Rapid neonatal weight gain increases risk of childhood overweight in offspring of diabetic mothers

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Abstract

Aim: Increased neonatal weight gain has been suggested as risk factor for later overweight. Offspring of diabetic mothers (ODM) have a long-term increased overweight risk. However, the role of early postnatal weight gain for later overweight has not been addressed so far in ODM. We investigated whether increased weight gain during the first 4 months is related to later overweight in ODM.

Methods: Determinants of childhood overweight and neonatal weight gain were analyzed in 152 ODM from the Kaulsdorf Cohort Study by MANOVA and regression analyses.

Results: Independent of birth weight, weight gain during the first 4 months was positively related to childhood relative body weight (P=0.001). Each 100 g-increase in weight during this period increased overweight risk by 65% (95% CI: 10–247%). ODM with rapid early weight gain had a more than six-fold increased risk of later overweight (OR: 6.77; 95% CI: 1.36–33.6). Early neonatal intake of breast milk from metabolically healthy mothers protected from rapid early weight gain (P=0.03).

Conclusions: Increased weight gain during the first 4 months of life is a strong, independent risk factor for childhood overweight in ODM. Preventing nutritionally-induced rapid early weight gain in ODM might be a promising strategy to lower their long-term overweight risk.

Keywords: Breastfeeding; diabetic pregnancy; neonatal weight gain; overweight; overweight prevention; perinatal programming.

Introduction

Offspring of diabetic mothers (ODM) are a population at increased overweight risk [5, 23, 27, 31]. However, exact pathophysiological mechanisms that lead to this increased risk are not completely understood. Especially, it is widely unknown whether and to what extent early postnatal factors may contribute [29]. An increasing body of data indicates that in the general population, increased early weight gain is a risk factor for later overweight. Associations between infantile growth and obesity risk in childhood, adolescence, and up to adulthood have been shown [11, 22, 32, 33]. In particular, in two independent large population-based studies Stettler et al. observed that high weight gain during the first 4 months of life has a strong influence on risk of overweight during later childhood and adolescence [32, 33].

So far, the role of early postnatal weight gain in the development and “perinatal programming” of overweight in ODM has not been investigated. Moreover, even in the studies performed in general populations it is not clear which causal factors might stand behind the association between increased early weight gain and increased overweight risk later on. As breastfed infants are leaner during the first months of life [6], and breastfeeding is known to protect against later overweight [15], the effects of early weight gain on later overweight risk are likely to be attributable to the mode of neonatal nutrition. Here, we analyzed the impact of weight gain during the first 4 months of life, a developmental period suggested to be of particular importance in studies performed in general populations [32, 33], on overweight risk in ODM of the prospective Kaulsdorf Cohort Study (KCS) [25–27], and aimed at identifying underlying causal factors.

Methods

Participants

The KCS is a prospective study on consequences of exposure to maternal diabetes during pregnancy for the offspring’s development. General data on the cohort and its sub-cohorts have been previously described in detail [25–27]. In total, 200 children of women with type 1 diabetes and 117 children of women with gestational diabetes (GDM) participated, born during 1980–1989 at the Clinic of Obstetrics and Gynecology, Berlin-Kaulsdorf, Germany (former East Germany). Each mother had the opportunity to let her child...
participate in pediatric follow-up including regular annual physical reexaminations. Whenever data were available for more than one age, we analyzed results for the highest available age, as the development of overweight is a progressive process throughout childhood [17]. A total of 152 infants were followed up with data on infant weight gain as well as anthropometric data from later follow-up investigations.

**Maternal data**

Maternal data included age and pre-pregnancy body mass index (BMI). Socioeconomic/educational status (SES) was categorized by maternal and paternal occupation: unemployed, manual worker, non-manual worker without high school diploma, or non-manual worker with high school diploma. Gestational age and birth weight were extracted from birth records.

