

Programming of Adiposity in Offspring of Mothers With Type 1 Diabetes at Age 7 Years

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OBJECTIVE— The goals of this study were to examine the influence of maternal type 1 diabetes during pregnancy on offspring adiposity and glucose tolerance at age 7 years and to assess whether metabolic factors at birth (neonatal leptin and insulin) predict adverse outcomes.

RESEARCH DESIGN AND METHODS— We examined 100 offspring of mothers with type 1 diabetes (OT1DM) and 45 offspring of control mothers. Mothers had previously been recruited during pregnancy, and, where possible, birth weight, umbilical cord insulin, and leptin were measured. Children were classed as overweight and obese using age-specific reference ranges.

RESULTS— OT1DM had similar height (control, 1.25 ± 0.06 m; OT1DM, 1.24 ± 0.06 m; $P = 0.81$) but were heavier (control, 25.5 ± 3.8 kg; OT1DM, 27.1 ± 5.7 kg; $P = 0.048$) and had an increased BMI (control, 16.4 kg/m²; OT1DM, 17.4 ± 2.6 kg/m², $P = 0.005$). Waist circumference (control, 56.0 ± 3.7 cm; OT1DM, 58 ± 6.8 cm; $P = 0.02$) and sum of skinfolds were increased (control, 37.5 ± 17.0 mm [$n = 42$]; OT1DM, 46.1 ± 24.2 mm [$n = 91$]; $P = 0.02$), and there was a marked increase in the prevalence of overweight and obese children (OT1DM, 22% overweight and 12% obese; control, 0% overweight and 7% obese; $\chi^2 P = 0.001$). Glucose tolerance was not different compared with that in control subjects. BMI at age 7 years correlated with cord leptin (OT1DM, $r = 0.25$; $n = 61$, $P = 0.047$), weakly with adjusted birth weight ($r = 0.19$; $P = 0.06$) and hematocrit ($r = 0.25$; $n = 50$, $P = 0.07$), but not cord insulin (OT1DM, $r = -0.08$; $P = 0.54$).

CONCLUSIONS— OT1DM are at increased risk of overweight and obesity in childhood. This risk appears to relate, in part, to fetal leptin and hematocrit but not insulin.

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There is increasing interest in the hypothesis that cardiovascular and metabolic diseases might be influenced by early life events. A number of studies have suggested that exposure to maternal diabetes prior to birth increases the risk of type 2 diabetes and obesity in later life (1). Notably, the best evidence comes from populations at a high underlying genetic risk of type 2 diabetes and

obesity (1) where observational studies and sibling studies suggest that the presence of maternal diabetes during pregnancy substantially increases risk of type 2 diabetes and obesity in childhood and early adult life. Similarly, exposure to maternal hyperglycemia increases the penetrance of maturity-onset diabetes of the young (MODY) (2). Offspring of mothers with type 1 diabetes (OT1DM) have been

found to have an increase in BMI in childhood in some (3) but not all series (4). Recently, an increase in BMI in OT1DM has been found in young adults in Denmark as well as in increase in the prevalence of impaired glucose tolerance (5). Importantly, presence of raised cord or amniotic fluid insulin in OT1DM has also been found to be associated with later offspring obesity (6,7,3).

In this study, we examined glucose tolerance and adiposity at age 7 years in children of mothers with type 1 diabetes previously examined in a multicenter pregnancy cohort study. Further, we used the extensive phenotyping of the cohort at birth to examine which of a number of changes previously identified at birth in this cohort—most notably raised birth weight, fetal hyperinsulinemia, and fetal hyperleptinemia (8), but also increased cord hematocrit (9), C-reactive protein (CRP) (10), and reduced adiponectin (11)—might be associated with risk of offspring obesity.

RESEARCH DESIGN AND METHODS

Recruitment for the original Fetal Insulin and Glycaemia Study (FIGS) began in January 1999 and ended in May 2001 and took place in eight hospital-based antenatal centers in Scotland (8). A total of 250 women with type 1 diabetes consented to participate in the study (a 94% participation rate of those enrolled and planning to deliver in the centers), and cord blood samples were obtained from the umbilical vein after placental separation at delivery for 200 (80%) women. Of these 200, 140 specimens met restriction criteria (no evidence of hemolysis of cord; cord blood collected within 20 min, centrifuged and plasma frozen within 60 min; antenatal glucocorticoids not administered in the 24 h before birth; and children delivered before 33 weeks' gestation) as previously described (8).

