Long-Term Impact of Breast-Feeding on Body Weight and Glucose Tolerance in Children of Diabetic Mothers

Role of the late neonatal period and early infancy

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OBJECTIVE — Offspring of diabetic mothers (ODM) are at increased risk of developing overweight and impaired glucose tolerance (IGT). Recently, we observed that early neonatal ingestion of breast milk from diabetic mothers (DBM) may dose-dependently increase the risk of overweight in childhood. Here, we investigate whether DBM intake during the late neonatal period and early infancy also influences later adipogenic and diabetogenic risk in ODM.

RESEARCH DESIGN AND METHODS — A total of 112 ODM were evaluated for influence of DBM ingestion during the late neonatal period (2nd–4th neonatal week) and early infancy on relative body weight (RBW) and glucose tolerance in early childhood.

RESULTS — Exclusive breast-feeding was associated with increased childhood RBW (P = 0.011). Breast-fed ODM had an increased risk of overweight (odds ratio 1.98 [95% CI 1.12–3.50]). Breast-feeding duration was also positively related to childhood RBW (P = 0.004) and 120-min blood glucose during an oral glucose tolerance test (P = 0.022). However, adjustment for the DBM volume ingested during the early neonatal period, i.e., 1st week of life, eliminated all these relations with late neonatal breast-feeding and its duration. Interestingly, no relationship was observed between maternal blood glucose in the middle of the third trimester and the outcome.

CONCLUSIONS — Neither late neonatal DBM intake nor the duration of breast-feeding has an independent influence on childhood risk of overweight or IGT in ODM. Therefore, the 1st week of life appears to be the critical window for nutritional programming in ODM by ingestion of maternal "diabetic" breast milk.

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Breast feeding was variously shown to protect against later overweight and diabetes (1–6). This effect is attributed to differences in the composition of formula compared with breast milk (3). Offspring of diabetic mothers (ODM) are at increased risk of developing overweight and impaired glucose tolerance (IGT) even in childhood (7–10). Underlying mechanisms are still not understood. Clinical (8–10) and experimental (11–13) studies have shown that a diabetic intrauterine environment plays a key role in programming of increased susceptibility to overweight and diabetes.

We recently observed that ingestion of breast milk from diabetic mothers (diabetic breast milk; DBM) during the 1st neonatal week may dose-dependently lead to increased rather than decreased risk of overweight in later childhood of ODM (14). This lasting deleterious effect of DBM ingestion might result from altered macronutrient and hormonal milk composition (15–18).

However, as the study addressed the early neonatal nutrition, results did not show whether breast-feeding after the 1st neonatal week also has any lasting influence. The vast majority of studies on the influence of breast-feeding on later disease risk ignored whether the mother was affected by a noncommunicable, i.e., metabolic disease, during lactation and, moreover, focused only on whether breast-feeding and/or the duration of breast-feeding has any lasting consequences. No attention was given to the role of the amount of breast milk ingested and/or a certain time point ("critical period") of development when breast milk was supplied or not. However, it might have enormous practical consequences to know whether breast-feeding in general or only during a circumscribed period may have later consequences, e.g., on risk of overweight. Following up on our earlier observations (14), here we investigated whether DBM intake during the late neonatal period and early infancy also influences risk of overweight and diabetes in ODM.

RESEARCH DESIGN AND METHODS

— Important general data concerning the cohort and its subpopulations were previously described in detail

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Abbreviations: AUCG, area under the curve of glucose; DBM, diabetic breast milk; GDM, gestational diabetes mellitus; IGT, impaired glucose tolerance; ODM, offspring of diabetic mothers; OGTT, oral glucose tolerance test; RBW, relative body weight.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