GDM was diagnosed between 26th and 28th gestational weeks, as described previously [25–27]. Glucose homeostasis was monitored weekly by 24-h day-night glucose profiles at the clinic. During monitoring, blood glucose was measured every 2 h (glucose oxidized weekly by 24-h day-night glucose profiles at the clinic. During monitoring, blood glucose was measured every 2 h (glucose oxidase-peroxidase method). Women maintaining mean 24-h profiles ≤ 5.5 mmol/L were treated with diet. When a mean profile was ≥ 5.5 mmol/L, insulin therapy was initiated [25–27]. Diurnal blood glucose profiles were used to monitor metabolism in women with type 1 diabetes too. Overall daily mean glucose levels were calculated from data obtained in the middle of the third trimester (34th gestational week) and the first week post partum, respectively.

**Nutritional data**

After delivery, all women stayed with their newborns at the maternity ward of the clinic for at least 1 week. Ad libitum breastfeeding was advised to all mothers. Depending on the status of maternal lactation, when necessary (as judged by the pediatrician at the ward) a supplementary feeding with banked donor breast milk was offered to the newborn. Donor breast milk was provided by the local center for donation of breast milk at the Clinic of Pediatrics Lindenhof, Berlin, former East Germany. Women with diabetes were excluded from donating breast milk; therefore, all banked breast milk was “non-diabetic” milk [25].

Nutritional data during the first neonatal week were assessed as previously described [25, 26]. In brief, children were weighed before and after every nursing during the first 7 days of life, and mean volume of milk ingested per day was calculated by summing up the volumes ingested during the first neonatal week and dividing by 7.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>25.4 ± 0.41</td>
</tr>
<tr>
<td>Pre-pregnancy BMI (kg/m²)</td>
<td>23.9 ± 0.35</td>
</tr>
<tr>
<td>Type of diabetes (GDM/type 1 diabetes; %)</td>
<td>74/26</td>
</tr>
<tr>
<td>Parity (1^st/2^nd/3^rd/4^th or more; %)</td>
<td>63/23/12/2</td>
</tr>
<tr>
<td>Maternal socioeconomic status (unemployed/manual/non-manual without diploma/non-manual with diploma; %)</td>
<td>1/21/61/17</td>
</tr>
<tr>
<td>Paternal socioeconomic status (unemployed/manual/non-manual without diploma/non-manual with diploma; %)</td>
<td>1/55/34/10</td>
</tr>
<tr>
<td>3^rd trimester mean blood glucose in GDM/type 1 diabetes (mmol/L)</td>
<td>4.93 ± 0.13/4.54 ± 0.11</td>
</tr>
<tr>
<td>1^st week post partum mean blood glucose in GDM/type 1 diabetes (mmol/L)</td>
<td>5.07 ± 0.14/6.81 ± 0.20</td>
</tr>
<tr>
<td>Mode of delivery (spontaneous/vacuum extraction/forceps delivery/cesarean section; %)</td>
<td>61/10/55/24</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38 ± 0.11</td>
</tr>
</tbody>
</table>

*Data are means ± SEM, or %, as appropriate.*

*BMI = body mass index, GDM = gestational diabetes.*

**Anthropometry at follow-up**

At regular follow-up examinations at 1–4 years, body weight and length or height, respectively, were recorded. Subtracting birth weight from weight at age 4 months revealed weight gain until 4 months of age. Relative body weight (RBW) in childhood was calculated in relation to age- and sex-related standard population measures [12], rounded to year, as follows: relative weight (individual weight divided by median standard weight for age and sex) divided by relative height (individual height divided by median standard height for age and sex) × 100 [23, 25, 27, 31]. RBW > 110% was defined as overweight [2, 25, 27].

In all cases, informed consent was given. All procedures were in accordance with the local ethical standards and the Helsinki Declaration of 1975, revised in 1983, and were approved by the local Ethical Committee.

**Statistical analysis**

Results are presented as means ± SD and/or SEM, or %, as appropriate. Multivariate analysis of variance (MANOVA) was used to investigate the effect of covariates on metric variables. Logistic regression analysis revealed odds ratios (OR) with 95% confidence intervals (95% CI). Linear regression analysis was performed to calculate β and P. SPSS 18.0 software was used for all calculations.

