Impact of Early Neonatal Breast-Feeding on Psychomotor and Neuropsychological Development in Children of Diabetic Mothers

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OBJECTIVE — In general, breast-feeding positively influences development of psychomotor function and cognition in children. Offspring of diabetic mothers (ODM) have delayed psychomotor and cognitive development. Recently, we observed a dose-dependent negative effect of early neonatal ingestion of breast milk from diabetic mothers (diabetic breast milk [DBM]) on the risk of overweight during early childhood. Here, we investigated the influence of early neonatal intake of DBM on neurodevelopment in ODM.

RESEARCH DESIGN AND METHODS — A total of 242 ODM were evaluated for age of achieving major developmental milestones (Denver Developmental Scale) according to the volume of DBM ingested during the first week of life, using Kruskal-Wallis and Kaplan-Meier analysis.

RESULTS — Children in the upper tertile of early neonatal ingestion of DBM achieved early psychomotor developmental milestones ("lifting head while prone," "following with eyes") earlier than those in lower tertiles ($P = 0.002$). In contrast, a delay in the onset of speaking was observed in children who had ingested larger volumes of DBM compared with those with lower DBM intake ($P = 0.002$). This negative impact of DBM ingestion was not confounded by birth characteristics, total milk intake, or socioeconomic/educational status.

CONCLUSIONS — Our data indicate differential effects of early neonatal DBM ingestion on psychomotor and cognitive development. Ingesting larger compared with smaller volumes of DBM may normalize early psychomotor development in ODM but delays onset of speaking as a parameter indicative of cognitive development. This effect may result from qualitative alterations in the composition of DBM. Further studies are urgently recommended on the benefits and harms of breast-feeding in ODM.

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Breast-feeding is the best way to nurture healthy-term offspring of healthy mothers. It is well known to have positive short- and long-term effects, e.g., decreased risk of obesity or type 2 diabetes (1,2). Furthermore, evidence exists of a positive influence of breast feeding on psychomotor and cognitive development (3,4), persisting into adult age (5).

Positive long-term effects of breast-feeding have been attributed to the composition of breast milk, including factors promoting neurodevelopment, such as long-chain polyunsaturated fatty acids (6). However, it has rarely been considered so far whether breast-feeding is still of advantage if the mother is affected by a noncommunicable disease, e.g., a metabolic disease, which may alter the composition of breast milk.

Offspring of diabetic mothers (ODM) have delayed psychomotor and cognitive development (7–10). Pathophysiologic mechanisms remain unknown. Recently, we showed that early neonatal intake of breast milk from diabetic mothers may dose-dependently lead to an increased risk of overweight and impaired glucose tolerance during early childhood (11). Here, we evaluated whether the early neonatal intake of diabetic breast milk (DBM) may also influence cognitive and psychomotor development in children of mothers with diabetes during pregnancy.

RESEARCH DESIGN AND METHODS

— Subjects were participants of the Kaulsdorf Cohort Study (KCS), a prospective cohort study on short- and long-term consequences of maternal diabetes during pregnancy and lactation for the offspring's development (11–13). The cohort consists of 317 offspring of women with type 1 diabetes ($n = 200$) or gestational diabetes (GDM; $n = 117$). They were derived from a population of 741 offspring of women with diabetes during pregnancy (type 1 diabetes, $n = 368$; GDM, $n = 373$) who delivered during the study period 1980–1989 at the Clinic of Obstetrics and Gynecology, Berlin-Kaulsdorf, Germany (former German Democratic Republic). GDM was diagnosed between 26 and 28 weeks' gestation using an oral glucose tolerance test with a 50-g glucose load, as described

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Abbreviations: DBM, diabetic breast milk; GDM, gestational diabetes mellitus; ODM, offspring of diabetic mothers.

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

previously (11–13). After diagnosis of GDM, 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. When a woman's mean profile was ≥5.5 mmol/l, insulin therapy was initiated (11).

Each mother was offered the opportunity to have her child participate in a pediatric follow-up assessment with regular physical examinations and record of developmental milestones. Complete data on nutrition during the first neonatal week (days 1–7) as well as data on developmental milestones were available for 242 of 317 (76%) ODM.

