Long-Term Prospective Evaluation of Offspring of Diabetic Mothers

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We have suggested that altered maternal metabolism may affect the subsequent anthropometric and neuropsychological development of children who were in utero during disturbances in maternal fuel economy. This study reports the physical growth through 8 yr of age and the neuropsychological development through 4 yr of age in offspring of diabetic mothers (ODM). At birth, 50% of infants had weights >90th percentile for gestational age. By 12 mo, length and weight were similar to the general population. Height remained normal until 7 yr of age, when it became slightly greater than average. After 5 yr of age, relative weight increased dramatically, and by 8 yr of age, half of the ODM had weights >90th percentile. This childhood obesity in ODM is correlated with maternal prepregnant weight and independently with amniotic fluid insulin at 32–38 wk gestation. The Brazelton Neonatal Behavioral Assessment Scale (BNBAS) was administered to 185 newborn ODM. Significant correlations were found between poorer second- and third-trimester glycemic regulation and lower scores in three of four newborn BNBAS dimensions. The Stanford-Binet Intelligence Scale was measured in 102 ODM at 4 yr of age. We found an inverse correlation between childhood IQ and second- and third-trimester maternal lipid metabolism (serum free fatty acids and β-hydroxybutyrate). This correlation is not explained by adverse perinatal events, socioeconomic status, maternal IQ, ethnicity, or diabetes type. These long-range associations between altered maternal metabolism and childhood growth and development continue to support Freinkel's hypothesis of fuel-mediated teratogenesis. *Diabetes* 40 (Suppl. 2): 121–25, 1991

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The possibility that fuel metabolism in a pregnant woman might exert a long-range impact on several developmental parameters in offspring was suggested by Freinkel (1) over a decade ago. The hypothesis of *fuel-mediated teratogenesis* was formulated as follows. Fuels of maternal origin may influence developmental events by modifying phenotypic gene expression in terminally differentiated poorly replicating cells during intrauterine development. The long-range effects depend on the cells undergoing differentiation, proliferation, or functional maturation during the disturbances in maternal fuel economy.

Data regarding the long-term effects of maternal diabetes on the offspring's growth and development have been gathered mostly from cross-sectional studies. In these reports, information regarding maternal metabolic control and metabolism has been limited. Detailed correlation between maternal and fetal metabolic perturbations and long-term effects on the offspring has been difficult to achieve.

To test for fuel-mediated teratogenesis on a prospective basis, the Diabetes in Pregnancy Center was established at Northwestern University in 1977. Diabetes was chosen as the operational paradigm because maternal fuels undergo the greatest abnormal perturbations in this disorder. This study is a long-term prospective evaluation of the effects of maternal diabetes mellitus on pregnant women and their offspring. We report the results of the correlations between antepartum maternal metabolism and childhood physical development through 8 yr of age and neuropsychological development through 4 yr of age.

RESEARCH DESIGN AND METHODS

Mothers. Gravidas with gestational diabetes mellitus (GDM) or pre-GDM were recruited from September 1977 to February 1983 for detailed longitudinal characterization of maternal metabolism and subsequent long-term evaluation of their

offspring. We excluded all women who chronically required medication other than insulin or were seriously noncompliant. All of the women with pre-GDM with modified White classes B_2–F received insulin (2). Of those women with GDM (White classes A_1, A_2, and B_1), 54% received insulin for the first time during pregnancy. All participating women gave written informed consent. The prepregnant weight was used to calculate the percentage of ideal body weight (PIBW) by comparison with the Metropolitan Life Insurance Company tables (3).

All women were seen at the outpatient clinic at least biweekly before 30 wk gestation and weekly thereafter. The details of antepartum care, including routine hospitalization, have been previously reported (4). Every 1–2 wk, blood samples were drawn after an overnight fast for fasting plasma glucose (FPG), free fatty acids, and β-*O*-hydroxybutyrate (β-OHB). In addition, all women were asked to record results of urine tests for acetonuria (Acetest) performed four times daily. The percentage of days in which one or more urine specimens tested positive for acetone (moderate or large) was calculated to provide an index of acetonuria in diabetic subjects reporting results of urine tests on >14 days per trimester. HbA_{1c} was measured monthly. The mean values for FPG, β-OHB, and HbA_{1c} for the second and third trimesters were used for correlations with postpartum events. Detailed demographic and socioeconomic data were collected, and the Wechsler Adult Intelligence Scale was administered to the mothers (5). Forty-three percent of the participants were white, 25% were Hispanic, 23% were black, and 9% were other ethnic groups.

