What Degree of Maternal Metabolic Control in Women With Type 1 Diabetes Is Associated With Normal Body Size and Proportions in Full-Term Infants?

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OBJECTIVE — To assess what degree of maternal metabolic control in women with type 1 diabetes is associated with normal fetal growth and results in normal neonatal body proportions in a group of full-term infants.

RESEARCH DESIGN AND METHODS — We investigated the anthropometric characteristics of 98 full-term singleton infants born to 98 Caucasian women with type 1 diabetes enrolled within 12 weeks of gestation. The type 1 diabetic mother-infant pairs were divided into three groups on the basis of the daily glucose levels reached during the second and third trimesters of pregnancy (group 1: 37 mother-infant pairs with an average daily glucose level during the second and third trimesters of ≤95 mg/dl; group 2: 37 mother-infant pairs with an average daily glucose level during the second trimester of >95 mg/dl and during the third trimester of ≤95 mg/dl; group 3: 24 mother-infant pairs with an average daily glucose level during the second and third trimesters of >95 mg/dl; control group: 1,415 Caucasian mother-infant pairs with full-term singleton pregnancies and normal glucose challenge test screened for gestational diabetes.

RESULTS — Infants of diabetic mothers in group 1 were similar to those of the control group in birth weight and in other anthropometric parameters. In contrast, offspring of diabetic mothers of groups 2 and 3 showed an increased incidence of large-for-gestational-age infants, significantly greater means of ponderal index and thoracic circumferences, and significantly smaller cranial/thoracic circumference ratios with respect to the control group.

CONCLUSIONS — The results of our study suggest that, in diabetic pregnancies, only overall daily glucose values ≤95 mg/dl throughout the second and third trimesters can avoid alterations in fetal growth.

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The introduction of intensive insulin therapy for the obstetric care of pregnant women with type 1 diabetes has resulted in a notable reduction of perinatal mortality and morbidity (1–5). Nonetheless, the results of what, up until now, has been considered a tight glycemic control (average daily glucose levels ranging from 115 to 104 mg/dl [5–8]) remain unacceptable with respect to the levels of large-for-gestational-age (LGA) infants, which range from 20 to 30% (6–9). Indeed, the level of hyperglycemia that contributes to the development of fetal macrosomia seems to be much lower than that for complications such as fetal malformation and/or sudden intrauterine death in late pregnancy (5,10); therefore, it would seem that these goals for metabolic control are not strict enough to normalize intrauterine growth.

The aim of our study was to assess what degree of maternal metabolic control in women with type 1 diabetes is associated with normal fetal growth and, in particular, results in normal neonatal body proportions in a group of full-term infants.

RESEARCH DESIGN AND METHODS

From January 1990 to December 1997, a consecutive series of 135 pregnancies in 111 women with pregestational type 1 diabetes diagnosed according to World Health Organization criteria (11) were attended at the Perinatal Medicine Unit of the Institute of Obstetrics and Gynecology of the University of Florence. From this population, we selected 98 mother-infant pairs who met the following inclusion criteria: first observation before the 12th week of pregnancy, Caucasian race, singleton pregnancy, and full-term (from 37 to 42 weeks completed) live-born infant without evidence of congenital malformation. For those women who had more than one delivery during the period under the study, data from only the most recent pregnancy were collected.

After the first visit, patients were hospitalized for a short period to achieve the required degree of metabolic control. The glucose targets were preprandial 70–90 mg/dl and postprandial (2 h after the meal) <120 mg/dl. The treatment was based on the following three approaches: *1*) diet (caloric intake was adjusted to meet recommended requirements during pregnancy, including a minimum of 30 kcal/kg); *2*) in 49 cases, continuous subcutaneous insulin infusion (CSII) was used (Microject Bolus II;

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Abbreviations: ANOVA, analysis of variance; CSII, continuous subcutaneous insulin infusion; LGA, large-for-gestational-age; SGA, small-for-gestational-age.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Maternal characteristics of study and control groups and pregnancy outcomes of diabetic mothers*

	Group 1	Group 2	Group 3	Control group	*P**
n	37	37	24	1,415	—
Maternal age (years)	29.2 (20–36)	27.8 (10–35)	30.5 (16–40)	29.6 (10–44)	NS
Height (cm)	162.2 ± 0.5	161.8 ± 0.7	162.5 ± 0.8	162.6 ± 0.1	NS
Obesity (%)	10.8	8.1	12.5	11.3	NS
Parity	0 (0–2)	0 (0–1)	0 (0–1)	0 (0–3)	NS
White class (%)					
B	32.4	32.4	25.0		NS
C	40.5	40.5	41.7		NS
D	21.6	18.9	25.0		NS
R	2.7	8.1	8.3		NS
F-R	2.7	—	—		—
Duration of diabetes (years)	12 (1–29)	8 (2–25)	12.5 (1–32)		NS
Gestational age at entry (weeks)	9 (5–12)	8 (4–12)	8.5 (4–12)		NS
Preeclampsia (%)	—	5.4	16.7		<0.01 (group 3 vs. 1 and 2)
Intrauterine growth retardation (%)	2.7	2.7	4.2		NS
Patient compliance (%)	90.2	89.1	91.3		NS

