ORIGINAL ARTICLE

Maternal Metabolic Control and Risk of Microcephaly Among Infants of Diabetic Mothers

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OBJECTIVE — To measure the incidence of microcephaly among infants of diabetic mothers (IDM) and assess its relationship to metabolic control during pregnancy.

RESEARCH DESIGN AND METHODS — Head circumference data for 556 consecutive live-born singleton infants of women with insulin-requiring diabetes antedating pregnancy delivered between 28 and 40 weeks of gestation and the results of 3,242 HbA_1 determinations collected during their pregnancies were examined.

RESULTS — There were fewer head circumferences at or below the 3rd percentile and more at or above the 97th percentile than expected. Head circumference was not related to maternal metabolic control as documented by the HbA_1 values.

CONCLUSIONS — The less-than-expected incidence of microcephaly observed in this patient population probably reflects the well-known tendency of IDM toward macrosomia.

In 1960, Driscoll et al. (1) reviewed the postmortem findings among 95 infants of diabetic mothers (IDM). Although the weights of most organs were not different from those found in similar-weight infants of nondiabetic women, they observed that the brains tended to be smaller. Head size is determined by brain growth, and microcephaly tends to be viewed as a clinical sign of inadequate brain growth. The association of head size with intelligence, however, is quite variable.

Several studies have examined the relationship between the neurological development of IDM and the degree of metabolic control of the maternal disease. The presence of ketone bodies in blood or urine has been used as an indicator of poor metabolic control and has been associated with impaired development. Churchill et al. (2) studied the neuropsychological development of 73 infants from the Collaborative Perinatal Project whose mothers had diabetes antedating pregnancy. When compared with matched nondiabetic control subjects, the 55 IDM with acetonuria had significantly lower neuropsychological test scores, while the 18 IDM without acetonuria had test scores comparable to their matched control infants. Naeye (3) later reinterpreted the same experience and concluded that the observed differences were due entirely to bacterial contamination of the amniotic fluid of the diabetic women and not to ketosis. In a recent long-term follow-up study of 89 children born to women with diabetes mellitus, elevated blood β-hydroxybutyrate levels in the 3rd trimester were associated with a small but statistically significant reduction in scores on tests of cognitive function (4).

Several ultrasonographic studies of fetal biparietal diameter and crown rump length have shown a tendency for slower growth during early gestation in diabetic women as compared with nondiabetic control subjects (5). As pregnancy progresses, the well-known tendency for IDM to become macrosomic causes growth to accelerate (6).

Older studies do not reflect the degree of metabolic control currently achieved in pregnant diabetic women, and recent studies have involved relatively small numbers of subjects. This study seeks to define the incidence of microcephaly and its potential relationship to metabolic control in a large cohort of IDM.

RESEARCH DESIGN AND METHODS

Data were collected prospectively for patients who registered for prenatal care at the Joslin Diabetes Center Prenatal Clinic after January 1, 1984, and delivered by December 31, 1991. All women were included who had insulin-requiring diabetes mellitus ante-

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IDM, infants of diabetic mothers.

Table 1—*Clinical characteristics of subjects*

	n	Mean ± SD
White class		
B	130	
C	181	
D	140	
F	21	
FR	34	
R	46	
H and T	4	
Total	556	
Maternal age at delivery (years)		29.3 ± 5.2
Diabetes before pregnancy (years)		12.6 ± 7.1
Gestational age at delivery (weeks)		37.5 ± 1.6
Birth weight (g)		3,587 ± 765
Birth weight ratio		1.22 ± 0.22

dating pregnancy (White's classes B and higher) and who delivered live, singleton infants between 28 and 40 weeks of gestation. The head circumferences were those recorded in the medical records during routine clinical examinations.

Throughout the study period, a single method was used to assess HbA_1 levels via electrophoresis after removal of the labile fraction (Corning Medical, Palo Alto, CA). The mean and SD for a nondiabetic population by this technique are 5.9 and 0.57%, respectively. HbA_1 levels were assessed at all first visits and monthly thereafter for the remainder of pregnancy.

Use of head circumference at birth poses problems when babies vary in gestational age at birth. To avoid these, we converted each baby's head circumference to a z score based on the location of the head circumference along the normal distribution for gestational age according to the reference standards of Niklasson et al. (7) for a Swedish population. We define microcephaly to be head circumference in the 3rd or lower percentile (z score ≤ -1.88) and macrocephaly to be in the 97th or higher percentile (z score $\geq$ 1.88).