Offspring. Amniotic fluid was sampled to monitor fetal lung maturation, and aliquots were frozen for later measurement of immunoreactive insulin concentrations. Amniocentesis was carried out every 2 wk starting at 32–34 wk gestation until delivery. We found no association between insulin concentration and gestational age during this period. When two or more measurements were available, the mean value was used.

At birth, cord blood was sampled for measurement of C-peptide and glucose. Gestational age was determined by the method of Dubowitz et al. (6). Weight and length were measured, and any malformations were noted on detailed physical examination standardized with a checklist. Size at birth was compared with gestational age–appropriate normative data (7,8). The study population was seen at 6 mo and then yearly for physical examination including measurements of height and weight. The data at 6 mo represent measurements taken from 5 to 7 months and at 1 yr from 10 to 14 months. Thereafter, measurements made within 6 mo of a child's birthday are included in the data for that year. By comparison with National Center for Health Statistics (NCHS) data (9), the standard deviation score (*Z* score) for exact decimal age was calculated, the values were ranked, and the study population's 25th, 50th, and 75th percentiles were located. The *Z* scores at each of these percentiles were used to construct physical growth charts for comparison with the NCHS data.

Relative obesity was assessed on the basis of the symmetry index (SI), a variant of a measurement first proposed by Farquhar (10). Relative weight is measured weight divided by the NCHS median weight for age. Relative height is measured height divided by the NCHS median height for age. The relative weight divided by the relative height yields the SI, which equals 1.0 in an average child. On the basis of our experience with newborn infants and young children, an SI >1.2 indicates obesity. The body mass index (BMI; wt/ht^2) was also calculated.

At birth, neurobehavioral development was assessed by the Brazelton Neonatal Behavioral Assessment Scale (BNBAS; 11). Term infants were seen on the 2nd or 3rd day of life, and preterm infants (<37 wk) were examined at 40 wk gestational age. Individual BNBAS responses were categorized into four dimensions: interactive, motoric, state control, and physiological control (12). To assess neuropsychological development in childhood, we used the Stanford-Binet Intelligence Scale at 4 yr of age (13). All tests were performed by trained psychologists in a single-blind study.

Data were analyzed by unpaired *t* test, Pearson correlation, and partial correlation.

RESULTS

Maternal metabolism during pregnancy. On average, women with pre-GDM were enrolled at 13.2 wk of gestation and those with GDM at 23.5 wk. As we reported previously (4), patients were given diabetes care consistent with the prevailing state of the art at the time of enrollment (1977–1983). Good to fair metabolic control was achieved after enrollment and sustained until delivery. Thus, in the third trimester, mean ± SD FPG was 5.82 ± 1.18 mM in the women with pre-GDM and 5.07 ± 0.68 mM in those with GDM. Over the same interval, HbA_{1c} was 6.0 ± 1.0% in the mothers with pre-GDM and 5.4 ± 0.7% in those with GDM (mean + 2SD in nondiabetic pregnant women = 5.7%).

Fetuses and neonates. Both indices of intrauterine pancreatic β-cell function suggested the presence of fetal hyperinsulinism. Mean amniotic fluid insulin was 91.8 ± 81.0 pM (n = 85) in the women with pre-GDM and 74.4 ± 76.2 pM (n = 120) in those with GDM. In a group of nondiabetic pregnancies, the mean amniotic fluid insulin was 39.0 ± 22.8 pM (n = 37). Values for the cord C-peptide–glucose ratio (pmol/mmol) were 148 ± 89 (n = 83), 130 ± 71 (n = 125), and 79 ± 44 (n = 35), respectively.

During the enrollment of these subjects, perinatal mortality was 1.9%. Birth weight was >90th percentile for gestational age in 50% of the offspring of diabetic mothers (ODM), and 36% had an SI >1.2.

Physical growth in childhood. The growth of the female ODM compared with the NCHS values for the American population is shown in Fig. 1. These girls were of average stature until 7–8 yr of age, when they became slightly taller than expected ($P < 0.05$). The weight curve demonstrates that at 12 mo of age, the median weight in this group was similar to that of the reference population. However, after 5 yr of age, there was a rapid weight gain to the point where at 8 yr of age, almost half of the female ODM had a weight >90th percentile. Male ODM also showed a marked upswing in weight after 5 yr of age (Fig. 2). By 8 yr of age, over half of the boys weighed more than the heaviest 10% of 8-yr-old offspring of nondiabetic mothers. Again, a slight upward trend in height was noted with male ODM taller than average boys at 7 ($P < 0.005$) and 8 ($P < 0.001$) yr of age.