Data are *n*, medians (range), means ± SEM, or %. *Determined by one-factor ANOVA, ANOVA for rank, and contingency table randomization test when appropriate.

Ames, Elkhart, IN) using exclusively regular insulin; in 49 cases, intensified conventional therapy, consisting of at least four daily doses of insulin, was used (the patients initially chose either multiple injections or CSII); and *3*) self-monitoring (patients were requested to check their blood glucose values by using a reflectance meter seven times a day: fasting, preprandial, postprandial, and at bedtime).

Patient compliance with self-monitoring of blood glucose was defined as the percent of the 196 glucose measurements prescribed by the protocol during the 4 weeks before delivery that were actually performed (12).

Patients were seen on an outpatient basis every 1–2 weeks, at which time their blood glucose results were reviewed. The monitoring protocol for the type 1 diabetic patients and the protocol for antepartum surveillance used in this study were described previously (9). Timing and mode of delivery were decided on the basis of the criteria outlined by Coustan (13). Severe hypoglycemic events were defined as episodes resulting in seizure or loss of consciousness (14). Obesity was defined as a prepregnancy BMI >25 kg/m^2 (15).

Study subjects

For the purpose of the analysis, the 98 type 1 diabetic mother-infant pairs were divided into the following three groups on the basis of the average daily glucose levels reached during the second (13th through 24th week) and third (from the 24th week to delivery) trimesters of pregnancy: group 1, 37 mother-infant pairs with an average daily glucose level during the second and third trimesters of ≤95 mg/dl; group 2, 37 mother-infant pairs with an average daily glucose level during the second trimester of >95 mg/dl and during the third trimester of ≤95 mg/dl; and group 3, 24 mother-infant pairs with an average daily glucose level during the second and third trimesters of >95 mg/dl.

All 1,415 Caucasian mother-infant pairs with full-term singleton pregnancies without congenital malformation and normal glucose challenge test screened for gestational diabetes (16) from January 1990 to December 1997 at the Perinatal Medicine Unit of the Institute of Obstetrics and Gynecology of the University of Florence formed the control group.

Infants were considered appropriate for gestational age when their birth weights ranged between the 11th and 89th percentiles, LGA when their birth weights were ≥90th percentile, and small-for-gestational-age (SGA) when their birth weights were ≤10th percentile on the basis of growth standard development for our population (17).

The following anthropometric parameters were taken within 24 h after birth according to standard methodology (17): *1*) birth weight, *2*) birth length, *3*) cranial circumference, *4*) thoracic circumference, *5*) ponderal index — the ratio between 100 times the weight in grams and the cube of the length in centimeters, and *6*) cranial/thoracic circumference ratio.

Statistical analysis

Categorical data were evaluated with contingency table randomization test and analysis of variance (ANOVA) for rank; continuous data were analyzed with one-way ANOVA. Comparisons of average neonatal anthropometric characteristics in infants among groups were performed with two-way ANOVA. ANOVA was used to analyze the effect of the sex (factor sex: female and male), the glucose levels reached during the second and third trimesters (factor

Table 2—*Daily blood glucose levels and severe hypoglycemic events in diabetic women during pregnancy*

	Group 1	Group 2	Group 3	*P**
n	37	37	24	—
Daily glucose, second trimester (mg/dl)	89.3 ± 3.9	100.9 ± 2.3	106.5 ± 6.6	<0.001 (group 1 vs. 2 vs. 3)
Daily glucose, third trimester (mg/dl)	89.8 ± 3.6	93.7 ± 1.3	105.4 ± 5.9	<0.001 (group 1 vs. 2 vs. 3)
Overall daily glucose (mg/dl)	89.5 ± 3.8	97.3 ± 1.8	105.9 ± 6.3	<0.001 (group 1 vs. 2 vs. 3)
Severe hypoglycemia	3/37 (8.1)	2/37 (5.4)	2/24 (8.3)	NS

Data are *n*, means ± SEM, or *n* (%). *Determined by one-factor ANOVA and ANOVA for rank when appropriate.