(14). All subjects were participants of the Kaulsdorf Cohort Study, a prospective study on consequences of maternal diabetes during pregnancy for the offspring's development (9,10,14). The study consisted of 317 offspring of women with type 1 diabetes ($n = 200$) or gestational diabetes mellitus (GDM; $n = 117$). They came from a population of 741 offspring of women with diabetes during pregnancy (type 1 diabetes: $n = 368$; GDM: $n = 373$) who delivered during 1980–1989 at the Clinic of Obstetrics and Gynecology, Berlin-Kaulsdorf, Germany (former German Democratic Republic). Each mother was offered the opportunity to have her child participate in pediatric follow-up with regular physical reexaminations, including oral glucose tolerance tests (OGTTs). Regular annual follow-up examinations were planned. Whenever data were available for more than one age, we used results for the highest available age, as the development of overweight is a progressive process throughout childhood. A total of 112 infants were followed-up with complete data on nutrition throughout the neonatal period, i.e., both the early neonatal period (1st neonatal week) and the late neonatal period (2nd–4th neonatal week), as well as data on duration of breast-feeding.

Maternal data

Maternal data included age, duration of diabetes (type 1), and prepregnancy BMI. Socioeconomic/educational status was categorized by maternal occupation: unemployed ($n = 2$), manual worker ($n = 20$), nonmanual worker without high school diploma ($n = 71$), or nonmanual worker with high school diploma ($n = 19$). Geographic origin was defined as urban ($n = 76$) or rural ($n = 36$). Gestational age and birth weight came from birth records.

GDM was diagnosed between the 26th and 28th gestational weeks, as described previously (9,10,14,19). Glucose homeostasis was monitored weekly by 24-h day-night glucose profiles at the clinic. During monitoring, blood glucose was measured every 2 h (glucoseoxidase-peroxidase method). Women maintaining mean 24-h profiles <5.5 mmol/l were treated with diet ($n = 14$). When a mean profile was ≥5.5 mmol/l, insulin therapy was initiated ($n = 15$) (9,10,14,19). Diurnal blood glucose profiles were also used to monitor metabolism in women with type 1 diabetes. The area under the curve of glucose (AUCG) was calculated from data obtained in the middle of the third trimester (34th gestational week).

Nutritional data

All mothers were encouraged to breast-feed their children ad libitum. Nutritional data during the 1st neonatal week were assessed as previously described (14). 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 1st neonatal week and dividing by seven. At regular follow-up examinations and interviews, embedded in the Kaulsdorf Cohort Study and performed from birth through infancy into childhood, mothers continuously provided information about breast-feeding, on the basis of which children were classified as fed with DBM only, some DBM, or no DBM during the late neonatal period (2nd–4th neonatal week). Furthermore, duration of breast-feeding (in weeks) was assessed.

Anthropometry at follow-up

Body weight and height were recorded during follow-up examinations. Relative body weight (RBW) was calculated in relation to age- and sex-related standard population measures (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 (7–9,14), as previously described (14). RBW >110% was defined as overweight (9,14).

OGTT at follow-up

OGTTs were performed as previously described (14). Capillary blood samples were collected in the fasting state and then 120 min after an oral load of 1.75 g glucose/kg body wt in a 40% glucose solution. IGT was defined according to the National Diabetes Data Group criteria recommended for children: fasting glucose in capillary whole blood <6.7 mmol/l and 120-min glucose concentration >6.7 mmol/l (20). 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 ± SE. Group differences were analyzed using ANOVA (followed by post hoc Student's t test) and χ^2 test. Logistic regression analysis was performed to obtain odds ratios (ORs) with 95% CIs. Influence of the duration of breast-feeding was analyzed using linear regression analysis. As a second step, multivariate analyses were performed using five different statistical models. In model I, adjustment was performed for birth weight, gestational age, age, type of maternal diabetes, maternal BMI, and maternal age. In model II, we adjusted only for maternal blood glucose in the third trimester of pregnancy, as indicated by AUCG of diurnal blood glucose profiles in the middle of third trimester. In model III, adjustment was performed only for DBM volume ingested during the 1st neonatal week and in model IV only for duration of breast-feeding. In model V, adjustment was performed for all of these potential confounders. SPSS 10.0 software was used.