Data

Demographic data included maternal age, maternal BMI, type of maternal diabetes, pregestational duration of diabetes (type 1 diabetes), parity, parental socioeconomic/educational status, mean maternal blood glucose concentrations during third trimester, gestational age, birth weight, sex, prevalence of neonatal hypoglycemia, and Apgar score at 1, 5, and 10 min postpartum.

Parental socioeconomic/educational status, focusing on educational level, was categorized into three groups: manual worker, nonmanual worker, and graduation/degree.

Neonatal blood glucose level was determined immediately after birth (glucoseoxidase-peroxidase method). A neonatal glucose level <1.7 mmol/l was defined as neonatal hypoglycemia (14). Apgar score was determined after 1, 5, and 10 min postpartum by an experienced pediatrician.

Infant nutrition during the 1st week of life

Data on infant nutrition during the 1st neonatal week were assessed as previously described (11). In brief, all mothers stayed with their newborns at the maternity ward for at least 1 week postpartum. Breast milk intake was determined during each feeding on days 1–7 postpartum, using a test-weighing protocol (11,15). Mean volume of ingested breast milk per day (DBM, g/day) was calculated by summing the ingested volumes during the 1st neonatal week and dividing them by 7 (11).

Developmental milestones

During follow-up examinations at 6, 12, 18, and 24 months of age, details on the age of achieving developmental milestones were obtained, according to the revised Denver Developmental Scale (16). The developmental milestones "lifting head while prone" and "following with eyes" were defined as "early" developmental milestones, whereas "walking without help" and "speaking first words" were defined as "late" developmental milestones, representing children's neurodevelopment. Information on the age of achieving these developmental milestones was obtained from the parents during structured interviews conducted by a pediatrician who had no knowledge about the details of infant nutrition. Whenever parents claimed that their child already had achieved a developmental milestone, this was clinically assessed by a trained and experienced pediatrician (R.K.). This resulted in different sample sizes for the various outcome parameters, ranging from $n = 84$ to $n = 201$. To avoid selection bias introduced by shrinkage of the sample sizes to a set of probands in whom all outcome parameters were available, we decided to use separate datasets for each parameter with the maximum available sample sizes for analysis.

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

Statistical analysis

Data are expressed as means ± SE or medians and range, as appropriate. Group differences in demographic data were analyzed using one-way ANOVA (followed by post hoc Student's t test) and χ^2 test. To analyze the relationship between volume of breast milk ingested during the first 7 days of life and age of achieving developmental milestones, and data on volumes of breast milk ingested were divided into tertiles. For analyzing differences in the age of achieving developmental milestones according to the tertiles of breast milk ingested, we first performed Kruskal-Wallis test. For further analysis, the cumulative incidence of achieving developmental milestones was calculated using Kaplan-Meier analysis, followed by log-rank test. A P value <0.05 was considered significant, using SPSS statistical software (version 10.0, SPSS, Chicago, IL).

RESULTS — Of the 242 children included, 152 were born to women with type 1 diabetes and 90 were born to women with GDM. Women with GDM were slightly older, had higher BMI, and were more likely to have more than one child than women with type 1 diabetes. No group difference was found regarding neonatal parameters (Table 1).

No relationship was observed between neonatally ingested DBM volume and duration of maternal diabetes, maternal BMI, parity, parental socioeconomic/educational status and maternal blood glucose during third trimester. Among those mothers whose infants received low DBM volumes, a lower percentage had GDM. Maternal age was slightly higher in mothers of children fed low volumes of DBM. We found no significant differences in birth weight and distribution of sex between the tertiles of neonatal intake of DBM. Newborns who ingested low volumes of DBM had lower gestational age, were more likely to develop neonatal hypoglycemia, and had a higher prevalence of Apgar scores <7. No relationship was found between DBM intake and total milk intake during the 1st neonatal week (Table 2).

ODM tended to achieve developmental milestones later than the general population, particularly "following with eyes" and "speaking first words" (Table 3).