**Results**

Descriptive population statistics are presented in Tables 1 and 2. As a first analytical step, we plotted relative body weight at the follow-up investigations during childhood as a function of birth weight and weight gain during the first 4 months of life, respectively. Figure 1A shows that both variables influenced childhood body weight: the higher birth weight as well as 4-months weight gain, the higher was the relative body weight at follow-up. Moreover, those infants who were in the highest tertile of birth weight as well as in the highest tertile of 4-months weight gain, were those who had the highest relative body weight during later childhood. MANOVA revealed significant independent effects of birth weight (P < 0.001) as well as weight gain until 4 months (P = 0.001) on childhood relative body weight.

We then performed univariate and multivariate logistic regression analyses to obtain a quantitative estimate of
Table 2  Neonatal and follow-up parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal parameters</td>
<td></td>
</tr>
<tr>
<td>Sex (male/female; %)</td>
<td>50/50</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.39 ± 0.05</td>
</tr>
<tr>
<td>SGA/AGA/LGA newborns (%)</td>
<td>14/72/14</td>
</tr>
<tr>
<td>Intake of &quot;diabetic&quot; breast milk (g/day; 1st week)</td>
<td>90.7 ± 5.12</td>
</tr>
<tr>
<td>Intake of &quot;non-diabetic&quot; banked breast milk (g/day; 1st week)</td>
<td>33.6 ± 3.05</td>
</tr>
<tr>
<td>Duration of breastfeeding (weeks)</td>
<td>13.7 ± 1.24</td>
</tr>
<tr>
<td>Weight gain until the end of month 4 (g)</td>
<td>2971 ± 73.5</td>
</tr>
<tr>
<td>Follow-up parameters</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>2.14 ± 0.09</td>
</tr>
<tr>
<td>Relative body weight (%)</td>
<td>103 ± 1.01</td>
</tr>
<tr>
<td>Overweight (%)</td>
<td>27</td>
</tr>
</tbody>
</table>

Data are means ± SEM, or %, as appropriate.

SGA = small for gestational age, AGA = appropriate for gestational age, LGA = large for gestational age.

the relation between early weight gain and later childhood overweight risk. After having calculated unadjusted OR with 95% CI for all variables (Table 3; first row from left), we constructed model 1 which included a minimal set of confounders, namely: birth weight, gestational age and sex (second row). Weight gain until the end of the fourth month of life was significantly associated with risk of overweight in later childhood, after adjustment for these confounding variables (OR: 1.52; 95% CI: 1.06–2.19). Then, model 2 was calculated which included further biologically plausible confounders of the relation between early weight gain and later overweight risk. In this fully adjusted model the OR further increased to a value of 1.65 (1.10–2.47), indicating that each 100 g-increase in weight during the first 4 months of life increased risk of overweight in childhood significantly by 65%. Performing a model comparable to the one used by Stettler and colleagues [33], which included adjustment for birth weight, gestational age, sex, parity, maternal BMI, maternal social status and age, revealed an OR for overweight by 100 g of weight gain until the end of the fourth month of life of 1.68 (1.14–2.48).

In order to allow the estimation of a more practicable “threshold” of early weight gain, we additionally aimed at calculating an OR for overweight due to “rapid” early weight gain. For this purpose, we calculated the risk of childhood overweight in those study participants who had a neonatal weight gain above mean±SD of the whole cohort. Figure 1B shows that infants who had a respective “rapid” early weight gain, i.e., a 4-months weight gain above the mean±SD of the cohort, had a more than six-fold increased risk of overweight during childhood, as compared to the reference range of mean±SD (OR: 6.77; 95% CI: 1.36–33.6). In contrast, those children who had a weight gain below mean–SD showed a clearly decreased tendency to become overweight during later life (OR: 0.14; 95% CI: 0.02–1.12). These results were found to be independent of birth weight, gestational age, sex, type of maternal diabetes, maternal BMI, SES, parity, maternal age and mode of delivery, according to the adjusted analyses.