A convenience sample of control mothers, who had no history of obstetric or metabolic disease and in whom routine screening for gestational diabetes mellitus (using national guidelines [http://www.sign.ac.uk/guidelines], SIGN [Scottish In-

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See accompanying articles, p. 964, 1115, and 1146.

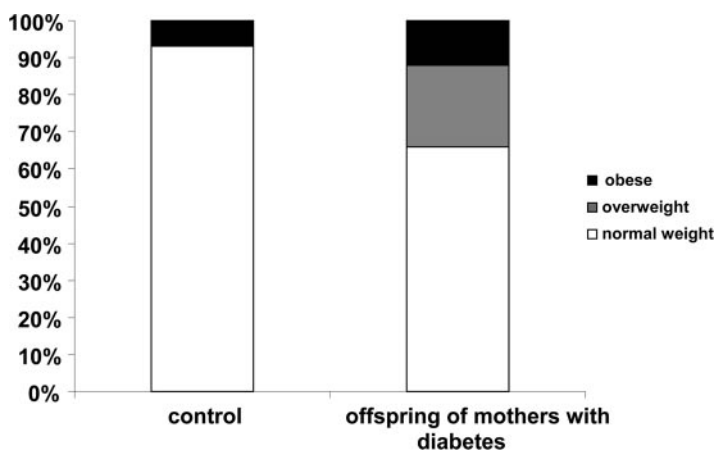


Figure 1—Proportion of overweight and obese in OT1DM.

tercollegiate Guidelines Network] 55) was negative, was recruited from routine obstetric follow-up clinics after the 34th week of pregnancy in the same centers. Of the 145 control women who gave initial consent, cord samples were attempted in 75 and obtained in 70. Forty-eight control collections met the above restriction criteria.

Data on clinical outcome including caesarean section, intercurrent medical conditions, and hypertensive conditions of pregnancy were obtained by case note review including maternal smoking history recorded as current, ex-smoker, or nonsmoker. Smoking history was not available in two cases. Gestational ages were calculated from estimated dates of delivery from chart review. This date was derived from dates of last menstrual period (LMP), where available, or by ultrasound if there was a conflict with dates as assessed by LMP (>6 days) or LMP was unavailable.

Cord blood assays

Plasma insulin, 32-33 split proinsulin, proinsulin, leptin, IGF-I (8), CRP (10), and adiponectin (11) were assayed by validated methods as previously described. Maternal A1C was measured centrally by one laboratory (8).

Examination in childhood

Children were invited to a study examination by a letter to their parent. Following written consent from the parent and assent from the child, data were obtained on weight (Marsden MPMS 230 portable personal scale; Marsden, Henley-on-Thames, U.K.), height (Marsden H226), five-point skinfold measurements (triceps, biceps, subscapular, suprailiac,

and para-umbilical, Holtain Tanner/Whitehouse skinfold calipers; Holtain, Crosswell, U.K.), blood pressure taken sitting three times after 5 min of rest (using Rossmax Mandaus II Pro Kit sphygmomanometer kit with stethoscope and young adult cuff 18–27 cm), and waist measurement using tape measure in centimeters (12). Participants were invited to have an oral glucose tolerance test 1.75 g of glucose/kg body wt up to a total of 75 g of glucose with blood sampling fasting and at 30 and 120 min and glucose tolerance categorized using World Health Organization (WHO) 1999 criteria. A total of 45 control offspring and 100 OT1DM were examined, representing 31% of the control subjects and 40% of OT1DM originally enrolled in the study. For both control subjects and OT1DM, those with follow-up at age 7 years had birth weight, maternal age at delivery, and gestation at delivery similar to those without follow-up and similar duration of diabetes in the OT1DM (data not shown).

SD scores for BMI, weight, and height were calculated using reference curves (13) based on population data from the U.K. in 1990. General overweight/obesity was defined using the International Obesity Taskforce (IOTF) age- and sex-specific thresholds for childhood BMI (14), and central obesity was defined as an age- and sex-specific waist circumference ≥ 90 th percentile (15), based on waist circumference percentile curves derived for British children (12).