Because head circumference is related to birth weight in normal samples (8,9), we wanted to appreciate how head circumference relates to birth weight among macrosomic babies. The head circumference index of Nishi et al. (10), defined as head circumference $(cm)^3$/birth weight (g), has a mean ± SD of 11.85 ± 1.26 in Japanese boys and 11.67 ± 1.29 in Japanese girls. Applied to a sample of Caucasian children, the mean was 12.9 in boys and 12.5 in girls (11). For the purposes of several comparisons, we assumed a mean of 12.5 for Caucasian children (regardless of sex) and an SD of 1.29. The birth weight ratio (birth weight:50th percentile birth weight for gestational age) was used as an index of macrosomia.

We expressed HbA_1 as a z score with the standard being the mean value (5.9%) in the nondiabetic population. Thus, one can easily see where each mother's HbA_1 falls relative to the nondiabetic mean.

RESULTS— A total of 556 patients were available for study (Table 1), of which 92% were Caucasian. The degree of macrosomia in the sample is demonstrated by the mean birth weight ratio of 1.22. The incidence of birth weight ≥4,000 g was 29.8% (n = 166). Only 20 neonates (3.6%) were growth-retarded (birth weight ≤10th percentile). A total of 3,242 HbA_1 determinations were available, with a minimum of 317 and a maximum of 449 at each gestational age interval. The distribution of the HbA_1 data throughout gestation is displayed in box and whisker plots in Fig. 1 according to the method of Tukey (12). Of HbA_1 determinations available in the 1st trimester (i.e., intervals ≤8 and 9–12 weeks), 59% (269) were 6 or more SDs above the nondiabetic mean and only 8.2% (37) were 12 or more SDs above the mean. By 29–32 weeks, however, only 8.7% (39) of the patients were 6 or more SDs above the mean.

In a sample of 550 infants, 16.5 (99% confidence interval 7.8, 29.7) would be expected to fall at or below the 3rd percentile (microcephalic) and at or

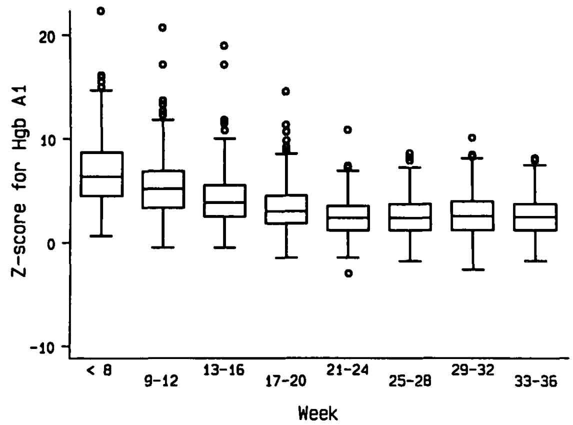

Figure 1—*Box and whisker plot of HbA_1 maximum z scores at various gestational age intervals. The three horizontal lines of the box indicate the 25th, 50th, and 75th percentile values. The circles represent extreme values.*

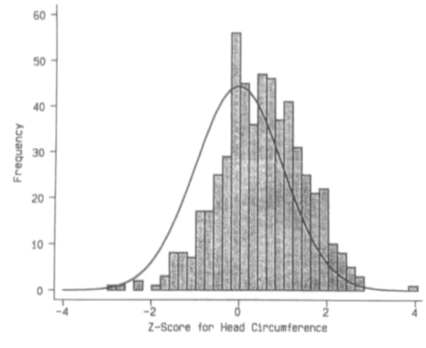

Figure 2—*Distribution of birth head circumference z scores. The bars summarize the data reported here. The line represents the expected normal distribution.*

above the 97th percentile (macrocephalic). We found significantly fewer infants (4) at or below the 3rd percentile and significantly more infants (41) at or above the 97th percentile. In both cases, the observed frequencies are outside the 99% confidence intervals for the expected frequencies. Figure 2 shows the distribution of *z* scores for head circumference in this sample and the expected distribution. Notice that the bars extend outside of the expected curve on the upper end and do not extend to the line on the lower end. When the head circumference *z* scores are replaced by the head circumference index *z* scores, the data closely approximate the normal distribution. This suggests that the head circumference distribution is in keeping with the macrosomia.

The relationship between head circumference and HbA_1 at each gestational age interval is demonstrated in the scattergrams in Fig. 3. The slopes of the regression lines for each of the gestational age-specific data sets shown in the figure were not statistically significantly different from 0. We conclude from this that there was no evidence that smaller head size was associated with poorer metabolic control at any gestational age within the range of metabolic control available for study.