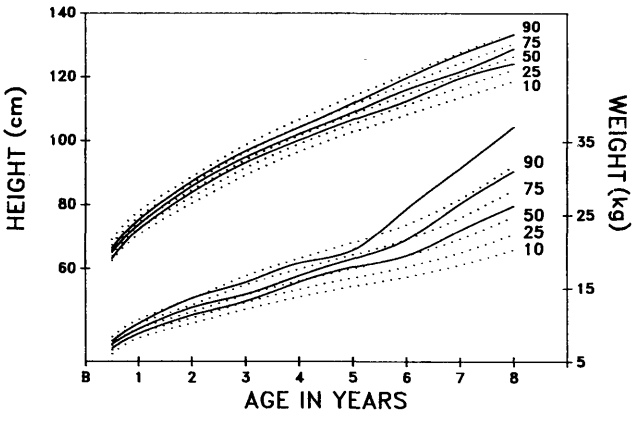

FIG. 1. Physical growth of female offspring of diabetic mothers (ODM). *Dotted lines*, National Center for Health Statistics 90th, 75th, 50th, 25th, and 10th percentiles for American girls; *solid lines*, 75th, 50th, and 25th percentiles for female ODM for height (*upper curves*) and weight (*lower curves*).

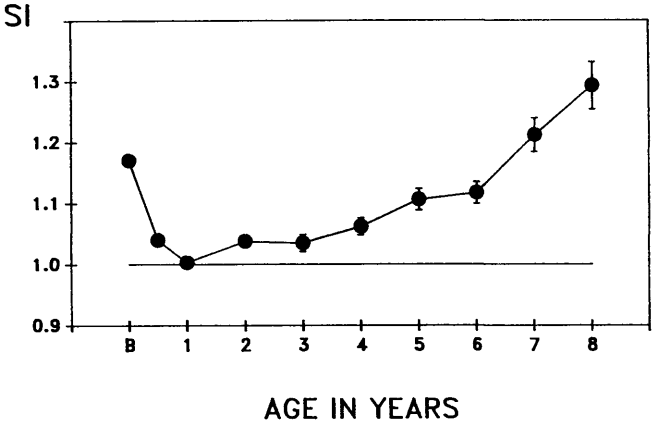

FIG. 3. Symmetry index (SI) (mean ± SEM) in offspring of diabetic mothers from birth to 8 yr of age. SI is greater than expected (1.0) at all ages except 12 mo ($P < 0.05$). Data points are means ± SE.

No significant difference between the growth of the boys and girls was observed. We therefore used the SI to combine the data from the two sexes for correlations with prenatal and perinatal events. The SI from birth through 8 yr of age is shown in Fig. 3. At birth, the ODM were relatively overweight, with an average SI of 1.17. By 1 yr of age, this neonatal obesity resolved, and on average, these ODM were no larger than other 12-mo-old children (SI = 1.0). However, after 1 yr of age, obesity recurred, first gradually, then in a striking manner at 6–8 yr of age. In this population, SI at 6–8 yr of age correlates very closely with BMI ($r = 0.98$) and the log of BMI ($r = 0.97$). Because there are not good age-specific reference data for BMI in North American infants and children, we have not used these derivations further in our analysis of childhood obesity.

Table 1 displays correlations with SI at 6–8 yr of age for the 124 ODM for whom we have height and weight measurements in this interval. The latest available measurement for each individual during this age range was used. In accord with the rapid increase in SI from 6–8 yr of age, we found a strong correlation between the child's age at the time of measurement and SI. SI also correlates with maternal weight. It is of great interest that SI values at 6–8 yr of age correlated strongly with prematurely activated insulin secretion throughout late fetal life as judged by amniotic fluid insulin content and the cord C-peptide–glucose ratio. SI at birth, sex, diabetes type (GDM vs. pre-GDM), and direct indices of maternal metabolic control (FPG, HbA_{1c}, and β-OHB) were not correlated with childhood obesity. After correction for the effects of the child's age and maternal PIBW, the partial correlation between amniotic fluid insulin and SI at 6–8 yr of age was retained ($r = 0.24$, $P < 0.05$, $n = 86$).

