Risk Factors for Childhood Overweight in Offspring of Type 1 Diabetic Women With Adequate Glycemic Control During Pregnancy

Nationwide follow-up study in the Netherlands

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OBJECTIVE — Pregnancy in type 1 diabetic women remains a high-risk situation for both mother and child. In this study, we investigated long-term effects on body composition, prevalence of overweight, and insulin resistance in children of type 1 diabetic women who had had adequate glycemic control during pregnancy (mean A1C 6.2%), and we related their outcome to perinatal factors, including macrosomia (birth weight >90th percentile).

RESEARCH DESIGN AND METHODS — Anthropometric measurements were performed at 6–8 years of age in 213 offspring of type 1 diabetic mothers who participated in a previous nationwide study. Homeostasis model assessment of insulin resistance (HOMA-IR) was determined from a fasting blood sample in 155 of these children. In addition, we studied BMI standard deviation score (SDS) growth trajectories. Results were compared with national reference data.

RESULTS — The prevalence of overweight in the study population was not different from that in the reference population. However, children who were born macrosomic showed twice as much overweight as nonmacrosomic children. Macrosomia and maternal overweight were independent predictors of childhood overweight. Overweight children showed an increase in BMI SDS starting already after 6 months of age and had a significantly increased HOMA-IR.

CONCLUSIONS — In type 1 diabetic women with adequate glycemic control during pregnancy, long-term effects on body composition and overweight in their offspring at school age are limited and related mainly to macrosomia at birth. Possible targets for prevention of childhood overweight are fetal macrosomia, maternal overweight, and an increase in BMI SDS during the first years of life.

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Perinatal outcome in diabetic pregnancies has improved dramatically over the past decades, mainly due to improvements in maternal glycemic control and in obstetric and neonatal care (1). However, despite these improvements, pregnancy in women with type 1 diabetes remains a high-risk situation for both mother and child as we have shown in a Dutch nationwide prospective study (2). The incidence of maternal and neonatal complications such as congenital malformations (9%) and macrosomia (45%) was still high despite good prepregnancy care and overall adequate glycemic control during pregnancy (mean A1C 6.2%).

Similar rates of complications have been found in Denmark (3) and in the U.K. (4) and have also been found in type 2 diabetic pregnancies (4–6). Evidence is accumulating that an altered intrauterine environment has long-term effects on the offspring’s development. Previous studies have shown the effects of a diabetic pregnancy on several aspects of development in the offspring such as body composition and glucose homeostasis (see ref. 7 for an overview). However, most studies included small or mixed study cohorts concerning offspring of women with gestational type 1 and type 2 diabetes as well as gestational diabetes mellitus. Furthermore, most studies considered offspring within a wide range of ages or those born >20 years ago when glycemic control was not as good as in current times. Therefore, we conducted a follow-up study in our nationwide Dutch cohort of type 1 diabetic women to investigate the long-term effects of current (adequate) control and treatment during pregnancy on body composition, childhood overweight, and BMI growth trajectories in their offspring at school age. Furthermore, we related these outcomes to perinatal factors, including macrosomia at birth, and investigated insulin resistance to determine whether possible effects on body composition would have metabolic consequences already at this young age.

RESEARCH DESIGN AND METHODS — The study group consisted of offspring of type 1 diabetic mothers (ODM) who participated in our nationwide study on pregnancy outcome in the Netherlands. In that study, type 1 diabetic women presenting for antenatal care were recruited by gynecologists, internists, and diabetes nurse educators from all 118 Dutch hospitals between 1 April 1999 and 1 April 2000. Included were 324 infants born after 24 weeks of gestation. All children were born between...
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July 1999 and December 2000 (2). There were six stillbirths and three neonatal deaths, and two infants died in the first month after birth, leaving 313 children eligible for follow-up.

Elements of this follow-up study protocol were a home visit for anthropometric measurements and neurocognitive tests, a fasting blood sample on a separate occasion after the home visit, and the collection of data concerning growth patterns (results from neuropsychological evaluations will be described elsewhere). From 313 ODM eligible for follow-up, 213 (99 boys and 114 girls) participated in the investigations performed at home and 155 of them agreed to additional blood sampling. Parents of another 33 and 155 of them agreed to additional blood sampling. Parents of another 33 children were too young to be subjected to (invasive) medical research. Mean age of ODM at the time of measurements was 6.6 ± 0.2 years (range 6.2–7.3 years) and at the time of blood sampling was 7.4 ± 0.4 years (range 6.5–8.5 years). Mean time between the home visit and blood sampling was 0.8 year (range 0.1–2.1 years). At the time of the measurements, the investigator was unaware of specific characteristics of the pregnancy and neonatal outcome. Information concerning pregnancy outcome, baseline maternal characteristics, and diabetes treatment during pregnancy was subsequently obtained from the previous study (2), and parents provided information regarding their current height and weight and breast-feeding during the first week of life.