Both the original FIGS and the current study received ethical approval from the appropriate research ethics committees.

Statistical analysis

Data were analyzed using standard software (SAS version 9.1, Cary, NC). For normally distributed variables, data are reported as means \pm SD; in several cases (insulin and leptin), measures were not normally distributed and unadjusted values are presented as median (interquartile range) and variables were logarithmically transformed to obtain normal distributions. For correlation and regression models, SD scores of birth weight and body weight at age 7 years are used. Intergroup differences were assessed by unpaired *t* test or, where further predictor variables were included, by general linear models. Spearman correlation coefficients are reported. Stepwise logistic regression was performed using an α of $P \leq 0.15$ for adding or removing predictors from the model.

RESULTS

A total of 100 OT1DM and 45 offspring of control mothers (control) consented to take part in the study. Mothers were of similar age and parity (supplementary Table A1, available at <http://care.diabetesjournals.org/cgi/content/full/dc09-1766/DC1>). OT1DM were born around 1.5 weeks earlier on average and more often by caesarean section. OT1DM were markedly heavier with *z* scores of birth weight 1.8 SD above the expected for the background population. Where available, cord insulin and leptin were increased in OT1DM (supplementary Table A1), in keeping with the larger dataset from the original cohort (8), while differences in hematocrit (9), CRP (10), and adiponectin previously found in the larger set (11) were in similar directions, although not formally significant in this subgroup (supplementary Table A1).

Children were examined at an average of 7.4 years in both groups (Table 1). Height was not different between OT1DM and control subjects either in absolute terms or when expressed as an SD score (Table 1). By contrast, weight, waist circumference, total sum of skinfolds, and BMI were significantly increased in OT1DM (by 1.6 kg, 2 cm, 9.6 mm, and 1.0 kg/m², respectively) with an accompanying significant increase in the SD score for BMI and waist circumference (Table 1). Glucose either fasting or after glucose load was not increased in OT1DM, and fasting insulin was not increased (Table 1). No children fulfilled WHO criteria for either impaired fasting glucose or impaired glucose tolerance.

Table 1—Anthropometric and biochemical measures in children at follow-up

	Control children	Children of mothers with type 1 diabetes	P
N	45	100	
Age (years)	7.4 ± 0.36	7.4 ± 0.45	0.81
Height (cm)	124.7 ± 6.0	124.5 ± 6.3	0.81
Height SD score	0.085 ± 1.03	0.06 ± 1.04	0.89
Weight (kg)	25.5 ± 3.8	27.1 ± 5.7	0.047
Weight SD score	0.23 ± 0.92	0.52 ± 1.24	0.12
BMI	16.4 ± 1.6	17.4 ± 2.6	0.005
BMI SD score	0.28 ± 0.78	0.69 ± 1.2	0.02
Skinfold (total in mm)	37.5 ± 17.0	46.1 ± 24.1	0.02
n		91	
Waist (cm)	56.0 ± 3.7	58.0 ± 6.8	0.02
Waist SD score	0.35 ± 0.91	0.86 ± 1.63	0.02
Fasting glucose (mmol/l)	4.5 ± 0.4	4.5 ± 0.3	0.99
n	19	53	
30-min glucose (mmol/l)	7.5 ± 1.7	7.7 ± 1.62	0.67
n	17	46	
120-min glucose (mmol/l)	5.7 ± 0.8	5.1 ± 1.3	0.12
n	12	34	
Fasting insulin (pmol/l)	16.9 (12.1–20.2)	17.9 (10.7–27.5)	0.84
n	19	51	

Continuous variables are presented as means ± SD or medians (25th–75th interquartile range) depending on distribution and examined using *t* test or Wilcoxon test, respectively.

In addition to the significant increase in BMI, there was a significant increase in children classified as either obese or overweight with 22 (22%) OT1DM overweight and 12 (12%) obese compared with no overweight children and 3 (6.7%) obese in the control group (*P* = 0.001) (Fig. 1). Central obesity (waist circumference ≥90th percentile) was present in 36% of OT1DM and 9% of control subjects (χ^2 *P* < 0.001).