Neuropsychological development. To assess the effects of maternal metabolism on neuropsychological development, ODM were examined by age-appropriate testing at birth and 4 yr of age. Soon after birth, the newborn infants of 73 women with pre-GDM, 112 gravidas with GDM, and 24 gravidas with documented normal carbohydrate metabolism during pregnancy were assessed by the BNBAS. Partial correlations were examined between each of the four BNBAS dimensions and three indices of maternal metabolism (HbA_{1c}, FPG, and β-OHB) after controlling for gestational age at delivery. Test scores on the interactive dimension were correlated to a marginally significant extent with second-trimester HbA_{1c} ($P = 0.07$) and FPG ($P = 0.06$) and third-trimester HbA_{1c} ($P = 0.06$), the motoric dimension

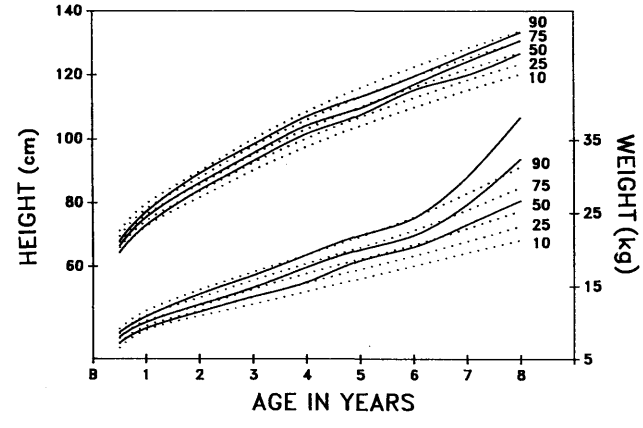

FIG. 2. Physical growth of male offspring of diabetic mothers (ODM). *Dotted lines*, National Center for Health Statistics 90th, 75th, 50th, 25th, and 10th percentiles for American boys; *solid lines*, 75th, 50th, and 25th percentiles for male ODM for height (*upper curves*) and weight (*lower curves*).

TABLE 1
Correlations with symmetry index (SI) at 6–8 yr of age

	r	*P*	*n*
Age at assessment	0.32	<0.001	124
Maternal PIBW	0.28	<0.005	116
Amniotic fluid insulin*	0.24	<0.05	86
Cord C-peptide/glucose*	0.23	<0.05	90
SI at birth	0.11	NS	121
Sex	0.05	NS	124
GDM vs. pre-GDM	0.05	NS	124

PIBW, prepregnancy percentage of ideal body weight; GDM, gestational diabetes mellitus.
*Log-transformed values were used for correlations.

correlated significantly with second- ($P < 0.05$) and third- ($P < 0.05$) trimester HbA_{1c}, and the physiological control dimension correlated significantly with second-trimester FPG ($P < 0.05$). None of the BNBAS dimensions correlated significantly with fasting β-OHB. Covariant corrections for the effects of various perinatal events (cesarean vs. vaginal delivery, macrosomia, cord glucose, cord pH, neonatal hypoglycemia, hyperbilirubinemia, and Apgar score) did not significantly alter the reported associations. Similarly, corrections for the effects of ethnicity and socioeconomic status had no significant effect.

The Stanford-Binet Intelligence Scale was obtained for 102 ODM at 4 yr of age. We found no significant correlations between either index of maternal glucoregulation, i.e., HbA_{1c} or FPG, and child IQ. However, several significant correlations were obtained with parameters of lipid metabolism: child IQ at 4 yr of age correlated with second- ($P < 0.05$) and third- ($P < 0.01$) trimester free fatty acids and third-trimester β-OHB ($P < 0.05$). In each case, with more aberrant maternal metabolism, the children's intellectual development was poorer. No significant correlations were found between our integrated index of acetonuria and child IQ. In fact, few of our subjects displayed acetonuria on more than one occasion. All correlations were controlled for possible interactions with socioeconomic status (including maternal IQ), ethnicity, and diabetes type (pre-GDM or GDM). Partial correlation analyses were repeated with gestational age at delivery, macrosomia, cord pH, hypoglycemia, hyperbilirubinemia, and 5-min Apgar score included as covariates. In no instance were the reported correlations significantly altered by any perinatal factor.