In a final analytical step, we were interested to know which factors might have influenced the extent of weight gain during the first 4 months of life. Therefore, we developed multivariate linear regression models with weight gain until the end of the fourth month of life as outcome parameter, including all potentially explanatory anthropometric, nutritional and socioeconomic variables which were significantly and independently associated with this parameter in the multivariate model. Besides birth weight (β = 0.37; P = 0.001), only the volume of donor breast milk ingested during the first week of life was found to be an independent predictor (β = 0.24; P = 0.03), indicating that a higher early intake of breast milk from metabolically healthy mothers prevented increased early weight gain.
Table 3  Risk of overweight in childhood by weight gain until 4 months of life: univariate and multivariate analyses (OR and CI).

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th>Multivariate analysis: model 1</th>
<th>Multivariate analysis: model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain (per 100 g/month)</td>
<td>1.12 (0.86–1.46)</td>
<td>1.52 (1.06–2.19)</td>
<td>1.65 (1.10–2.47)</td>
</tr>
<tr>
<td>Birth weight (per kg)</td>
<td>2.07 (1.13–3.80)</td>
<td>9.72 (3.03–31.2)</td>
<td>9.57 (2.79–32.8)</td>
</tr>
<tr>
<td>Gestational age (per week)</td>
<td>0.98 (0.75–1.27)</td>
<td>0.58 (0.37–0.92)</td>
<td>0.56 (0.35–0.90)</td>
</tr>
<tr>
<td>Sex (female vs. male)</td>
<td>0.71 (0.35–1.47)</td>
<td>1.06 (0.35–3.18)</td>
<td>1.22 (0.37–3.98)</td>
</tr>
<tr>
<td>Type of maternal diabetes (T1DM vs. GDM)</td>
<td>1.69 (0.78–3.70)</td>
<td>–</td>
<td>1.92 (0.36–10.1)</td>
</tr>
<tr>
<td>Maternal SES (four grades)</td>
<td>0.75 (0.44–1.31)</td>
<td>–</td>
<td>0.59 (0.20–1.76)</td>
</tr>
<tr>
<td>Paternal SES (four grades)</td>
<td>1.41 (0.85–2.33)</td>
<td>–</td>
<td>1.81 (0.74–4.43)</td>
</tr>
<tr>
<td>Parity (four grades)</td>
<td>1.09 (0.77–1.56)</td>
<td>–</td>
<td>1.26 (0.65–2.46)</td>
</tr>
<tr>
<td>Maternal age (per year)</td>
<td>0.99 (0.92–1.06)</td>
<td>–</td>
<td>1.00 (0.87–1.16)</td>
</tr>
<tr>
<td>Maternal BMI (per kg/m²)</td>
<td>0.96 (0.87–1.05)</td>
<td>–</td>
<td>0.90 (0.75–1.08)</td>
</tr>
<tr>
<td>Mode of delivery (four modes)</td>
<td>0.99 (0.74–1.31)</td>
<td>–</td>
<td>1.43 (0.86–2.39)</td>
</tr>
</tbody>
</table>

T1DM= type of maternal diabetes, GDM=gestational diabetes, SES=socioeconomic/educational status, BMI=body mass index.

Discussion

Offspring of diabetic mothers are at increased risk of becoming overweight during later life. An increasing body of data obtained in the general population suggests that rapid early weight gain increases later overweight risk. Therefore, we analyzed the impact of weight gain during the first 4 months of life, a period which has been repeatedly proven to be particularly important in the general population, on childhood overweight in a cohort of ODM. Our main observation is that rapid weight gain from birth to the age of 4 months shows a significant independent effect on later overweight risk in ODM, which appeared to be even stronger than reported for general populations. Remarkably, rapid early weight gain was prevented by early neonatal intake of breast milk from metabolically healthy mothers.