Measurements
The children’s height, weight, and waist and hip circumference were measured twice and skinfolds (biceps, triceps, suprailiac, and subscapular) were measured three times at the right side of the body, and the averages were used for analysis. BMI and waist-to-hip ratio were calculated. All measurements were performed by one investigator (M.R.) to exclude interobserver variability. A fasting blood sample was taken to determine glucose and insulin levels. All blood samples were analyzed at one research laboratory.

Definitions
Macrosomia was defined as birth weight >90th percentile corrected for gestational age, sex, and parity according to the Netherlands Perinatal Registry data from 2001 (available at http://www.pernatreg.nl). To investigate the possible effects on outcome of different levels of macrosomia, we defined moderate macrosomia as birth weight between the 90th and 97.7th percentile and severe macrosomia as birth weight >97.7th percentile. Maternal and paternal educational level was categorized as low, intermediate, or high according to international standards (8). Childhood overweight and obesity were defined according to the International Obesity Task Force cutoff points for BMI-for-age, which are incorporated in the Dutch reference BMI growth diagrams (9). The homeostasis model assessment (HOMA) formula was used to estimate fasting insulin resistance (HOMA-IR) from fasting glucose and insulin levels (10).

Statistical methods
Anthropometric measurements at 6–8 years of age and BMI data from the child welfare clinics were converted into a standard deviation score (SDS) according to the Dutch age- and sex-specific growth diagrams (11) using Growth Analyser 3.5 software (2007, Dutch Growth Foundation). An SDS of 0 equals the age- and sex-specific mean (or 50th percentile) of the national reference population.

For normally distributed variables, means ± SD were used, and differences between groups were tested by t test; otherwise, median and interquartile range and the Mann-Whitney U test were used. For categorical variables, group differences were tested by χ² analysis or Fisher exact test as appropriate. The prevalence of overweight in ODM was compared with the national reference data using a χ² goodness-of-fit test. Differences between nonmacrosomic and macrosomic ODM and between moderately and severely macrosomic ODM were analyzed with analysis of variance using age and sex (unless otherwise stated) as covariates. If residuals were not normally distributed, log-transformed geometric means were compared and then back-transformed. Multiple logistic regression analysis was performed to determine independent predictors of childhood overweight with macrosomia, sex, parity, current maternal and paternal overweight, low maternal and paternal educational level, mean pregnancy A1C >7%, and breast-feeding during the first week as predictor variables. Results are expressed as odds ratios (ORs) with 95% CIs. Data were analyzed using SPSS 15.0 for Windows (SPSS, Chicago, IL). P < 0.05 was considered to be statistically significant.

Results — Maternal age, parity, prepregnancy maternal BMI, highest achieved educational level, first/second/third trimester A1C and mean A1C during pregnancy, duration of diabetes and prevalence of diabetic complications, pre-eclampsia, severe hypoglycemia during pregnancy, and cesarean section in participating mothers were not statistically significantly different from those of nonparticipating mothers. There were no statistically significant differences in gestational age, sex, birth weight, or prevalence of macrosomia, congenital malformations, and neonatal morbidity between participating and nonparticipating children.

Compared with the national reference population, mean SDS in ODM was −0.05 ± 1.05 for height, 0.15 ± 1.12 for weight, 0.26 ± 1.01 for weight-for-height, 0.24 ± 0.98 for BMI, 0.53 ± 1.05 for waist circumference, 0.58 ± 0.99 for hip circumference, and −0.01 ± 0.96 for waist-to-hip ratio. The prevalence of both overweight and obesity in the ODM group was not significantly higher than that in the reference population at 7 years of age (9) (15.2 vs. 13.5% for overweight [P = 0.8] and 3.8 vs. 2% for obesity [P = 0.2]). Because of the low prevalence of obesity at this age, we considered overweight and obesity together as “overweight” for further analyses. Univariate analysis with possible predictors of childhood overweight showed that the prevalence of macrosomia at birth and of current maternal overweight was significantly higher in ODM who developed overweight at 6–8 years of age (Table 1). Multiple logistic regression analysis showed that macrosomia and maternal overweight were independent predictors of childhood overweight (adjusted OR
4.4 [95% CI 1.6–11.8] and 2.8 [1.2–6.6], respectively) (Table 1). HOMA-IR in ODM (mean 0.56; median 0.96 [interquartile range 0.71–1.38]) was not higher than that of healthy 7-year-old Dutch children (1.10 ± 0.53; no median mentioned) (12). There were no statistically significant differences in mean SDS for anthropometric measurements, prevalence of overweight, and mean HOMA-IR between boys and girls (data not shown).

