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.

Short running title: Offspring of type 1 diabetic women

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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 HbA1c 6.2%) and we related their outcome to perinatal factors, including macrosomia (birth weight ≥p90).

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. HOMA insulin resistance was determined from a fasting blood sample in 155 of these children. Additionally, we studied BMI standard deviation score (SDS) growth trajectories. Results were compared to 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 non-macrosomic 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 insulin resistance.

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 mainly related to macrosomia at birth. Possible targets for prevention of childhood overweight are fetal macrosomia, maternal overweight and an increase of BMI SDS during the first years of life.
Offspring of type 1 diabetic women

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 pre-pregnancy care and overall adequate glycemic control during pregnancy (mean HbA1c 6.2%). Similar rates of complications have been found in Denmark (3) and in the United Kingdom (4) and have also been found in type 2 diabetic pregnancies (4-6). Evidence is accumulating that an altered intra-uterine 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 (6) and (7) for an overview). However, most studies included small or mixed study cohorts concerning offspring of type 1, type 2 and/or gestational diabetic women. Furthermore, most studies considered offspring within a wide range of ages or born over 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

Study population. 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 April 1st 1999 and April 1st 2000. 324 Infants born after 24 weeks of gestation were included. All children were born between July 1999 and December 2000 (2). There were 6 stillbirths, 3 neonatal deaths and 2 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 evaluation will be described elsewhere). From 313 ODM eligible for follow-up, 213 (99 boys, 114 girls) participated in the investigations performed at home and 155 of them agreed to additional blood sampling. Parents of another 33 ODM provided only growth data, resulting in a total participation rate of 79% (246/313), with 17 children lost to follow-up and 50 non-participants. The most frequent reason for
parents for not participating in the investigations at home and/or blood sampling was the consideration that their children were too young to be subjected to (invasive) medical research. Mean age of ODM at time of measurements was 6.6±0.2 years (range 6.2-7.3) and at time of blood sampling 7.4±0.4 years (range 6.5-8.5). Mean time between the home visit and blood sampling was 0.8 years (range 0.1-2.1). 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 were subsequently obtained from the previous study (2) and parents provided information regarding their current height and weight and breast feeding in the neonatal period. Information concerning growth in the offspring was derived from child welfare clinics, which monitor growth during childhood at 1, 2, 3, 4, 6, 7½, 9, 11, 14, 18, 24, 36 and 45 months of age. BMI was calculated from height and weight at these ages. This study was approved by the medical ethics committee of the University Medical Center Utrecht and parents gave written informed consent.

**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.perinatreg.nl). To investigate 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 cut-off points for BMI-for-age which are incorporated in the Dutch reference BMI growth diagrams (9). The Homeostatic 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, as well as 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 zero equals the age- and sex specific mean (or 50th percentile) of the national reference population. For normally distributed variables mean and standard deviation (SD) were used and differences between groups were tested by t-test; otherwise median and interquartile range (IQR) and the Mann-Whitney test were used. For categorical variables group differences were tested by χ²-analysis or Fisher’s Exact test as appropriate. The prevalence of overweight in ODM was compared to the
national reference data using a \( \chi^2 \)-goodness-of-fit test. Differences between non-macrosomic 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 HbA1c \( \geq 7\% \) and breast feeding during the first week as predictor variables. Results were expressed as odds ratio (OR) with 95% confidence interval (CI). Data were analyzed using SPSS 15.0 for Windows® (SPSS Inc., Chicago, Illinois). A p-value of less than 0.05 was considered to be statistically significant.

RESULTS

Maternal age, parity, pre-pregnancy maternal BMI, highest achieved educational level, 1\textsuperscript{st}/2\textsuperscript{nd}/3\textsuperscript{rd} trimester HbA1c and mean HbA1c 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 different from non-participating 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 non-participating children.

Compared to 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 were not significantly higher than 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 were 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 (95% CI 1.2-6.6) respectively, Table 1). HOMA-IR in ODM (mean±SD 1.05±0.56; median [IQR] 0.96 [0.71-1.38]) was not higher compared to healthy 7 year old Dutch children (mean±SD 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, thicker skinfolds and showed more than twice as much overweight compared to non-macrosomic ODM (26 vs. 12%, p=0.01; Figure 1). 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 (Figure 1, Table 2).

