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, 2.55 ± 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; χ² 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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Received 22 September 2009 and accepted 30 December 2009.
DOI: 10.2337/dc09-1766
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See accompanying articles, p. 964, 1115, and 1146.
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 (76 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 assessed by validated methods as previously described. Maternal A1C was measured centrally by a letter to their parent. Follow-up and similarity to those without follow-up and similar duration of diabetes in the OT1DM (data not shown).

Statistical analysis
Data were analyzed using standard software (SAS version 9.1, Cary, N.C.). For normally distributed variables, data are reported as means ± 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 ≤ 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 a score 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 age 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.

Figure 1 — Proportion of overweight and obese in OT1DM.

- 60% - 80% - 90%
- 0% - 40% - 50% - 70%

- control

- offspring of mothers with diabetes

100%

- obese

- overweight

- normal weight

- 0%

- 100%
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 $\geq 90$th percentile) was present in 36% of OT1DM and 9% of control subjects ($\chi^2 P < 0.001$).

Importantly, mothers with diabetes were heavier at follow-up (mean $\pm$ SD maternal BMI: OT1DM, 27.3 $\pm$ 5.2 kg/m$^2$ and control, 24.8 $\pm$ 4.4 kg/m$^2$; $P < 0.004$)—a difference that was not apparent in fathers (OT1DM, 27.5 $\pm$ 3.7 kg/m$^2$; control, 26.5 $\pm$ 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 $\pm$ SEM: OT1DM, 0.67 $\pm$ 0.11 and control, 0.33 $\pm$ 0.16; $P = 0.08$) (child BMI mean adjusted for maternal BMI $\pm$ SEM: OT1DM, 17.3 $\pm$ 0.24 and control, 16.4 $\pm$ 0.35; $P = 0.03$). Differences in children’s BMI were more apparent in subgroups of mothers currently normal weight (child BMI SD score mean $\pm$ SEM: OT1DM, 0.63 $\pm$ 0.21 and control 0.14 $\pm$ 0.13; $P = 0.0013$) compared with those currently overweight or obese (child BMI SD score mean $\pm$ SEM: OT1DM, 0.73 $\pm$ 0.14 and control 0.52 $\pm$ 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, leptin, adiponectin, IGF-1, 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 interuterine 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/m$^2$), 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, 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).

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 $\pm$ 0.36   | 7.4 $\pm$ 0.45                          | 0.81 |
| **Height (cm)**     | 124.7 $\pm$ 6.0  | 124.5 $\pm$ 6.3                         | 0.81 |
| **Height SD score** | 0.085 $\pm$ 1.03 | 0.06 $\pm$ 1.04                        | 0.89 |
| **Weight (kg)**     | 25.5 $\pm$ 3.8   | 27.1 $\pm$ 5.7                          | 0.047|
| **Weight SD score** | 0.23 $\pm$ 0.92  | 0.52 $\pm$ 1.24                        | 0.12 |
| **BMI**             | 16.4 $\pm$ 1.6   | 17.4 $\pm$ 2.6                         | 0.005|
| **BMI SD score**    | 0.28 $\pm$ 0.78  | 0.69 $\pm$ 1.2                          | 0.02 |
| **Skinfold (total in mm)** | 37.5 $\pm$ 17.0 | 46.1 $\pm$ 24.1                      | 0.02 |
| **Waist (cm)**      | 56.0 $\pm$ 3.7   | 58.0 $\pm$ 6.8                          | 0.02 |
| **Waist SD score**  | 0.35 $\pm$ 0.91  | 0.86 $\pm$ 1.63                        | 0.02 |
| **Fasting glucose (mmol/l)** | 4.5 $\pm$ 0.4 | 4.5 $\pm$ 0.3                          | 0.99 |
| **n**               | 19               | 53                                      |      |
| **30-min glucose (mmol/l)** | 7.5 $\pm$ 1.7 | 7.7 $\pm$ 1.62                       | 0.67 |
| **n**               | 17               | 46                                      |      |
| **120-min glucose (mmol/l)** | 5.7 $\pm$ 0.8 | 5.1 $\pm$ 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 $\pm$ SD or medians (25th–75th interquartile range) depending on distribution and examined using $t$ test or Wilcoxon test, respectively.
Table 2 — Characteristics at birth of OT1DM obese or overweight in childhood

| Characteristic | Control children | Normal weight at age 7 years | Overweight or obese at age 7 years | P OT1DM obese or overweight vs. OT1DM normal weight |
|---------------|------------------|-------------------------------|-----------------------------------|---------------------------------------------------|
| N             | 45               | 66                           | 34                                |                                                   |
| Gestational age at delivery (weeks ± SEM) | 39.9 ± 0.3 | 37.6 ± 0.24* | 37.1 ± 0.33* | 0.30 |
| Birth weight (kg) | 3.44 ± 0.1 | 3.57 ± 0.08* | 3.76 ± 0.1* | 0.19 |
| Total skinfolds at birth (mm) | 11.2 ± 1.4 | 13.9 ± 0.9 | 15.3 ± 1.1* | 0.34 |
| z score of birth weight | 0.23 ± 0.22 | 1.61 ± 0.19* | 2.13 ± 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 ± 0.01 | 0.52 ± 0.01 | 0.56 ± 0.01* | 0.03 |
| n             | 18               | 31                           | 19                                |                                                   |
| Cord adiponectin | 21.6 ± 1.5 | 18.9 ± 1.0 | 19.7 ± 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 ± 0.2 | 8.2 ± 0.4 | 0.11 |
| n             | —                | 29                           | 18                                |                                                   |
| Maternal A1C, weeks 16–24 (%) | — | 6.7 ± 0.14 | 6.9 ± 0.2 | 0.43 |
| n             | —                | 36                           | 22                                |                                                   |
| Maternal A1C, weeks 26–34 (%) | — | 6.8 ± 0.1 | 7.1 ± 0.2 | 0.10 |
| n             | —                | 46                           | 30                                |                                                   |
| Maternal A1C, weeks 35–40 (%) | — | 6.5 ± 0.2 | 6.9 ± 0.2 | 0.12 |
| n             | —                | 31                           | 22                                |                                                   |

Continuous variables are presented as means ± SE or geometric means with range ± 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 in adiposity in young adult 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 ± SD) in the control group of the current study (boys, 16.4 ± 1.8 kg/m²; girls, 16.4 ± 1.4 kg/m²; all, 16.4 ± 1.6 kg/m²) is slightly higher than that reported in the Avon Longitudinal Study of Parents and Children (ALSPAC) at a similar age (1.2 kg/m²) (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.

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
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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 hyperinsulinaemia 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 (3). 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.

Acknowledgments — This study was funded with the kind support of the British Heart Foundation (BHF 05/0775). The original FIGS data were collected with the support of the Chief Scientist Office (K/MRS/50/C2726) and Glasgow Royal Infirmary Endowment (05REF007).

No potential conflicts of interest relevant to this article were reported.

We acknowledge the expert help of Keith Burling and Fiona Tulloch, Core Biochemical Assay Laboratory (CBAL), Department of Clinical Biochemistry, Addenbrooke’s Hospital, Cambridge, U.K., for assay of glucose and insulin.

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