ODM who were macrosomic at birth had increased height, weight, BMI, waist and hip circumference, and thicker skinfolds and showed more than twice as much overweight compared with nonmacrosomic ODM (26 vs. 12%, P = 0.01) (Fig. 1, Table 2). Waist-to-hip ratio and HOMA-IR did not differ between those groups. There were no statistically significant differences in anthropometric measurements, prevalence of overweight, and HOMA-IR between children who had been moderately macrosomic or severely macrosomic at birth (data not shown).

Figures 2A shows the BMI SDS growth trajectories for macrosomic and nonmacrosomic ODM. A course along the baseline in this figure equals growth along the 50th percentile line according to the reference BMI growth diagram (11). In nonmacrosomic ODM, the course of the BMI SDS was continuously around the reference population’s mean (i.e., the baseline). In macrosomic ODM, however, BMI SDS initially declined in the first months after birth but started to rise at ~7 months of age. The course of the BMI SDS growth trajectory in children who developed overweight showed an increase already at 6 months of age (Fig. 2B).

CONCLUSIONS—The results of this nationwide follow-up study showed that, with adequate control and treatment during type 1 diabetic pregnancies, the long-term effects on body composition in offspring at 6–8 years of age were limited and that fasting HOMA-IR and the prevalence of overweight were not different compared with those for the reference population. Fetal macrosomia and maternal overweight were independent predictors of childhood overweight, and the BMI SDS growth trajectory in children who developed overweight showed an increase already very early in life. Despite an increased prevalence of childhood overweight and increased anthropometric measurements, ODM who were macrosomic at birth showed no increase in insulin resistance. However, insulin resistance was significantly higher in overweight children than in children with a normal weight at 6–8 years of age.

Previous studies in offspring of diabetic mothers have shown that they are at risk for long-term effects such as overweight and type 2 diabetes (7). Most of these studies concerned mixed cohorts of women with pregestational type 1 and type 2 diabetes.
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Table 2—Anthropometric measurements and HOMA-IR in ODM according to level of macrosomia at birth (birth weight ≤90th vs. >90th percentile and birth weight 90th–97.7th vs. >97.7th percentile)

|                | n     | BW ≤90th percentile | BW >90th percentile | P     | BW 90th–97.7th percentile | BW >97.7th percentile | P     |
|----------------|-------|---------------------|---------------------|-------|--------------------------|----------------------|-------|
| Height (cm)    | 103   | 122.5 (121.6–123.4) | 124.0 (123.0–124.9) | 0.031 | 124.6 (123.2–126.0)      | 124.2 (123.1–125.3) | 0.7   |
| Weight (kg)    | 110   | 24.3 (23.7–24.8)    | 25.4 (24.8–26.0)    | 0.007 | 25.7 (24.7–26.6)         | 26.1 (25.3–27.0)    | 0.5   |
| BMI (kg/m²)*   | 46    | 15.7 (15.3–16.0)    | 16.6 (16.3–17.0)    | <0.001| 16.4 (15.9–17.0)         | 16.7 (16.3–17.2)    | 0.4   |
| Waist (cm)*    | 64    | 55.3 (54.3–56.3)    | 57.8 (56.8–58.8)    | 0.001 | 57.4 (55.8–59.0)         | 58.0 (56.7–59.4)    | 0.5   |
| Hip (cm)       | 64    | 63.0 (61.9–64.0)    | 65.7 (64.7–66.7)    | <0.001| 65.6 (64.0–67.2)         | 65.7 (64.3–67.0)    | 0.9   |
| WHR            | 64    | 0.88 (0.87–0.89)    | 0.88 (0.87–0.89)    | 0.9   | 0.88 (0.87–0.89)         | 0.89 (0.88–0.90)    | 0.4   |
| S4S (mm)*      | 64    | 27.9 (26.0–29.9)    | 31.9 (29.8–34.2)    | 0.006 | 31.0 (28.0–34.3)         | 32.7 (29.9–35.6)    | 0.4   |
| HOMA-IR*       | 64    | 0.93 (0.79–1.09)    | 0.93 (0.79–1.01)    | 0.6   | 0.93 (0.73–1.18)         | 0.85 (0.68–1.05)    | 0.6   |

Numbers represent adjusted means with 95% CI or *back-transformed geometric means with 95% CI if data were log transformed for analysis. All means were adjusted for age and sex, height was also adjusted for maternal and paternal height, and weight was also adjusted for height. BW, birth weight; S4S, sum of four skinfolds; WHR, waist-to-hip ratio.

Figure 2—BMI SDS growth trajectories in macrosomic and nonmacrosomic ODM (A) and in overweight and normal weight ODM (B). Data are means ± SEM.