In ODM, increased birth weight, resulting from exposure to the hyperglycemic intrauterine milieu, is known to be associated with increased overweight risk during later life [27, 31]. Fetal hyperinsulinism, resulting from overstimulation of the fetal pancreatic B-cells with consecutive B-cell hyperplasia, has been identified to be an etiopathogenetic key factor for these outcomes [1, 8]. Animal experiments show that perinatal hyperinsulinism induces malorganization and consecutive malfunction of hypothalamic regulatory centers of food intake, body weight and metabolism which might play a central role here [8], being preventable by normalization of maternal glucose metabolism [13]. Moreover, fetal hyperinsulinism seems also to be related to other deleterious outcomes beyond overweight, such as benign and even malignant tumor growth [34]. The predisposing influence of prenatal excessive (“rapid”) weight gain has been clearly confirmed in our study by a strong correlation between birth weight and later overweight risk. In the final model, each 1 kg increase in birth weight was associated with a more than nine-fold increased risk of overweight during childhood. In a recent meta-analysis of all published studies, Philips et al. confirmed an increased risk of overweight in ODM [24]. Moreover, a profound impact of increased prenatal weight gain and resulting birth weight, i.e., overweight at birth, on later risk of overweight is also present in the general population [16]. Philips et al. found that part of the effect of GDM on childhood overweight risk might be attributable to maternal overweight [24], which is plausible, e.g., given the role of overweight as major risk factor for developing GDM. Here, we did not observe an independent effect of maternal pre-pregnancy BMI on overweight risk in ODM. Noteworthy, however, women in our cohort had a mean BMI within the normal range, i.e., below 25 kg/m², possibly explaining lack of an independent, additional effect of maternal BMI on the offspring’s adipogenic outcome. Accordingly, and worthy to note, our observations underline that maternal-fetal hyperglycemia may increase the immediate as well as long-term overweight risk in affected offspring even irrespective of maternal overweight.

Given the strong impact of excessive prenatal weight gain and fat deposition on later overweight risk, it appears to be of similar importance to ask whether such a relation also exists between neonatal weight gain and later overweight. Moreover, while prenatal weight gain has been suggested to be even a target for therapeutic guidance in women with GDM [3, 20], comparable approaches are completely missing regarding neonatal weight gain in ODM. Although research on the relation between early weight gain and later overweight risk has only recently achieved broad attention, first studies on this subject date back to the 1970s. Already in 1977, Dörner et al. reported that excessive weight gain during the first months of life was a decisive risk factor for later overweight ([7, 9, 10]; for review see [8]). During recent years, the body of data showing that increased early weight gain is an independent risk factor for later overweight has been increasing continuously. A number of groups looked at the predictive value of weight gain during relatively large time windows of early childhood, like, e.g., Ong et al. who showed an association between weight gain from birth to the age of 2 years and obesity risk at the age of 5 years [22]. Other studies focussed on the impact of weight gain during infancy, demonstrating an independent influence of weight gain from birth to the age of 6 months on body mass index at the age of 17 years [11]. Stettler and colleagues looked at an even smaller time window and observed that higher weight gain from birth until the age of 4 months is associated with increased overweight risk at the age of 7 years [33]. Moreover, this group could replicate their findings in a second independent and large population-based study [32].
In accordance with the results of the latter studies, in our analysis in ODM weight gain until the end of the fourth month showed a significant impact on later overweight, uncovered after adjustment for birth weight and gestational age which both are established confounders of the investigated relationship. Performing a model identical to the one used by Stettler and colleagues [33], analysis revealed an OR for overweight by 100 g of weight gain until the end of the fourth month of life of 1.68 (1.14–2.48) in our cohort. Thus, the effect of weight gain until the end of the fourth month of life on later overweight risk was even stronger in ODM than observed in a general population [33], where an OR of only 1.38 (95% CI 1.32–1.44) occurred. This difference might indicate that ODM, who carry an increased “baseline risk” acquired due to prenatal exposure to maternal diabetes and accompanying growth stimulation in utero [8, 14, 23, 27, 31], are particularly vulnerable also during early postnatal life.

In the context of research on long-term consequences of weight gain during early infancy one important question is how to define “rapid” neonatal weight gain, beyond common definitions of “percentile crossing” which, however, finally are based on the assumption of a genetically predetermined growth trajectory. Ultimately, such complementary measures might serve to better estimate research observations and, especially, to develop respective recommendations for practical medicine considering effects of neonatal environmental programming. To address this question, we performed an additional analysis for which we defined a weight gain above the mean±SD of the whole cohort as “rapid”. Note, this cut-off corresponds in absolute values to the 65th percentile of the WHO growth charts [36]. In fact, using this rather very “liberal” definition, rapid weight gain during the first 4 months of life resulted in a more than six-fold increased risk of overweight during later childhood, independent of birth weight, gestational age, sex, type of maternal diabetes, maternal BMI, SES, parity, maternal age and mode of delivery.