RESULTS — Basic parameters for our subcohort did not differ significantly from the remaining children of the cohort: maternal age (25.6 ± 0.49 vs. 26.6 ± 0.37 years, $P = 0.53$), maternal BMI (25.8 ± 0.49 vs. 27.3 ± 0.32 kg/m^2, $P = 0.69$), gestational age (38.6 ± 0.13 vs. 38.7 ± 0.10 weeks, $P = 0.82$), sex (54 vs. 121 boys, 58 vs. 84 girls, $P = 0.08$), and children's birth weight (3,396 ± 59.8 vs. 3,502 ± 41.6 g, $P = 0.95$). Mean daily milk intake during the first neonatal week was 91.7 ± 64.9 g/day.

Of the 112 children, 83 were born to women with type 1 diabetes and 29 to women with GDM. Age at follow-up was 2.1 ± 0.1 years. No differences were found between types of maternal diabetes regarding maternal age, maternal BMI, or gestational age. Mean maternal blood glucose during 24-h glucose monitoring in the third trimester of pregnancy did not show a significant difference between women with GDM (5.3 ± 0.14 mmol/l, $n = 29$) and those with type 1 diabetes (4.9 ± 0.14 mmol/l, $n = 83$, $P = 0.12$ by unpaired t test). Pregestational duration of type 1 diabetes was 9.6 ± 0.62 years. Regarding type of maternal diabetes, infant data did not show significant differences in mean age at follow-up, RBW, percentage of overweight children, fasting

Table 1—*Population characteristics according to type of nutrition during the late neonatal period (i.e., 2nd–4th week of life)*

Parameter	Type of late neonatal nutrition			*P**
	No DBM	Some DBM	DBM only	
n	31	36	45	
Maternal age (years)	28 ± 1.2	25 ± 0.73†	24 ± 0.60‡	0.009
Maternal BMI (kg/m²)	27 ± 1.1	24 ± 0.74	24 ± 0.58§	0.036
Type of maternal diabetes (% type 1 diabetes)	27 (87)	23 (64)	33 (73)	0.25
Maternal blood glucose (mmol/l × h)‖	5.2 ± 0.19	4.8 ± 0.21	5.1 ± 0.17	0.46
Gestational age (weeks)	38 ± 0.29	39 ± 0.21	39 ± 0.19	0.37
Infant sex (% male)	11 (35)	20 (56)	23 (51)	0.23
Infant birth weight (g)	3,410 ± 146	3,411 ± 94	3,441 ± 76	0.97
Duration of breast-feeding (weeks)	0.64 ± 0.09	13 ± 1.7¶	15 ± 1.7¶	<0.001
Mean age at follow-up (years)	2.3 ± 0.16	2.2 ± 0.18	2.0 ± 0.18	0.33

Data are means ± SE or *n* (%). *By ANOVA or χ^2 test for trend; †$P = 0.049$; ‡$P = 0.009$; §$P = 0.037$; ‖, area under the curve of maternal blood glucose in the middle of the third trimester; ¶$P < 0.001$ vs. no DBM (post hoc *t* test).

and 120-min results of OGTT, or IGT prevalence (data not shown here; [14]).

Regarding AUCG in the middle of third trimester in all women, univariate regression analysis showed no significant relation with children's RBW at follow-up ($\beta = -0.13$, $P = 0.16$), fasting blood glucose ($\beta = 0.14$, $P = 0.14$), or 120-min glucose ($\beta = -0.10$, $P = 0.28$). No significant influence was detected of maternal third trimester glucose on overweight (OR 0.86 [95% CI 0.58–1.27]) or IGT (0.97 [0.56–1.67]).

Accordingly, also in separate analysis of women with GDM, no influence of AUCG of maternal OGTT in the third trimester was observed in children's RBW ($\beta = -0.08$, $P = 0.67$), fasting glucose ($\beta = 0.16$, $P = 0.41$), or 120-min glucose ($\beta = 0.17$, $P = 0.38$). No significant impact of AUCG of maternal third-trimester OGTT was observed on overweight (OR 1.35 [95% CI 0.80–2.28]) or IGT (0.73 [0.34–1.55]).