Importantly, mothers with diabetes were heavier at follow-up (mean ± SD maternal BMI: OT1DM, 27.3 ± 5.2 kg/m² and control, 24.8 ± 4.4 kg/m²; *P* < 0.004)—a difference that was not apparent in fathers (OT1DM, 27.5 ± 3.7 kg/m²; control, 26.5 ± 2.8; *P* = 0.19). Despite this, the difference in offspring BMI did not appear to be explained by differences in mothers' weights. Maternal and child BMI were related in the control group (*r* = 0.34; *P* = 0.02) but not OT1DM (*r* = 0.10; *P* = 0.34). Differences between OT1DM and control were maintained after addition of maternal BMI as a predictor term (BMI SD score mean adjusted for maternal BMI ± SEM: OT1DM, 0.67 ± 0.11 and control, 0.33 ± 0.16; *P* = 0.08) (child BMI mean adjusted for maternal BMI ± SEM: OT1DM, 17.3 ± 0.24 and control, 16.4 ± 0.35; *P* = 0.03). Differences in children's BMI were more appar-

ent in subgroups of mothers currently normal weight (child BMI SD score mean ± SEM: OT1DM, 0.63 ± 0.21 and control 0.14 ± 0.13; *P* = 0.0013) compared with those currently overweight or obese (child BMI SD score mean ± SEM: OT1DM, 0.73 ± 0.14 and control 0.52 ± 0.21; *P* = 0.39).

Characteristics at birth of children OT1DM overweight or obese at age 7 years were examined. Notably, OT1DM found to be overweight or obese at age 7 years had age at delivery, cord insulin, CRP, and adiponectin very similar to those in normal weight OT1DM at age 7 years. Although birth weight and skinfolds at birth were significantly increased in the OT1DM found to be overweight or obese at age 7 years compared with control subjects, these measures showed only nonsignificant increases compared with those in OT1DM found to be normal weight at age 7 years (Table 2). OT1DM who were overweight or obese at age 7 years had significantly higher values of cord leptin at birth and hematocrit compared with those in normal-weight OT1DM. When analyzed as continuous variables, there were no significant relationships of BMI, waist circumference, or sum of skinfolds to measures at birth (cord insulin, cord leptin, cord CRP, and birth weight) in the control group. By

contrast, cord leptin was positively associated with BMI at age 7 years (*r* = 0.24; *P* = 0.04) and cord hematocrit with total skinfolds (*r* = 0.33; *P* = 0.02) and waist circumference (*r* = 0.28; *P* = 0.049) (supplementary Table A2).

In stepwise multivariate analysis, BMI centile at age 7 years was related only to hematocrit (9% of variance *P* = 0.05 in a model also potentially including birth weight, cord insulin, leptin, adiponectin, IGF-I, and maternal and paternal BMI [*n* = 50]). Inclusion of maternal smoking history did not influence the relationship of fetal hematocrit and BMI at age 7 years in OT1DM (effect of hematocrit *P* = 0.03; effect of maternal smoking category *P* = 0.31). When hematocrit was excluded, cord leptin accounted for 4.6% of the variance of BMI at age 7 years (*P* = 0.11, *n* = 74).

CONCLUSIONS— Detailed analyses from the Pima Indian population have demonstrated that fetal exposure to maternal diabetes increases the risk of obesity and type 2 diabetes for the offspring in later life (1). While critical in this population, it has been less clear whether programming of childhood glucose tolerance would be observed in populations at less severe genetic risk of obesity and type 2 diabetes. Further, there are few studies exploring whether markers at birth might highlight the mechanisms by which in utero programming is occurring.

For obesity, our data suggest that the presence of maternal diabetes may indeed program later adiposity in children. It is notable that while the overall increase in BMI is modest (1.0 kg/m²), there is a change in the distribution of weight in the population of OT1DM with a marked increase in children in the overweight and obese categories suggesting a potential upward shift in the distribution of weight. It is unclear at this stage whether other children will be at increased risk of overweight in later life or whether risk will be concentrated in a susceptible subgroup. Our data are in agreement with the data from the Pima Indian population (1) and examination of a mixed population of OT1DM and with gestational diabetes (7). Although the data from the Pima Indian population are compelling, teasing apart the relative effects of maternal obesity and hyperglycemia along with potential genetic and environmental effects is complex in a population at high underlying genetic risk of obesity and type 2 diabetes. There are fewer studies of OT1DM,

