

A Tincture of Time Does Not Turn the Tide

Type 2 diabetes trends in offspring of type 2 diabetic mothers

The Barker hypothesis (1) suggests that low birth weight predicts subsequent physiological disturbances in adult life. Small-for-gestational-age infants and/or intrauterine growth-retarded fetuses have reported to be at risk for subsequent hypertension, type 2 diabetes, impaired glucose intolerance, and insulin resistance (1–9). In regard to the high birth weights, the Peder-sen hypothesis (10) suggests that large-for-gestational-age infants are also at an increased risk (11–14). An analysis of all of these reports would generate the theory that there is a U-shaped curve to describe the relationship between birth weight and these metabolic abnormalities in adult life. Thus, an optimal birth weight that would predict the lowest risk for these metabolic defects in adult life would be between 3,000 and 4,000 g.

A correlate to this U-shaped curve theory would suggest that treatment during pregnancy should optimize birth weight to decrease the prevalence of these physiological disturbances in adult life. Factors assumed causative for small-for-date infants and/or intrauterine growth retardation include maternal hypertension, smoking, intrauterine infection, prematurity, placental insufficiency, and protein malnutrition. The explanation suggested for the association between low birth weight and adult obesity and type 2 diabetes is that the fetus does not have sufficient substrate during organogenesis to promote β -cell growth and normal insulin secretory responses (2,5). Factors assumed causative for large-for-gestational-age infants include maternal obesity and maternal hyperglycemia. The explanation suggested for the association of macrosomia to adult obesity and type 2 diabetes is that maternal hyperglycemia results in over-nutrition for the fetus and thereby promotes fetal hyperinsulinemia, excess adipose tissue, and the insulin resistance syndrome. The old controversy concerning the cause of type 2 diabetes, insulin resistance, or β -cell defects may prove that both obesity and in utero hyperglycemia play a role in the etiology of type 2 diabetes; it just depends on the fetal conditions.

The optimal treatment strategy during pregnancy would therefore be to prevent both low birth weight and high birth weight neonates. Low birth weight prevention programs should include treating maternal hypertension, promoting smoking cessation, surveillance for infection, and instituting adequate medical nutritional therapy. High birth weight prevention programs should include medical nutritional therapy to limit overnutrition, along with early initiation of insulin therapy to normalize maternal glucose levels. However, if macrosomia and subsequent adult obesity and type 2 diabetes were all a result of intrauterine overnutrition and/or maternal hyperglycemia, then treatment of maternal nutrition and diabetes care should decrease the risk of subsequent obesity and diabetes in the offspring. With the advent of self-monitoring of blood glucose and HbA_{1c} values over the past 20 years, which has allowed for improved glucose control, there has been a trend toward decreasing morbidity and mortality of the infant of the diabetic mother. However, these treatment strategies have not succeeded in reducing the rates of macrosomia in all reports (15). Thus, there is still controversy in the field of diabetes regarding the impact that intensive care protocols to normalize maternal glucose levels have on the adult outcome of the fetus. (16)

Based on the historical improvements in the management of diabetes and pregnancy that were observed in four 10-year intervals since 1955, the study by Lindsay et al. (17) was designed to observe a decrease in the late risk of diabetes and obesity in the offspring of diabetic mothers. The authors concluded that the increased risk of diabetes and obesity that was manifested in the offspring of diabetic mothers does not seem to diminish with time. Although the study was an attempt to longitudinally observe the impact of improved diabetes care on a decreased risk of adult obesity and diabetes, the authors do not provide the requisite data to support this hypothesis. They hypothesized that, because the tools for metabolic control in general have improved over the 4 decades of observation, the increasing rate of type 2 diabetes and obe-

sity is not related to improved glucose control. Unfortunately, they have no documentation of actual glycemic improvement in their population of pregnant diabetic women. However, this study is just a start. We are all keenly interested in finding out just how important maternal glucose control is for the long-term outcome of the child. A long-term study of pregnancy outcome, coupled with real data on glucose control, is needed. Of course, the truth may be that measurements of HbA_{1c} and/or self-monitoring of blood glucose data may not have been adequate to observe the impact of glycemia on the adult status of these offspring. Also, we are just beginning to learn that, in predisposed populations, minor elevations of maternal glucose levels, which are insufficient to significantly raise HbA_{1c} levels, are sufficient to produce neonatal macrosomia (18). In fact, if postprandial glucose plays a major role in the etiology of macrosomia (19), it may be that we need a continuous glucose sensor to detect all of the episodes of postprandial hyperglycemia in high-risk populations.

Until we have studied and carefully monitored the glycemic levels of a population of pregnant women for a continuous duration that equals that of the Pima Indian studies, then we will not know whether children born to mothers with type 2 diabetes will benefit from the initiation of programs to normalize maternal blood glucose levels during pregnancy. Until then, we must continue to advocate programs of intensive glucose control during pregnancies that are complicated by all types of diabetes.

LOIS JOVANOVIĆ, MD

From the Sansum Medical Research Institute, Santa Barbara, California.

Address correspondence to Lois Jovanovic, MD, Sansum Medical Research Foundation, 2219 Bath St., Santa Barbara, CA 93105. E-mail: lois@samsun.org.

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