Table 3—*Neonatal outcomes*

	Group 1	Group 2	Group 3	Control group	*P**
n	37	37	24	1,415	—
Gestational age at delivery (weeks)	38.5 ± 0.1	38.6 ± 0.1	38.0 ± 0.1	39.1 ± 0.0	NS
LGA	5.4	37.8	54.2	8.5	<0.0001 (group 1 and control vs. 2 vs. 3)
Appropriate for gestational age	86.5	51.4	41.7	87.1	<0.0001 (group 1 and control vs. 2 vs. 3)
SGA	8.1	10.8	4.2	4.5	NS
Hyperbilirubinemia	—	5.4	—	3.1	NS
Hypocalcemia	2.7	—	16.7	0.5	<0.009 (groups 1, 2, and control vs. 3)
Hypoglycemia	2.7	2.7	4.2	0.6	NS
RDS	—	2.7	8.3	1.3	NS
Clavicular fracture	—	2.7	4.2	—	<0.02 (group 3 vs. 1, 2, and control)
Overall morbidity	16.2	51.4	70.8	13.9	<0.0003 (group 1 and control vs. 2 and 3)

Data are *n*, means ± SEM, or %.*Determined by one-factor ANOVA and contingency table randomization test when appropriate.

group: group 1, group 2, group 3, and control group), and the interactions between the two factors. Where significant differences were found on ANOVA, pairwise comparisons were performed using the Duncan multiple range test without any adjustment for multiple comparisons.

RESULTS — There were no significant differences between the three groups and the control group with respect to maternal age, maternal height, maternal obesity, and parity (Table 1).

Selected maternal characteristics and pregnancy outcome of diabetic women are also presented in Table 1. In group 3, there was a significantly higher incidence of preeclampsia, whereas comparable rates of intrauterine growth retardation were found among the three groups.

Daily blood-glucose levels and severe hypoglycemic events in diabetic women during pregnancy are shown in Table 2. The average daily glucose levels in group 1 were 89.3 and 89.8 mg/dl during the second and third trimesters, respectively. In group 2, the average daily glucose levels were 100.9 and 93.7 mg/dl during the second and third trimesters, respectively. In group 3, the average daily glucose levels were 106.7 and 105.4 mg/dl in the second and third trimesters, respectively.

The neonatal outcomes in the three groups and in the control group are listed in Table 3. Group 1 showed an incidence of LGA infants not significantly different compared with the control group. Group 2 showed a very pronounced increase in the incidence of LGA infants with respect to both group 1 and the control group. Group 3 also showed an increased incidence of LGA infants when compared with group 1 and the control group and also when compared with group 2. The infants of group 3 had significantly higher rates of clavicular fracture compared with group 1, group 2, and the control group. The overall neonatal morbidity in group 1 was not significantly different compared with the control group; overall neonatal morbidity in groups 2 and 3 was signifi-

Table 4—*Neonatal anthropometric data*

	Female sex (*n* = 750)				Male sex (*n* = 763)					
	Group 1	Group 2	Group 3	Control group	Group 1	Group 2	Group 3	Control group	Main effect of ANOVA	Group differences by Duncan's multiple range test
n	17	17	14	702	20	20	10	713		
Birth weight (g)	3,188.2 ± 103.4	3,354.1 ± 103.4	3,353.6 ± 113.9	3,202.0 ± 16.1	3,135.0 ± 95.3	3,449.5 ± 95.3	3,512.0 ± 134.8	3,321.9 ± 16.0	0.0001	Group 1 vs. 2 and 3
Length (cm)	49.1 ± 0.5	49.1 ± 0.5	48.2 ± 0.5	49.3 ± 0.1	49.2 ± 0.5	49.5 ± 0.5	49.8 ± 0.6	49.8 ± 0.6	<0.0001*	
Ponderal index (U)	2.70 ± 0.1	2.81 ± 0.1	2.95 ± 0.0	2.66 ± 0.0	2.66 ± 0.0	2.81 ± 0.0	2.89 ± 0.1	2.67 ± 0.0	<0.0001†	Group 1 and control vs. 2 and 3
Circumferences (cm)										
Cranial	34.5 ± 0.4	34.1 ± 0.4	33.7 ± 0.5	34.2 ± 0.1	34.5 ± 0.4	34.7 ± 0.4	34.4 ± 0.1	34.7 ± 0.1	<0.0001*	
Thoracic	32.5 ± 0.5	34.5 ± 0.5	34.9 ± 0.5	32.7 ± 0.1	32.4 ± 0.3	34.6 ± 0.3	35.4 ± 0.4	32.7 ± 0.1	<0.0001	Group 1 and control vs. 2 and 3
Cranial/thoracic	1.06 ± 0.01	0.99 ± 0.01	0.96 ± 0.01	1.04 ± 0.00	1.06 ± 0.00	0.99 ± 0.00	0.96 ± 0.01	1.04 ± 0.00	<0.0001†	Group 1 and control vs. 2 vs. 3

Data are *n* or means ± SEM. *Significant difference only for sex; †significant difference only for group.

cantly higher compared with group 1 and the control group.