Table 2—Characteristics at birth of OT1DM obese or overweight in childhood

	Control children	Children of mothers with type 1 diabetes		P OT1DM obese or overweight vs. OT1DM normal weight
		Normal weight at age 7 years	Overweight or obese at age 7 years	
N	45	66	34	
Gestational age at delivery (weeks \pm SEM)	39.9 \pm 0.3	37.6 \pm 0.24*	37.1 \pm 0.33*	0.30
Birth weight (kg)	3.44 \pm 0.1	3.57 \pm 0.08	3.76 \pm 0.1*	0.19
Total skinfolds at birth (mm)	11.2 \pm 1.4	13.9 \pm 0.9	15.3 \pm 1.1*	0.34
z score of birth weight	0.23 \pm 0.22	1.61 \pm 0.19*	2.13 \pm 0.26*	0.11
Cord insulin (pmol/l)	27.9 (20.7–37.7)	139.8 (114.8–170.6)*	128.9 (101–167.2)*	0.82
n	16	38	23	
Cord leptin (mcg/ml)	8.25 (6.4–10.7)	20.5 (17.2–24.4)*	37.7 (30.1–47.2)*	0.03
n	21	47	28	
Cord hematocrit	0.52 \pm 0.01	0.52 \pm 0.01	0.56 \pm 0.01*	0.03
n	18	31	19	
Cord adiponectin	21.6 \pm 1.5	18.9 \pm 1.0	19.7 \pm 1.2	0.59
n	18	44	29	
Cord CRP	0.17 (0.15–0.19)	0.19 (0.18–0.20)	0.21 (0.19–0.24)	0.42
n	20	45	27	
Maternal A1C, weeks 5–12 (%)	—	7.6 \pm 0.2	8.2 \pm 0.4	0.11
n	—	29	18	
Maternal A1C, weeks 16–24 (%)	—	6.7 \pm 0.14	6.9 \pm 0.2	0.43
n	—	36	22	
Maternal A1C, weeks 26–34 (%)	—	6.8 \pm 0.1	7.1 \pm 0.2	0.10
n	—	46	30	
Maternal A1C, weeks 35–40 (%)	—	6.5 \pm 0.2	6.9 \pm 0.2	0.12
n	—	31	22	

Continuous variables are presented as means \pm SE or geometric means with range \pm 1 SE. *Difference from control $P < 0.05$. Boldface data indicates $P < 0.05$ for OT1DM obese or overweight different from OT1DM normal weight.

but such studies might serve to examine the more isolated effects of maternal hyperglycemia in pregnancy. Manderson et al. (4) in Northern Ireland found no increase in BMI in children born to mothers with type 1 diabetes aged 8.6 years, although specific analysis of overweight and obese was not undertaken and the age distribution of children was broad (5–11 years). In a small study (15 cases), Sobngwi et al. (16) did not find an increase in adiposity in young adult OT1DM, whereas Weiss noted an increase of 1.6 kg/m² in 71 OT1DM examined between 5 and 15 years of age (3). More recently, Clausen et al. (5) reported an increase in BMI of 1.1 kg/m² in OT1DM at 26.5 years and an increase in rates of overweight (41%) and obese (10%) compared with the control population (24% overweight and 5% obese) (17). Taken together, these studies would suggest that maternal hyperglycemia is acting to increase the risk of overweight and obesity in childhood and into adult life.

One criticism of such studies is whether the control group is truly representative of the general population. In our

case, it is notable that there were no children in the control group in the overweight category. In boys, BMI (mean \pm SD) in the control group of the current study (boys, 16.4 \pm 1.8 kg/m²; girls, 16.4 \pm 1.4 kg/m²; all, 16.4 \pm 1.6 kg/m²) is slightly higher than that reported in the Avon Longitudinal Study of Parents and Children (ALSPAC) at a similar age (16.2 \pm 2.0 kg/m² at age 7.5 years with no differences between sexes) (18). Both average BMI in ALSPAC and rates of obesity (9.2% in boys and 8.1% in girls) (19) are similar to those in our control group and lower than those observed in OT1DM in our study.