Regarding the type of late neonatal nutrition, no significant differences were observed for type of maternal diabetes or gestational age or for birth weight, sex, or mean age at follow-up (Table 1). Mothers of breast-fed infants were younger than those not breast-feeding. Children who were not breast-fed during the late neonatal period had ingested significantly less DBM in the early neonatal period compared with those partly or solely breast-fed (no DBM: 26 ± 6.9 g/day [$n = 31$] vs. some DBM: 111 ± 8.9 g/day [$n = 36$] vs. DBM only: 122 ± 8.3 g/day [$n = 45$]; $P < 0.001$ by ANOVA, $P < 0.001$ for no DBM vs. some DBM and vs. DBM only; by post hoc *t* test). Maternal blood glucose during 24-h glucose monitoring within 1 week postpartum did not show a relation to late neonatal nutrition of the infant (no DBM: 6.2 ± 0.24 mmol/l [$n = 31$] vs. some DBM: 5.6 ± 0.29 mmol/l [$n = 36$] vs. DBM only: 5.9 ± 0.23 mmol/l [$n = 45$], $P = 0.27$ by ANOVA).

Table 2 shows separate analyses of outcome parameters in children of mothers with GDM and in children of mothers with type 1 diabetes. In both cases, DBM volume ingested during the 1st neonatal week was positively associated with RBW

Table 2—*RBW, fasting blood glucose, and 120-min blood glucose during OGTT at mean age of 2 years in children of mothers with GDM and those with type 1 diabetes, according to tertiles of DBM ingestion during the 1st week of life (early neonatal period) and type of nutrition during the late neonatal period (i.e., 2nd–4th week of life): separate analyses*

Parameter	Tertile of DBM ingestion during the early neonatal period				Type of neonatal nutrition during the late neonatal period			
	Lower tertile	Middle tertile	Upper tertile	*P**	No DBM	Some DBM	DBM only	*P**
n	38	36	38		31	36	45	
GDM								
RBW (%)	98 ± 4.2	108 ± 2.7	109 ± 4.1	0.08	91 ± 2.8	103 ± 3.5	111 ± 2.9	0.01
Fasting blood glucose (mmol/l)	4.3 ± 0.20	4.2 ± 0.18	4.7 ± 0.19	0.25	4.3 ± 0.43	4.2 ± 0.12	4.7 ± 0.17	0.12
120-min blood glucose (mmol/l)	4.9 ± 0.44	5.5 ± 0.33	5.8 ± 0.31	0.18	5.1 ± 0.94	5.3 ± 0.31	5.7 ± 0.29	0.62
Type 1 diabetes								
RBW (%)	99 ± 2.0	103 ± 2.0	108 ± 3.6	0.07	99 ± 2.1	104 ± 2.1	107 ± 3.1	0.14
Fasting blood glucose (mmol/l)	4.3 ± 0.15	4.3 ± 0.11	4.4 ± 0.13	0.70	4.4 ± 0.13	4.4 ± 0.16	4.3 ± 0.11	0.69
120-min blood glucose (mmol/l)	5.0 ± 0.18	5.3 ± 0.15	5.3 ± 0.17	0.39	5.1 ± 0.21	5.2 ± 0.17	5.3 ± 0.12	0.52

Data are means ± SE. *By ANOVA.

Table 3—*RBW, fasting blood glucose, and 120-min blood glucose during OGTT and prevalence of overweight (RBW >110%) and IGT at mean age of 2 years according to type of nutrition during the late neonatal period (i.e., 2nd–4th week of life) in offspring of mothers with GDM or type 1 diabetes: combined analysis*

	Type of late neonatal nutrition			Statistical analysis [*P* or OR (95% CI)]*				
					Adjusted			
Parameter	No DBM	Some DBM	DBM only	Unadjusted	Model I†	Model II‡	Model III§	Model IV‖	Model V¶
n	31	36	45						
RBW (%)	98 ± 1.9	104 ± 1.8	108 ± 2.4#	*P* = 0.011	*P* = 0.009	*P* = 0.003	*P* = 0.17	*P* = 0.07	*P* = 0.37
Fasting blood glucose (mmol/l)	4.4 ± 0.12	4.3 ± 0.11	4.4 ± 0.10	*P* = 0.97	*P* = 0.53	*P* = 0.87	*P* = 0.38	*P* = 0.85	*P* = 0.33
120-min blood glucose (mmol/l)	5.1 ± 0.21	5.2 ± 0.15	5.4 ± 0.12	*P* = 0.30	*P* = 0.22	*P* = 0.13	*P* = 0.56	*P* = 0.64	*P* = 0.99
Overweight	4 (13)	9 (25)	17 (38)	1.98 (1.12–3.50)	2.09 (1.10–3.98)	1.98 (1.12–3.51)	1.64 (0.86–3.11)	1.85 (0.99–3.47)	1.61(0.76–3.42)
IGT	5 (16)	2 (5.5)	4 (8.9)	0.70 (0.33–1.50)	0.70 (0.29–1.71)	0.70 (0.32–1.50)	0.59 (0.23–1.54)	0.63 (0.24–1.60)	0.66 (0.22–2.02)