An examination of the anthropometric characteristics (Table 4) of offspring of diabetic mothers revealed that male and female infants of diabetic mothers in group 1 were similar to those of the control group in birth weight and in other anthropometric parameters. In contrast, offspring of diabetic mothers of groups 2 and 3 showed significantly greater values of ponderal index and thoracic circumferences and significantly smaller cranial/thoracic circumference ratios with respect to the control group. In addition, infants of group 3 showed a cranial/thoracic circumference ratio significantly smaller than that of group 2.

CONCLUSIONS — It is generally believed that glycemic targets in diabetic pregnancies should mimic those found in normal pregnancies (18), and treatment of type 1 diabetes should be aimed at producing a metabolic state such that the fetus does not recognize its mother as diabetic (19).

The degree of maternal glycemic control is most accurately indicated by overall mean daily glucose values obtained from preprandial and postprandial testing (10). In this study, we used a cutoff value of 95 mg/dl to divide the study group into three subgroups with different glycemic control; this value was selected because it seemed an appropriate compromise between the threshold mean glucose value of 100 mg/dl, below which the incidence of macrosomia is comparable with that in the general population (10), and the threshold of 90 mg/dl for mean pre- and postprandial glucose values, above which there is a risk of fetal hyperinsulinemia (19). In our study, normal body size and mass in infants of diabetic mothers were achieved only when the mean maternal glucose values fell significantly below 95 mg/dl, well below the currently accepted upper physiological levels (6,9,10), reaching values $<$90 mg/dl as early as possible and essentially in the second trimester (group 1). Such a level of maternal glycemia seems not to impede intrauterine growth. In fact, the study demonstrates that the incidence of SGA infants in group 1 is the same as that of the control group; moreover, the occurrence of severe hypoglycemia in this study is comparable with that reported in recent articles (6,14).

The incidence of LGA infants in group 2, where daily glucose values of $\leq$95 mg/dl were achieved only during the third trimester, confirms this result. Here, a 37.8% incidence of LGA infants, with altered anthropometric ratios, was produced. This also confirms the results reported by Persson and Hanson (6) that diabetic mothers with LGA infants tended to have elevated glucose levels before week 32 and significantly so between 27 to 32 weeks of pregnancy. This period of pregnancy coincides with the time of rapid fetal growth, as determined by serial ultrasound examinations by Rossavik et al. (20). The presence of hyperglycemia during the second trimester may increase secretion of insulin and β-cells and islet hyperplasia stimulation, the primary determinant of diabetic fetopathy (21). Furthermore, the ensuing fetal hyperinsulinemia may promote the development of macrosomia, even if metabolic control is satisfactory during late gestation (22).

What should be stressed from the results of our study is that there seems to be a continuous relationship between maternal glucose levels and infant birth weight; the effect of only marginally higher than physiological glucose values on offspring is notable. Once the maternal glucose value moves from 89 (group 1) to 100 mg/dl in the second trimester and 93 mg/dl in the third trimester (group 2), the incidence of LGA infants rises from 5.4 to 37.8%.

The results of group 3 with maternal glucose values of 106 and 105 mg/dl confirm the pronounced effect of only marginally higher than physiological values and further illustrate its increase with 54.2% LGA infants. However, the increase of incidence of LGA infants between groups 2 and 3 is not so marked as that between groups 1 and 2, being a progression rather than a leap.

Offspring of diabetic mothers in groups 2 and 3 are not only LGA, as defined by birth weight, but they show significantly greater means of ponderal index and thoracic circumferences and significantly smaller cranial/thoracic circumference ratios when compared with offspring of nondiabetic mothers; these findings most likely reflect the preferential growth of insulin-sensitive tissues (i.e., adipose tissue and liver) in infants of groups 2 and 3. The anthropometric disproportion of offspring of diabetic mothers is further confirmed, and the progressive effect of higher glucose values demonstrated by the fact that infants of group 3 show a cranial/thoracic circumference ratio significantly smaller than that of group 2.

The results of our study suggest that it is not sufficient to achieve near-normal glucose values in diabetic pregnancies to avoid alteration in fetal growth but that only overall daily glucose values $\leq$95 mg/dl reached as early as the second trimester and maintained throughout the third trimester are associated with normal body size and proportions of the infants.

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