DISCUSSION

The Northwestern University Diabetes in Pregnancy Center was established to conduct prospective evaluations of Freinkel's (1) hypothesis that maternal metabolism may exert long-range effects on progeny. This study reports the observed long-term anthropometric and neuropsychological consequences of maternal diabetes mellitus.

Detailed analysis of physical growth in our subjects demonstrates that neonatal macrosomia disappears by 1 yr of age. This is an unusual pattern of growth. In the general population, large neonates tend to remain larger than average size for at least the first 5 yr of life (14). After 2–3 yr of age, the ODM tended to gain weight faster than other children, and rapid weight gain was observed after 5 yr of age. Childhood obesity in ODM has been noted in the past (15–19); however, details of the maternal metabolic milieu have not been available for analysis in these studies.

We have previously reported that obesity in 6-yr-old ODM correlates with both obesity at birth and amniotic fluid insulin (20). With continuing follow-up, we now find a marked upswing in weight after 6 yr of age, but the correlation with increased amniotic fluid insulin remains. Thus, the children who had the greatest maturation of islet secretory function in utero also were destined to show the greatest relative obesity at 6–8 yr of age. This difference cannot be attributed simply to maternal obesity as defined by the mothers PIBW. Similarly, another index of prenatal insulin secretion, the cord C-peptide–glucose ratio, also correlates with obesity at 6–8 yr of age.

After 6 yr of age the SI at birth is no longer predictive of childhood obesity in this group of ODM. This is similar to the findings in Pima Indians, in whom childhood obesity develops in ODM regardless of birth weight (19,21).

The small increase in height observed at 7–8 yr of age in ODM is similar to the pattern observed in other obese children. Obese children have higher serum concentrations of insulinlike growth factor I (22) and display rapid growth in childhood (23) but achieve normal adult height.

Whether fetal insulinization affects subsequent anthropometrics by modifying postnatal sensitivity to insulin in the periphery, the dynamics of insulin secretion, or the neuroendocrine aspects that govern energy expenditure or fuel intake are questions that we are addressing in our continuing prospective study.

In addition to its effects on physical growth, maternal diabetes can influence neuropsychological development. In this regard, we studied the effects of altered maternal metabolism at birth and 4 yr of age. At birth, the BNBAS was chosen to gauge neurobehavioral status because it has gained wide acceptance as one of the premier instruments for integrative characterization of nervous system function in the newborn period. We found significant correlations between antepartum maternal glucoregulation and three of the four BNBAS dimensions. In each case, poorer regulation of maternal glucose was followed by poorer BNBAS ratings of the neonate. Note that these correlations were established within a population of subjects in whom metabolic status was normal to moderately impaired.

The Stanford-Binet Intelligence Scale for Children was chosen to assess intellectual performance in early childhood. This test has been demonstrated to predict adult intelligence. After controlling for socioeconomic status (including maternal IQ), ethnicity, and diabetes type (pre-GDM or GDM), we found no significant correlations between two indices of maternal glucoregulation (HbA_{1c} or FPG) and child IQ. However, several significant correlations were obtained with parameters of lipid metabolism: child IQ at 4 yr of age correlated with second- and third-trimester free fatty acids and third-trimester β-OHB. In each case, with more-aberrant maternal metabolism, the children's intellectual development was poorer.

Although the findings are not entirely consistent (24), much of the earlier retrospective epidemiological evidence suggested that maternal ketonuria in women with or without diabetes may be associated with lower childhood IQ (25,26). We found no significant correlations between our integrated index of acetonuria and child IQ. However, ketonuria was mild and infrequent in our population. Thus, these correlations were established within a population of subjects in whom maternal serum ketone concentrations remained below the threshold for ketonuria and were not significantly affected by numerous perinatal conditions (e.g., prematurity and neonatal asphyxia). Moreover, the observed correlations occur within the range of normal IQ. These associations between maternal ketonemia and lower child IQ speak for continued efforts to avoid ketosis and accelerated starvation in management strategies for all pregnant women.

Insofar as most of the women with pre-GDM have insulin-dependent diabetes mellitus and the women with GDM are at risk for later development of non-insulin-dependent dia-

betes mellitus, the observed correlations for both anthropometric and neuropsychological measures are determined by phenotypic factors (i.e., the degree of the disturbance in the metabolism of the mother during pregnancy) rather than genotypic considerations (i.e., the nature of the mother's diabetes. These long-range effects of altered maternal metabolism continue to support the hypothesis of fuel-mediated teratogenesis.

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