Data are means ± SE or *n* (%). *By ANOVA or logistic regression analysis; †multivariate analysis, adjusted for birth weight, gestational age, sex, age at reexamination, type of maternal diabetes, maternal BMI, and maternal age; ‡multivariate analysis, adjusted only for 24-h maternal blood glucose profile in the middle of the third trimester; §multivariate analysis, adjusted only for volume of DBM ingested during the 1st week of life; ‖multivariate analysis, adjusted only for duration of breast-feeding; ¶multivariate analysis, adjusted for all confounders (i.e., birth weight, gestational age, sex, age at reexamination, type of maternal diabetes, maternal BMI, maternal age, maternal 24-h blood glucose profile in the middle of the third trimester, volume of DBM ingested during the 1st week of life and duration of breast-feeding); #*P* = 0.008 vs. no DBM group (post hoc *t* test).

later in childhood, confirming earlier results obtained for the entire cohort (14). Similarly, higher DBM intake during the 2nd–4th neonatal weeks was associated with higher RBW in childhood in both subgroups. We therefore decided to combine both subgroups for further analysis, which also increased the power of the multivariate analysis.

Table 3 shows results of the combined analysis (GDM plus type 1 diabetes) with and without adjustment for confounders. RBW was lowest in children who had not ingested DBM during the late neonatal period and highest in those fed with DBM only. However, the difference became nonsignificant when adjustment was made for DBM volume ingested during the 1st neonatal week. DBM volume ingested during the 1st week still showed a significant association with RBW in childhood ($P = 0.02$). Univariate logistic regression analysis revealed a twofold increased risk of overweight in children fed with DBM. Additionally, the prevalence of obesity in children (RBW >120%) only fed with DBM during the late neonatal period was nearly doubled compared with those of ODM fed with some or no DBM (no DBM: 6% [2/31]; some DBM: 6% [2/36]; only DBM: 11% [5/45]). The group difference in risk of overweight became nonsignificant after adjustment for DBM volume ingested during the 1st neonatal week. DBM volume ingested during the 1st neonatal week itself still significantly influenced the risk of becoming overweight in the fully adjusted model (OR 2.77 [95% CI 1.05–7.34]). Neither univariate nor multivariate analysis showed a significant group difference for fasting blood glucose, 120-min glucose, or IGT according to type of late neonatal nutrition. Interestingly, multivariate analysis revealed no influence of maternal blood glucose profile in the third trimester on any group difference.

Univariate linear regression analysis showed that duration of breast-feeding was positively related to later RBW ($\beta = 0.27$, $P = 0.004$). However, no significant relationship remained after adjustment for DBM volume ingested during the 1st neonatal week ($\beta = 0.13$, $P = 0.22$). Similarly, duration of breast-feeding with DBM showed a positive association with 120-min glucose during OGTT ($\beta = 0.22$, $P = 0.02$), and this group difference turned nonsignificant after adjustment

for DBM volume ingested during the 1st neonatal week ($\beta = 0.15$, $P = 0.13$). Regarding fasting glucose in childhood, no influence of the duration of breast-feeding was found by univariate or multivariate analysis (data not shown). Finally, logistic regression analysis revealed no significant influence of duration of breast-feeding on overweight (OR 1.03 [95% CI 0.99–1.07]) or IGT (0.99 [0.94–1.06]).

