

## **Secular trends in birth weight, BMI, and diabetes in the offspring of diabetic mothers**

Lindsay RS, Hanson RL, Bennett PH, Knowler WC. **An epidemiological survey of the Pima Indian community of the trend over a 40 year time span in the development of childhood diabetes in infants born to mothers with diabetes during pregnancy compared to infants born to mothers who developed diabetes after pregnancy or who had not developed diabetes.** Diabetes Care 2000;23:1249-54.

### **QUESTION**

Has the improvement in the recognition and treatment of maternal diabetes resulted in a reduction in the development of childhood diabetes and obesity in offspring of diabetic mothers compared to their peers?

### **DESIGN**

Retrospective examination of data collected as part of the epidemiological survey of the Gila River Indian Community in Arizona over a 40 year period.

### **SETTING**

NIH study of the Pima Indian community

### **PATIENTS**

Subjects of the study were at least half Pima or Tohono O'odham Indians or a mixture of these closely related groups. Members of the community >5 years of age were invited to participate in biennial research which included a 75g OGTT. Birth weight and presence of maternal diabetes (either preexisting Type 2 or gestational diabetes) were known for 3,638 children who were divided into 4 birth year cohorts (1955-1964; 1965-1975; 1975-1984; 1985-1994) from birth certificate data and review of hospital records. To control for both genetic and environmental factors in the later development of diabetes in the offspring, 2 groups of offspring of mothers who did not have diabetes at the time of pregnancy were used for comparison. Accordingly, the mothers of these children were divided into 3 groups; offspring of diabetic mothers (ODM), offspring of prediabetic mothers defined as mothers who developed diabetes within 10 years AFTER the pregnancy (OPDM), and offspring of nondiabetic mothers who had at least 1 normal 75 gram glucose tolerance after pregnancy and no record of diabetes onset within 10 years after birth (ONDM). Childhood diabetes incidence rates were calculated in 5-year age groups from birth, after stratification for sex, birth cohort categories, and maternal diagnosis.

### **INTERVENTION**

None

### **MAIN OUTCOME MEASURES**

Birth weight, BMI, and diabetes in offspring were examined in infants born to mothers with maternal diabetes, mothers who developed diabetes after the index pregnancy, and mothers who had no evidence of diabetes at least 10 years after delivery in four 10-year time intervals since 1955.

### **MAIN OUTCOME RESULTS**

The birth weights of the offspring of mothers with maternal diabetes were significantly higher compared to other offspring and the cohort with the highest birth weight was the one born in 1955-1964. The BMI increased over the course of the study from the first birth cohort to the last cohort in all groups and was significantly higher up to age 20 years in the offspring of diabetic mothers compared to the offspring of non-diabetic mothers and compared to the majority of offspring of prediabetic mothers. Over the study, the incidence of childhood diabetes for Pima children in the offspring of diabetic mothers was far higher than their peers in the other groups. At age 10-14 years, the incidence of childhood diabetes in the offspring of diabetic mothers was >20X that of the offspring of nondiabetic mothers and 5X the incidence of the offspring of prediabetic mothers. By age 15-19 yrs, the incidence of childhood diabetes was 3.5% in the offspring of diabetic mothers compared to 0.46% in the offspring of nondiabetic mothers and 1.46% in the offspring of prediabetic mothers. The childhood diabetes incidence increased in all age groups over time in all cohorts.

### **CONCLUSIONS**

Changes in the management of diabetes in pregnancy have not lead to a decreased incidence in childhood diabetes in offspring born to diabetic mothers compared to their peers. If the risk attributable to the effect of in utero diabetes cannot be modified and the incidence of Type 2 diabetes and gestational diabetes is increasing as the prevalence of obesity increases, we can expect childhood diabetes to increase from this effect as well as from the overall effect of the increase in childhood obesity.

#### **COMMENTARY**

The incidence of Type 2 diabetes is increasing at an alarming rate in the United States and the NIH is identifying it as a leading health risk for the adult population. The incidence of childhood glucose intolerance and teenage Type 2 diabetes is following suit. There is a growing body of literature that supports that an in utero milieu of excess nutrient supply to the fetus from abnormal fuel metabolism in the mother (insulin resistance) has far greater implications than simply fetal macrosomia and the risk of shoulder dystocia (1). These infants have a much higher risk of developing Type 2 diabetes as children and young adults compared to children born to mothers who developed their diabetes after pregnancy (2). Women with gestational diabetes and high amniotic fluid insulin levels (fetal hyperinsulinemia as a result of maternal hyperglycemia) give birth to offspring who as teenagers have a much higher incidence of teenage obesity and impaired glucose tolerance. One-third of these teenagers have impaired glucose tolerance at age 17 years (3).

The authors of this epidemiological study underscore that the problem appears to be getting worse, not better, in this Indian population that has a strong genetic predisposition to insulin resistance and the development of Type 2 diabetes. Their concern is that despite improved care and a decrease in perinatal mortality over time in infants born to diabetic mothers (with Type 2 DM or gestational diabetes), the incidence of childhood diabetes is increasing, and highest in offspring of diabetic mothers. These offspring should be genetically similar to the offspring of prediabetic mothers (mothers who have the same genetic predisposition to insulin resistance but do not expose their infants to an abnormal in utero metabolic environment because they develop DM after the pregnancy), yet their incidence of childhood diabetes is at least 2-5 fold greater. However, it may not be time to throw in the towel and surrender to the increasing incidence of both adult and adolescent Type 2 diabetes in the United States as both populations face an epidemic of rapidly increasing obesity. There was no indication in this article that diabetic control was in fact better over time (although the birth weights were greatest in the earliest birth cohort) and childhood diabetes increased in all cohorts as the age-adjusted BMI of the children increased over time. Both animal and human studies have demonstrated that shunting less glucose, amino acids, and free fatty acids to the fetus can decrease macrosomia and may favorably effect fetal pancreatic islet cell hyperplasia (4). Gestational diabetes is becoming a significant public health concern for both the mothers who subsequently develop Type 2 DM and the affected offspring. It appears to be an significant risk factor for the development of childhood carbohydrate intolerance, independent of both genetic predisposition and obesity. Identifying these high risk mothers and offspring and targeting interventional strategies designed to improve insulin sensitivity (diet modification and exercise) during and after pregnancy may result in important gains against these overwhelming trends.

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