. In general, plasma ketone body (β-hydroxybutyrate, acetoacetate, and acetone) concentrations reflect the rate of fatty acid oxidation in the liver. The rate of fatty acid oxidation is controlled primarily by concentrations of plasma insulin and fatty acids. When insulin concentrations are low, ketogenesis is accelerated; when insulin concentrations are high, ketogenesis is inhibited. Three clinical conditions are classically associated with accelerated ketogenesis: 2 are generally applicable to mammalian physiology and 1 specifically to pregnancy. The 2 generally applicable conditions are energy deprivation and diabetes mellitus. In each instance, cells are deprived of glucose in association with a diminished concentration or insufficient action of insulin, thereby accelerating ketogenesis. The same physiology applies in pregnancy, but ketogenesis is especially accelerated in the third trimester because of a decline in maternal glucose concentrations attributed mainly to fetal glucose utilization (5), a parallel fall in plasma insulin concentrations (6), and enhanced mobilization of fatty acids caused by the lipolytic hormones of pregnancy (5–7). Overall, this metabolic realignment can progress to the “accelerated starvation” of pregnancy if energy intake is deficient (8). Hyperketonemia in pregnancy has been implicated in the pathogenesis of congenital malformations and in mental impairment of the offspring of ketogenic mothers (9).

Montelongo et al (10) observed that plasma fatty acid concentrations increased to 50–100% above control values and that plasma β-hydroxybutyrate concentrations increased 3–5 fold in both pregnant women with gestational and type 1 diabetes. The

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Diabetes In Early Pregnancy Study Group (11) confirmed the report of Montelongo et al (10), showing that β-hydroxybutyrate concentrations in the diabetic groups were significantly higher than those in the control groups. The hypothesis that good glycemic control is associated with lower ketone body concentrations was shown by the positive relation between plasma glucose and β-hydroxybutyrate in the diabetic subjects. In women with gestational diabetes managed with diet alone, carbohydrate restriction may potentiate the accelerated ketosis of pregnancy and increase ketone body concentrations above those of normal control subjects. Thus, in these diabetic women, β-hydroxybutyrate concentrations were negatively associated with fasting plasma glucose concentrations, perhaps reflecting accelerated fat oxidation during carbohydrate deprivation. The negative association of β-hydroxybutyrate with birth outcome in the Diabetes In Early Pregnancy Study (11) also lends credence to the concern that there may be a deleterious effect of ketone bodies per se on infant growth, as has been seen at higher ketone body concentrations in embryo cultures. Higher ketone body concentrations are an indicator of energy insufficiency, reflecting its inverse association with plasma glucose rather than a direct toxic effect. Further evidence for the deleterious effect of high-fat diets was reported by Moses et al (12), who reported that the dietary intake of fat increased with a proportionate reduction in carbohydrate intake in women with recurrent gestational diabetes.

The diets that have been prescribed to lower glucose concentrations may be the same diets that create the other metabolic abnormalities associated with gestational diabetes. The inverse association of β-hydroxybutyrate with normal-range glucose concentrations may reflect maternal energy insufficiency, whereas the positive association of β-hydroxybutyrate with glucose in the elevated range may reflect maternal hypoinsulinemia. Therefore, treatment protocols must pay attention to both consequences of the maternal nutritional prescription. Until definitive studies are conducted, the prudent treatment protocol for both normal and diabetic women is to provide sufficient energy to maintain the pregnancy and, hence, prevent starvation ketosis and other metabolic consequences of hyperglycemia and hyperinsulinemia. In pregnant women with diabetes, careful attention must be given to avoid both hyperglycemia- and starvation-induced ketogenesis because both conditions are associated with high rates of fetal morbidity. The clinical goal must be normalization of glycemic status to attain ideal pregnancy outcome in women with gestational diabetes (13) and encourage further research on the relation of diverse maternal fuels, including β-hydroxybutyrate, with fetal growth and development.

REFERENCES