Figure 2A shows the BMI SDS growth trajectories for macrosomic and non-macrosomic 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 non-macrosomic 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 about 7 months of age. The course of the BMI SDS growth trajectories in children who had been moderately macrosomic or severely macrosomic at birth was similar (data not shown). Furthermore, we determined HOMA-IR and the BMI SDS growth trajectory in ODM who developed overweight to investigate how these differed from ODM with a normal weight at 6-8 years of age. HOMA-IR was higher in overweight ODM compared to normal weight ODM (adjusted means with 95% CI 1.20 (0.92-1.57) and 0.85 (0.76-0.95), respectively, p=0.019) and the BMI SDS trajectory in overweight ODM showed (after an initial decline) an increase starting already at 6 months of age (Figure 2B).

CONCLUSIONS

The results of this nationwide follow-up study showed that, with adequate control and treatment during type 1 diabetic pregnancies, long term effects on body composition in the offspring at 6-8 years of age were limited and that fasting HOMA insulin resistance as well as prevalence of overweight were not different compared to 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 compared to 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 as well as gestational diabetes. Our cohort concerned offspring of exclusively type 1 diabetic women who were well prepared before pregnancy (84% planned pregnancies, 70% pre-pregnancy folic acid supplementation) and achieved adequate glycemic control during pregnancy (mean HbA1c 6.2%) (2). Extrapolating Freinkel’s hypothesis on fuel-mediated teratogenesis (13), it could be hypothesized that in case of adequate glycemic control during pregnancy, long term outcome in the offspring should be better. Indeed, prevalence of childhood overweight in ODM was not higher and effects on anthropometric measurements were minimal when compared to 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 are 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 cut-off increase in prevalence of overweight in infants with a birth weight ≥p90 (Figure 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 that showed 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 gestational diabetic women (17, 18). The number of infants with a birth weight <p20 (n=5, Figure 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 non-macrosomic ODM, there was no difference in fasting HOMA insulin resistance. Further follow-up may show if these children will develop insulin resistance or impaired insulin secretion later in life, as has been shown by others (7).

Interestingly, anthropometric measurements, prevalence of childhood overweight and HOMA insulin resistance in ODM who were severely macrosomic at birth (birth weight ≥p97.7) were not increased compared to moderately macrosomic ODM (birth weight p90-p97.7). A possible explanation for this observation could be that glycemic control during pregnancy in mothers of severely macrosomic children was not different from mothers of moderately macrosomic children (mean HbA1c 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 in this study 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 about 6 months of age. Eriksson et al. 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 (22). Also in our study infants with a high birth weight showed an initial decline in BMI SDS followed by an increase after about 6 months of age (although this increase was smaller than in the ODM who developed overweight at school age). Touger et al. and Silverman et al. showed comparable growth patterns in ODM (23, 24). Based on the findings by Eriksson et al., the BMI SDS growth trajectories in our cohort may suggest that these children are at risk for developing type 2 diabetes later in life, although this 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 conclusion, our findings suggest that in our cohort of type 1 diabetic women with adequate glycemic control during pregnancy, long term effects on body composition at 6-8 years of age are limited. The prevalence of overweight is comparable to 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, prevention of macrosomia remains important. The more so since overweight children showed an increased insulin resistance at 6-8 years of age compared to normal weight children. Possibly continuous glucose monitoring during pregnancy may be an effective tool to reduce the risk of fetal macrosomia (25). Also reducing maternal overweight could be a target for prevention of childhood overweight in ODM. Additionally, close monitoring of the infants’ BMI SDS growth trajectory in the first years of life may be helpful in identifying those ODM at risk for 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.

ACKNOWLEDGEMENTS

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Disclosure. All authors state that they have no relevant conflict of interest to disclosure.
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Table 1. Possible risk factors for developing childhood overweight in ODM.

<table>
<thead>
<tr>
<th></th>
<th>Normal weight (n=171*)</th>
<th>Overweight (n=40)</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parity (multiparity)</td>
<td>47</td>
<td>48</td>
<td>0.8</td>
<td>0.8 (0.4-2.0)</td>
</tr>
<tr>
<td>Sex (girls)</td>
<td>51</td>
<td>63</td>
<td>0.2</td>
<td>0.9 (0.4-2.2)</td>
</tr>
<tr>
<td>Mean pregnancy HbA1c ≥7%</td>
<td>15</td>
<td>21</td>
<td>0.5</td>
<td>1.4 (0.5-3.8)</td>
</tr>
<tr>
<td>Birth weight ≥p90</td>
<td>47</td>
<td>70</td>
<td>0.01</td>
<td>4.4 (1.611.8)</td>
</tr>
<tr>
<td>Current maternal BMI ≥25</td>
<td>37</td>
<td>59</td>
<td>0.02</td>
<td>2.8 (1.2-6.6)</td>
</tr>
<tr>
<td>Current paternal BMI ≥25</td>
<td>49</td>
<td>63</td>
<td>0.1</td>
<td>1.6 (0.7-3.8)</td>
</tr>
<tr>
<td>Low maternal education</td>
<td>21</td>
<td>23</td>
<td>0.9</td>
<td>0.8 (0.2-2.4)</td>
</tr>
<tr>
<td>Low paternal education</td>
<td>18</td>
<td>30</td>
<td>0.1</td>
<td>2.7 (0.9-8.1)</td>
</tr>
<tr>
<td>Breast feeding at 1 week</td>
<td>66</td>
<td>59</td>
<td>0.4</td>
<td>0.7 (0.3-1.6)</td>
</tr>
</tbody>
</table>