Due to the availability of cord measures, we are able to go beyond previous studies. Silverman et al. (6,20) and Weiss et al. (3) reported that higher amniotic fluid insulin was associated with increased BMI in childhood. By contrast, children in our cohort who were overweight and obese had cord insulin concentrations similar to those in OT1DM found to be normal weight at follow-up, although both groups have markedly raised cord insulin concentrations compared with those in control subjects.

There is a strong correlation between cord insulin at birth and amniotic fluid insulin toward the end of pregnancy (21), and this should not account for the difference between the studies. Interpretation of the study of Silverman et al. is made more complex by the mix of mothers with type 1 and gestational diabetes included. In our series, leptin rather than insulin acts as a marker of later adiposity. Leptin is a robust marker of neonatal fat mass (22), and indeed there is a trend toward higher birth weight and skinfolds in offspring later developing overweight or obesity in our series. To our knowledge, no other series has related obesity risks to such markers in OT1DM at birth. We have described a number of hormonal and other changes at birth in this cohort of OT1DM. Cord insulin, leptin, and birth weight (8) are markedly raised, hematocrit (9) and CRP (10) are more modestly increased, and adiponectin decreased (11). While several of these changes are intercorrelated, insulin and leptin are not particularly strongly related in OT1DM ($r = 0.22$) (8). Neither leptin nor insulin are related to hematocrit at birth (9). As such, changes in insulin, leptin, and hematocrit

may be reflecting different aspects of the adverse fetal environment in OT1DM. Of all of these markers, only leptin and hematocrit emerge as markers of later overweight and obesity in childhood in our population, although notably these measures at birth explain a relatively small proportion (<10%) of the overall variance of BMI at age 7 years.

Hematocrit has been known for some time to be increased in offspring of mothers with diabetes (23) and proposed to increase in response to fetal hypoxia, adverse placental function, or as direct effects of insulin (23). In our cohort, while the increase in hematocrit is fairly typical of other series, there was no convincing relationship of hematocrit to insulin, suggesting that fetal hyperinsulinemia was not playing a direct role in stimulating erythropoiesis (9), although hematocrit showed a modest relationship to maternal A1C ($r = 0.30$; $P = 0.02$) (9). Interestingly, there is a broader literature suggesting that maternal smoking, a known determinant of hematocrit, is associated with an increase in offspring obesity, a finding noted in the ALSPAC (19) as well as other series (24), although the mechanistic basis of this remains unknown. We have recently shown only subtle structural changes in the placenta in the same series. The hypothesis that structural or functional changes in the placenta underpin programming of obesity in the cohort remains to be tested.

There is keen interest at present into understanding determinants of fetal and neonatal fat mass and the extent to which the fetal environment will increase adult disease. It is known that leptin acts as a marker of fetal fat mass (22), and it may be that increased fetal adiposity rather than leptin per se is the key intermediary between the intrauterine environment and later risk of adiposity in offspring. Alternatively, leptin has a range of effects on appetite and insulin sensitivity (22), and it is therefore possible that leptin is programming, for example, appetite at a more fundamental level. At present, there is not an extensive literature examining cord leptin as a marker of later obesity. Ong et al. (25) have reported an inverse relationship between cord leptin and weight gain in 197 healthy children at age 2 years; with assessment of adiposity so early in life, it is difficult to judge the relevance of such findings to our study.

Maternal hyperglycemia has also been associated with an increased risk of later impaired glucose tolerance and type

2 diabetes. Again, the largest follow-up is from the Pima Indians (1), but an increase in impaired glucose tolerance has also been reported in OT1DM in early adulthood in Paris (16) and an increase in a composite of type 2 diabetes and pre-diabetes in the larger Danish series (5). We found no difference in glucose tolerance. This may reflect the younger age of our cohort and is in keeping with the findings of Manderson et al. (4) at a similar age.

In conclusion, we demonstrate that maternal type 1 diabetes is associated with an increased risk of overweight and obesity in childhood. Both cord leptin and hematocrit emerge as intermediate markers of this risk. Our data suggest that obesity may be programmed in utero via hyperglycemia, and interventions in pregnancy may be critical to try to influence long-term risk of disease in offspring.

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