CONCLUSIONS — In a previous study, we observed a positive dose-dependent relation between DBM volume ingested during the 1st neonatal week and later risk of overweight in ODM (14). Here, we additionally investigated the influence of DBM ingestion during the late neonatal period and early infancy. Our study shows that DBM ingestion during the late neonatal period is also associated with increased risk of overweight and diabetogenic disturbances. However, after adjusting for the amount of DBM intake during the 1st neonatal week, no significant influence on RBW or on glucose tolerance at mean age of 2 years remains with respect to the kind of nutrition (solely, partly, or not breastfed) during the late neonatal period. Comparable results were obtained for the duration of breast-feeding. That means, neither late neonatal DBM intake nor the duration of breast-feeding has an independent influence on childhood risk of overweight or IGT in ODM.

Studies (1–6) performed in general populations indicate protective effects of breast-feeding. Comparison of exclusive breast-feeding with exclusive formula feeding revealed protective effects of breast-feeding against becoming overweight. A longer duration of breast-feeding was associated with reduced risk of developing overweight or type 2 diabetes.

However, none of these studies evaluated a possible presence of noncommunicable diseases, such as maternal diabetes, or even considered this. In a previous study (14), however, we found an adverse effect of DBM volume ingested by ODM during the early neonatal period on RBW in later childhood. We know of only two other studies (21,22) that have investigated consequences of breast-feeding of mothers with diabetes for risk of overweight in their offspring. And considering that the majority of population-based studies described effects on risk of overweight based on breast-feeding during the late neonatal period and far beyond into the first year of life, the question is whether DBM ingestion during this late neonatal period also has discernible effects.

In addition to the early nutritional measurements used in our prior study, data on later neonatal nutrition were based on regular maternal information here. It is noteworthy that our information on infant nutrition was not obtained retrospectively, but the current state of nutrition was continuously updated during regular interviews from birth through infancy into childhood, as an integral part of the prospective Kaulsdorf Cohort Study. The data used for our analyses can therefore be regarded as of particular high validity.

Analyzing crude data revealed that DBM ingestion during the late neonatal period was associated with increased body weight and a doubled risk of overweight. Comparable findings in outcome parameters were observed in both subgroups, i.e., in children of both GDM and type 1 diabetes. Therefore, to increase statistical power, we combined these subgroups for further analyses. We found that adjustment for the DBM volume ingested during the early neonatal period (1st neonatal week) resulted in a decrease of risk estimates and made results nonsignificant. In other words, DBM ingestion during the late neonatal period per se showed no significant influence on later risk of overweight or diabetes. We therefore hypothesize that the 1st neonatal week represents the critical period, when exposure to DBM may have a negative long-term influence on risk of overweight and diabetes in ODM. This might have important practical consequences.

The composition of colostrum and transitional milk of women with diabetes could play a particularly critical role. Note, milk glucose concentrations have been shown to be proportional to blood glucose concentrations (16,23), leading to increased glucose levels in the colostrum of diabetic mothers (18). As colostrum is synthesized even in late pregnancy (24), one has to expect metabolic alterations in this period to be mirrored in colostrum, possibly even regardless of maternal metabolism postpartum. And if a mother with GDM does not show complete normalization of glucose metabolism after pregnancy (25), increased glucose could be expected in breast milk produced postpartum. Furthermore, insulin concentrations in breast milk from diabetic mothers are several times higher (16), and insulin can cross the intestinal blood-mucosa barrier neonatally (26). Consequently, increased insulin levels in breast milk might lead to increased insulin in the child's blood. A number of studies indicate, however, that children exposed to increased concentrations of glucose and insulin in utero are at increased risk of overweight and insulin resistance later in life (7–10). Alterations in colostrum might therefore be responsible for lasting consequences of early neonatal DBM ingestion on increased risk of overweight. Altogether, these aspects point to the particular importance of the early neonatal period regarding a nutritional and hormonal programming in ODM.