Numbers represent percentages, p-value for χ²-test and adjusted OR’s with 95% CI for multiple logistic regression analysis. *Data on weight (and thus BMI) are missing for 2 children.

Table 2. Anthropometric measurements and HOMA-IR in ODM according to level of macrosomia at birth (birth weight <p90 vs. ≥p90 and birth weight p90-p97.7 vs. ≥p97.7)

<table>
<thead>
<tr>
<th></th>
<th>BW &lt;p90 (n=103)</th>
<th>BW ≥p90 (n=110)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>122.5 (121.6-123.4)</td>
<td>124.0 (123.0-124.9)</td>
<td>0.031</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>24.3 (23.7-24.8)</td>
<td>25.4 (24.8-26.0)</td>
<td>0.007</td>
</tr>
<tr>
<td>BMI (kg/m²) *</td>
<td>15.7 (15.3-16.0)</td>
<td>16.6 (16.3-17.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist (cm) *</td>
<td>55.3 (54.3-56.3)</td>
<td>57.8 (56.8-58.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hip (cm)</td>
<td>63.0 (61.9-64.0)</td>
<td>65.7 (64.7-66.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WHR</td>
<td>0.88 (0.87-0.89)</td>
<td>0.88 (0.87-0.89)</td>
<td>0.9</td>
</tr>
<tr>
<td>S4S (mm) *</td>
<td>27.9 (26.0-29.9)</td>
<td>31.9 (29.8-34.2)</td>
<td>0.006</td>
</tr>
<tr>
<td>HOMA-IR *</td>
<td>0.93 (0.79-1.09)</td>
<td>0.89 (0.79-1.01)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>BW p90-p97.7 (n=46)</th>
<th>BW ≥p97.7 (n=64)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>124.6 (123.2-126.0)</td>
<td>124.2 (123.1-125.3)</td>
<td>0.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>25.7 (24.7-26.6)</td>
<td>26.1 (25.3-27.0)</td>
<td>0.5</td>
</tr>
<tr>
<td>BMI (kg/m²) *</td>
<td>16.4 (15.9-17.0)</td>
<td>16.7 (16.3-17.2)</td>
<td>0.4</td>
</tr>
<tr>
<td>Waist (cm) *</td>
<td>57.4 (55.8-59.0)</td>
<td>58.0 (56.7-59.4)</td>
<td>0.5</td>
</tr>
<tr>
<td>Hip (cm)</td>
<td>65.6 (64.0-67.2)</td>
<td>65.7 (64.3-67.0)</td>
<td>0.9</td>
</tr>
<tr>
<td>WHR</td>
<td>0.88 (0.87-0.89)</td>
<td>0.89 (0.88-0.90)</td>
<td>0.4</td>
</tr>
<tr>
<td>S4S (mm) *</td>
<td>31.0 (28.0-34.3)</td>
<td>32.7 (29.9-35.6)</td>
<td>0.4</td>
</tr>
<tr>
<td>HOMA-IR *</td>
<td>0.93 (0.73-1.18)</td>
<td>0.85 (0.68-1.05)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

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, weight was also adjusted for height. BW = birth weight; WHR = waist-to-hip ratio; S4S = sum of 4 skinfolds; HOMA-IR = HOMA insulin resistance.
FIGURE LEGENDS

FIGURE 1  Prevalence of childhood overweight according to birth weight percentile. The total bars represent the percentage of ODM born per birth weight percentile group, the dark parts represent the percentage of ODM with overweight at school age (* weight and thus BMI is missing for one child in these birth weight percentile groups).

FIGURE 2  BMI SDS growth trajectories in macrosomic and non-macrosomic ODM (Figure A) and in overweight and normal weight ODM (Figure B). Data are presented as means with standard error of the mean (SEM).

Fig 1
Offspring of type 1 diabetic women

Fig 2

A
- - macrosomic ODM
- - non-macrosomic ODM

B
- - overweight ODM
- - normal weight ODM