To explore the possibility that improvement in metabolic control might influence head circumference, we evaluated the relationship between head circumference *z* score and the *z* score for change of HbA_1. For patients whose fetuses were at greatest risk (1st trimester HbA_1 >9 SDs above the mean), we calculated the changes in HbA_1 from the 1st trimester values to the 33- to 36-week values and compared them with the head circumference *z* scores. The slope of the regression line was -0.02 with $P = 0.5$, indicating no difference from 0.

CONCLUSIONS — These data clearly show that IDM tend to have larger head circumferences than other newborns. The major strength of this study is the large number of closely followed pregnant diabetic women with moderately good blood glucose control. The major limitation is that head circumference does not directly measure either brain weight or brain function. Despite a large sample size, which was adequate to find an increased incidence of microcephaly, none was found. The observation by Driscoll et al. (1) that fetal brain weights of IDM tended to be smaller than those of similar-weight infants of nondiabetic women is not manifested as decreased head size in our series. Similarly, the findings of relatively subtle effects on neuropsychological development and intellectual performance of Churchill et al. (2) and Rizzo et al. (4) are not reflected in an increased incidence of microcephaly.

There are several potential explanations for our failure to find corroboration of previous reports. It is possible that the fetal deaths that made the specimens available for study by Driscoll et al. (1) were due to a severe degree of poor metabolic control not prevalent among the women in our series. Only 8.2% had HbA_1 values of 12 or more SDs above the mean in the 1st trimester. That was the level at which a significantly increased risk for teratogenesis was observed in a prior study (13). These data do not rule out the possibility that significantly poorer control, as might have prevailed during the 1950s and 1960s, is associated with reduced head size. It seems probable from the work of Dobbing and Sands (14) that adverse metabolic circumstances in later pregnancy have the greatest impact on brain size. By later pregnancy, most of

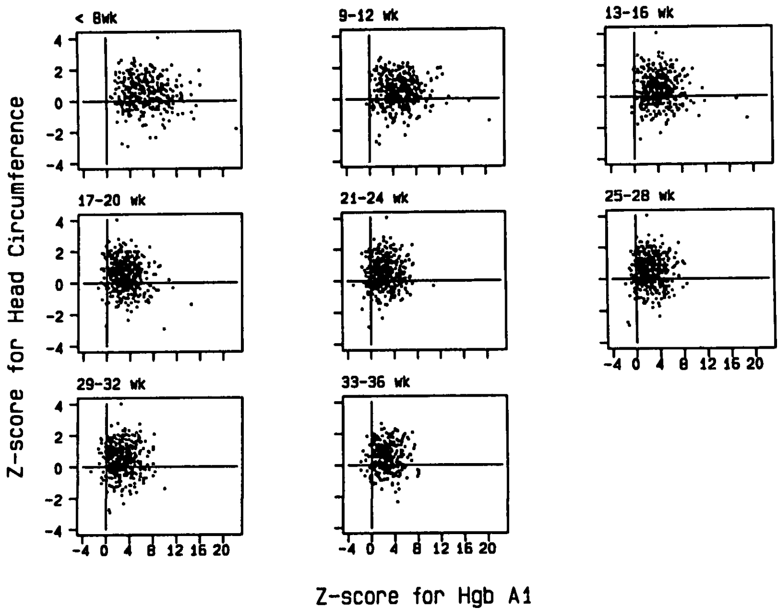

Figure 3—*Scatter plots of head circumference z scores by mothers' HbA_1 maximum z score at various gestational age intervals.*

these patients were in relatively good control.

A second hypothesis postulates that metabolic disorders are not capable of causing reduced brain growth of a degree that would be clinically evident as microcephaly. This seems unlikely in view of the experience with maternal phenylketonuria, which is clearly capable of causing clinical microcephaly and mental deficiency (15).

A third hypothesis is that the macrosomia in these patients masked small brain size. Generally, skull growth keeps pace with and is dictated by brain growth (16). Fetuses of diabetic women tend to be hyperinsulinemic, however, resulting in accretion of bone, muscle, and fat (17). This was certainly evident in this series by the large average size of the neonates. The shift of the head circumference distribution curve to the right reflects the macrosomia in the study population. Failure to find a relationship between head circumference at birth and maternal metabolic control should not be misinterpreted to mean that there is no relationship between fetal size at birth and metabolic control during pregnancy. Although there has been controversy on this issue (18), the best evidence is that there is a relationship between size at birth and metabolic control (19), albeit a weak one modified by other important factors (20).

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