Surprisingly, we did not observe a significant relationship between maternal blood glucose in the middle of the third gestational trimester and later body weight or glucose tolerance. It is noteworthy, however, that these results confirm other similar observations (27). To the best of our knowledge, this study is the first to investigate directly, that is, quantitatively in terms of correlative relations, the consequences of altered maternal blood glucose concentrations during pregnancy on later risk of overweight, IGT, etc., in the offspring. Our observations seem to contradict the pathophysiological key role of hyperglycemia and its direct and indirect consequences in diabetic pregnancies on children's outcome. However, for all women investigated in our case, therapy led to normal average blood glucose levels in graviditate, as estimated by blood glucose profiles in the middle of the third trimester. As a crude indicator of successful therapy, moreover, mean birth weight was also normal. In this context, it should be noted that Silverman and colleagues (8,28) found a positive relationship between amniotic insulin concentration (which is strongly indicative of maternal glycemia) and later risk of overweight and IGT in ODM. The absence of a significant relation between maternal gestational glycemia, normalized under therapeutic control during pregnancy, and the offspring's outcome might therefore point to the particular importance of neonatal nutrition in ODM. This conclusion has to be confirmed in further studies. Remarkably, however, mean maternal blood glucose during

24-h glucose profiles postpartum was higher than in the middle of the third trimester, indicating a nonnormalized or even aggravated maternal glucose metabolism, thereby further underlining the importance of adequate metabolic control immediately postpartum.

Breast feeding is the best way for healthy mothers to nurture healthy term children. Fortunately, diabetic women are encouraged and choose to breast-feed their newborns as often as healthy women do (29). Our findings, if they can be extrapolated to other populations, might pose a dilemma for pregnant women with diabetes, making them doubt whether breast-feeding is really beneficial or may even increase their child's risk of becoming overweight and developing associated metabolic disorders. At least regarding breast-feeding during the late neonatal period and early infancy, that is after the 1st week of life, these potential concerns should be allayed by our study. Nevertheless, our findings again strongly underline the urgent need to address potential lasting advantages but also possible disadvantages of breast-feeding by mothers with diabetes during pregnancy (14). Such consequences need to be further clarified in future studies of lasting, possibly life-long persisting benefits and harms of ingesting DBM during critical periods of neonatal programming and development.