In the general population, Dörner et al. [7] reported that a 3-months weight gain of more than 3.0 kg resulted in a four-fold increase of overweight risk during adolescence. The fact that mean±SD in our study corresponds approximately to a 4-months weight gain of >3.6 kg, which was followed by a more than six-fold increase in later overweight risk, could speak for an increased vulnerability of ODM to rapid neonatal weight gain. Given these data, one might speculate that an increased “baseline risk” acquired due to prenatal exposure to maternal diabetes and accompanying growth stimulation in utero [8, 14, 23, 27, 31], is particularly vulnerable also during early postnatal life.

Another potential source of bias might be reverse causality that is sometimes suggested to be present in studies on infant nutrition and weight gain. However, this is unlikely here, as in our study the pediatricians’ decision to provide supplementary feeding with banked breast milk during the first week of life did not and could not depend on infantile weight gain but exclusively on maternal lactational performance.

Remarkably, no significant influence on early weight gain was observed resulting from intake of breast milk from the biological, i.e., diabetic mothers. We have previously reported from the KCS that intake of breast milk from diabetic mothers during the first week of life has a dose-dependent increasing effect on overweight risk in later childhood [25]. A number of subsequent studies addressed this question and came to heterogeneous results. While two studies pointed towards unfavourable consequences of breastfeeding for risk of overweight and impaired glucose tolerance in ODM [4, 19], some recent studies showed beneficial effects of a prolonged breastfeeding, i.e., longer than 4 months, in this special risk group [5, 18, 21]. For the interpretation of these different results, it is important to realize that a number of confounders must be considered, including e.g., time point of exposure, type of maternal diabetes, age at follow-up and maternal body weight [29]. Especially, it is crucial for the interpretation of the results from the KCS that those infants who did not receive breast milk from their diabetic mothers were alternatively not nourished with formula, but with banked breast milk from non-diabetic donor mothers. This, in fact, creates a unique reference exposure which differs from those used in all other studies mentioned above, as they tested breastfeeding against formula [28–30].

As usual, our study has some limitations that should be critically addressed here. General concerns regarding the observational, longitudinal design of the KCS might be potential occurrence of a selection bias and impact of loss to follow up. While both aspects, however, might potentially affect studies in which different exposure groups are compared, they are unlikely to be relevant in cases like here where continuous relations between exposure and outcome variables are analyzed in terms of an intra-individual risk estimation. In this sense, it was the aim here to evaluate a potential role of early weight gain in the pathogenesis of overweight within this particular risk population by intra-individual regression analysis. Another potential source of bias might be reverse causality that is sometimes suggested to be present in studies on infant nutrition and weight gain. However, this is unlikely here, as in our study the pediatricians’ decision to provide supplementary feeding with banked breast milk during the first week of life did not and could not depend on infantile weight gain but exclusively on maternal lactational performance.

Most importantly, however, according to the data presented here breast milk ingested from diabetic mothers during the first week of life does not seem to increase neonatal weight gain. Moreover, by showing here that breast milk from non-diabetic mothers even protects from increased early weight
gain in ODM and, thereby, may prevent later overweight, these data serve as further indication that breast milk of normal composition, as it will result from good metabolic control also in women with diabetes [35], is as beneficial to prevent later obesity in ODM as in the general population [29].

Taken together, preventing increased early weight gain might be an important new approach to prevent childhood overweight in the risk population of ODM. Precise anthropometric, biochemical and nutritional causes of this relation and its preventive potential remain to be established.

Acknowledgements

Parts of this study were presented by A.P. as an invited contribution at the 71st ADA Scientific Sessions, San Diego 2011. Support from the German Research Foundation is acknowledged (DFG; PL 241/5-1).

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The authors stated that there are no conflicts of interest regarding the publication of this article.