Offspring of type 1 diabetic women as well as gestational diabetes mellitus. Our cohort concerned offspring of exclusively type 1 diabetic women who were well prepared before pregnancy (84% planned pregnancies and 70% prepregnancy folic acid supplementation) and achieved adequate glycemic control during pregnancy (mean A1C 6.2%) (2). By extrapolating Freinkel’s hypothesis on fuel-mediated teratogenesis (13), it could be hypothesized that with adequate glycemic control during pregnancy, long-term outcome in the offspring should be better. Indeed, the prevalence of childhood overweight in ODM was not higher, and the effects on body composition were minimal compared with those for the reference population, especially in the children who were born with a birth weight appropriate for gestational age. Further follow-up and comparison with more recent reference data (as the reference growth diagrams date from 1997) should show whether the slightly higher SDS of some anthropometric measurements in ODM is a result of a continuing positive secular growth change in the Netherlands (14) or should be attributed to the diabetic pregnancy.

There seemed to be a clear cutoff increase in the prevalence of overweight in infants with a birth weight >90th percentile (Fig. 1). Multiple logistic regression analysis with possible predictors for childhood overweight showed that fetal macrosomia, together with maternal overweight, was indeed an independent predictor for overweight in ODM. These results are in accordance with other studies showing that childhood overweight was associated with fetal macrosomia in children of type 1 diabetic women (15,16) and with maternal overweight as...
well in children of women with gestational diabetes mellitus (17,18). The number of infants with a birth weight <20th percentile (n = 6) (Fig. 1) was too small to determine whether there was also an increased prevalence of overweight in the low birth weight categories, as has been found in some studies (19).

Despite differences in body composition between macrosomic and nonmacrosomic ODM, there was no difference in fasting HOMA-IR. Further follow-up may show whether these children will develop insulin resistance or impaired insulin secretion later in life. Interestingly, anthropometric measurements, the prevalence of childhood overweight, and HOMA-IR in ODM who were severely macrosomic at birth (birth weight >97.7th percentile) were not increased compared with those of moderately macrosomic ODM (birth weight 90th–97.7th percentile). A possible explanation for this observation could be that glycemic control during pregnancy in mothers of severely macrosomic children was not different from that in mothers of moderately macrosomic children (A1C 6.37 ± 1.02 and 6.43 ± 0.81, respectively, P = 0.7). Follow-up is necessary to show possible differences in the further development between severely macrosomic and moderately macrosomic children.

Breast-feeding has recently been shown to protect against later overweight in children of type 1 diabetic mothers (15). In contrast, others have found that ingestion of breast milk from diabetic mothers, especially in the first week of life, may increase the risk of becoming overweight (20). In our cohort, we did not find an effect of early breast-feeding on overweight at 1 year of age (21) nor at 6–8 years of age, although our study lacked detailed information on volume of breast milk ingested, as was used by Rodekamp et al. (20).

The BMI SDS growth trajectory in ODM who had developed overweight at school age showed an initial decline after birth, followed by a steep rise after ~6 months of age. Erikkson et al. (22) found a similar rise in the BMI z score growth pattern in the first years of life in individuals who developed type 2 diabetes later in life, especially if they had a higher birth weight. In addition, in our study infants with a high birth weight showed an initial decline in BMI SDS followed by an increase after ~6 months of age (although this increase was smaller than that in the ODM who developed overweight at school age). Touger et al. (23) and Silverman et al. (24) showed comparable growth patterns in ODM. Based on the findings by Eriksson et al. (22), the BMI SDS growth trajectories in our cohort may suggest that these children are at risk of developing type 2 diabetes later in life, although this suggestion has to be substantiated in our population at further follow-up. Despite the latter limitation, we hypothesize that these findings may be helpful in identifying those children of diabetic mothers who are at risk for future health problems.

In summary, our findings suggest that in our cohort of type 1 diabetic women with adequate glycemic control during pregnancy, the long-term effects on body composition of their offspring at 6–8 years of age are limited. The prevalence of overweight is comparable to that in the reference population, provided that the child is born with a birth weight appropriate for gestational age. However, because of the high prevalence of macrosomia and its clear association with the development of childhood overweight, the prevention of macrosomia remains important, more so because overweight children showed increased insulin resistance at 6–8 years of age compared with that in normal weight children. It is possible that continuous glucose monitoring during pregnancy may be an effective tool to reduce the risk of fetal macrosomia (25). In addition, reducing maternal overweight could be a target for the prevention of childhood overweight in ODM, and close monitoring of the infants’ BMI SDS growth trajectory in the first years of life may be helpful in identifying those ODM at risk of developing overweight at school age. Further research is needed to assess the possible influence of such interventions on the prevalence of childhood overweight in ODM.

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