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References

1. Dörner G: Influence of early postnatal nutrition on body height in adolescence. *Acta Biol Med Germ* 37:1149–1151, 1978
2. Kramer MS, Barr RG, Leduc DG, Boisjoly C, Pless B: Infant determinants of childhood weight and adiposity. *J Pediatr* 107: 104–107, 1985
3. Dewey KG, Heinig MJ, Nommsen LA, Peerson JM, Lönnerdal B: Breast-fed infants are leaner than formula-fed infants at 1 y of age: the DARLING study. *Am J Clin Nutr* 57:140–145, 1993
4. Von Kries R, Koletzko B, Sauerwald T, von Mutius E, Barnert D, Grunert V, von Voss H: Breast feeding and obesity: cross sectional study. *BMJ* 319:147–150, 1999
5. Pettitt DJ, Forman MR, Hanson RL, Knowler WC, Bennett PH: Breast feeding and incidence of non-insulin dependent diabetes mellitus in Pima Indians. *Lancet* 350:166–168, 1997
6. Gillman MW, Rifas-Shiman SL, Camargo CA, Berkey CS, Frazier AL, Rockett HRH, Field AE, Colditz GA: Risk of overweight among adolescents who were breastfed as infants. *JAMA* 285:2461–2467, 2001
7. Pettitt DJ, Baird HR, Aleck KA, Bennett PH, Knowler WC: Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. *N Engl J Med* 308:242–245, 1983
8. Silverman BL, Rizzo T, Green OC, Cho NH, Winter RJ, Ogata E, Richards GE, Metzger BE: Long-term prospective evaluation of offspring of diabetic mothers. *Diabetes* 40 (Suppl. 2):121–125, 1991
9. Plagemann A, Harder T, Kohlhoff R, Rohde W, Dörner G: Overweight and obesity in infants of mothers with long-term insulin-dependent diabetes or gestational diabetes. *Int J Obes Relat Metab Disord* 21: 451–456, 1997
10. Plagemann A, Harder T, Kohlhoff R, Rohde W, Dörner G: Glucose tolerance and insulin secretion in children of diabetic mothers with pregestational insulin-dependent diabetes mellitus or gestational diabetes. *Diabetologia* 40:1094–1100, 1997
11. Plagemann A, Harder T, Melchior K, Rake A, Rohde W, Dörner G: Elevation of hypothalamic neuropeptide Y-neurons in adult offspring of diabetic mother rats. *Neuroreport* 10:3211–3216, 1999
12. Aerts L, Holemans K, Van Assche FA: Maternal diabetes during pregnancy: consequences for the offspring. *Diabetes Metab Rev* 6:147–167, 1990
13. Plagemann A: 'Fetal programming' and 'functional teratogenesis': on epigenetic mechanisms and prevention of perinatally acquired lasting health risks. *J Perinat Med* 32:297–305, 2004
14. Plagemann A, Harder T, Franke K, Kohlhoff R: Long-term impact of neonatal breast-feeding on body weight and glucose tolerance in children of diabetic mothers. *Diabetes Care* 25:16–22, 2002
15. Neubauer SH: Lactation in insulin-dependent diabetes. *Prog Food Nutr Sci* 14:333–370, 1990
16. Jovanovic-Peterson L, Fuhrmann K, Hedden K, Walker L, Peterson CM: Maternal milk and plasma glucose and insulin levels: studies in normal and diabetic subjects. *J Am Coll Nutr* 8:125–131, 1989
17. Neubauer S, Ferris AM, Fanelli J, Lammi-Keefe CJ, Jensen RG: Breast milk composition and mastitis incidence in insulin-dependent diabetic women (Abstract). *FASEB J* 3:A770, 1989
18. Van Beusekom CM, Zeegers TA, Martini IA, Velvis HJ, Visser GH, van Doormaal JJ, Muskiet FA: Milk of patients with tightly controlled insulin-dependent diabetes mellitus has normal macronutrient and fatty acid composition. *Am J Clin Nutr* 57: 938–943, 1993
19. Fuhrmann K: Gestational diabetes, significance of risk factors and results of follow-up study 8 years after delivery. In *Gestational Diabetes*. Weiss PAM, Coustan DR Eds. New York, Springer, 1988, p 93–98
20. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28:1039–1057, 1979
21. Pettitt DJ, Knowler WC: Long-term effects of the intrauterine environment, birth weight, and breast-feeding in Pima Indians. *Diabetes Care* 21 (Suppl. 2): B138–B141, 1998
22. Kerssen A, Evers IM, de Valk HW, Visser GH: Effect of breast milk of diabetic mothers on bodyweight of the offspring in the first year of life. *Eur J Clin Nutr* 58: 1429–1431, 2004
23. Neville MC, Allen JC, Archer P, Casey CE, Seacat J, Keller RP, Lutes V, Rasbach J, Neifert M: Studies in human lactation: milk volume and nutrient composition during weaning and lactogenesis. *Am J Clin Nutr* 54:81–92, 1991
24. Kulski JK, Hartmann PE: Changes in human milk composition during the initiation of lactation. *Aust J Exp Biol Med Sci* 59:101–114, 1981
25. Kjos SL, Buchanan TA, Greensporn JS, Montoro M, Bernstein GS, Mestman JH: Gestational diabetes: the prevalence of glucose intolerance and diabetes mellitus in the first two months post-partum. *Am J Obstet Gynecol* 163:93–98, 1990
26. Grosvenor CE, Picciano MF, Baumrucker CR: Hormones and growth factors in milk. *Endocr Rev* 14:710–728, 1992
27. Harder T, Franke K, Kohlhoff R, Plagemann A: Early nutrition and later blood pressure: effect of maternal diabetes. *J Pediatr* 139:905–906, 2001
28. Silverman BL, Metzger BE, Cho NH, Loeb CA: Impaired glucose tolerance in adolescent offspring of diabetic mothers. *Diabetes Care* 18:611–617, 1995
29. Ferris AM, Neubauer SH, Bendel RB, Green KW, Ingardia CJ, Reece EA: Perinatal lactational protocol and outcome in mothers with and without insulin-dependent diabetes mellitus. *Am J Clin Nutr* 58: 43–48, 1993