Comparing the age at which the children were able to perform early developmental milestones, a significant difference between the tertiles of DBM intake was observed: The infants who were in the highest tertile of neonatal DBM intake achieved these milestones earlier than those in the lower tertiles (Table 3). Kaplan-Meier analysis supported this finding: Neonatal intake of DBM significantly influenced the cumulative incidence of achieving the milestones "lifting head while prone" ($P = 0.02$; Fig. 1*A*) and "following with eyes" ($P = 0.02$).

When comparing the age at which the children performed late developmental milestones, we found no significant difference for "walking without help." However, children who had ingested higher volumes of DBM (upper tertile) performed the developmental milestone

Table 1—*Population characteristics according to type of maternal diabetes*

	Type 1 diabetes	GDM	*P**
n	152	90	
Maternal parameters			
Maternal age (years)	25 ± 0.40	28 ± 0.54	<0.001
Maternal BMI (kg/m²)	25 ± 0.23	24 ± 0.15	0.01
Pregestational duration of diabetes (years)	8.4 ± 0.50	Not applicable	—
Gestational age (weeks)	39 ± 0.10	39 ± 0.15	0.14
Parity (1/2/≥3; *n*)	98/37/17	34/33/23	<0.001
Maternal socioeconomic/educational status (man/non-man/grad; *n*)	29/103/20	21/57/12	0.72
Mean maternal blood glucose (third trimester) (mmol/l)	5.1 ± 0.01	5.3 ± 0.01	0.35
Neonatal parameters			
Sex (male/female)	77/75	53/37	0.22
Birth weight (g)	3,449 ± 49	3,481 ± 56	0.68
Total milk intake (g/day)	158 ± 4.9	148 ± 5.5	0.18
DBM intake (g/day)	83 ± 5.8	100 ± 7.1	0.06
Neonatal hypoglycemia	4.6% (7)	6.7% (6)	0.56
5-min Apgar score <7	3.9% (6)	4.4% (4)	0.85
Any Apgar score <7	15% (23)	20% (18)	0.33
Age of achieving developmental milestones			
"Lifting head while prone" (weeks)	7.0 (1.0–28.0)	10.0 (3.0–24.0)	0.61
"Following with eyes" (weeks)	9.0 (3.0–24.0)	8.0 (3.0–20.0)	0.61
"Walking without help" (weeks)	52.0 (36.0–72.0)	52.0 (44.0–72.0)	0.29
"Speaking first words" (weeks)	48.0 (31.0–100.0)	48.0 (24.0–96.0)	0.57

Data are means ± SE, median (range), or % (*n*), as appropriate. *By unpaired Student's *t* test, Mann-Whitney *U* test, or χ^2 test, as appropriate. Man, manual worker; non-man, nonmanual worker; grad, graduation/degree.

"speaking first words" only 2 weeks later than those children in the middle tertile and 4 weeks later than those in the lower tertile (Table 3). Again, these results were supported by Kaplan-Meier analysis: A significant, dose-dependent difference between the tertiles of DBM intake was observed for the parameter "speaking first words" ($P = 0.02$; Fig. 1*B*) but not for the milestone "walking without help" ($P = 0.06$).

Table 3 further shows that the number of delayed infants was unrelated to neonatal intake of DBM in all but one parameter. For the late psychomotor developmental milestone "walking without help," we observed that early neonatal ingestion of larger volumes of DBM was associated with fewer delayed infants.

The age of achieving the developmental milestone "following with eyes" was significantly influenced by parental socioeconomic/educational status. The higher the parental socioeconomic/educational status, the earlier the children were able to perform the developmental milestone ($P = 0.01$). No relationship was observed between parental socioeconomic/educational status and the age of achieving the other developmental milestones (data not shown).

Table 2—*Population characteristics according to tertiles of mean daily consumption of DBM during the first 7 days of life*

	Tertiles of DBM volume (g/day)			
Parameters	First (≤47)	Second (48–119)	Third (≥120)	*P**
n	81	80	81	
Maternal BMI (kg/m²)	25 ± 0.31	25 ± 0.30	25 ± 0.20	0.39
Maternal age (years)	27 ± 0.71	26 ± 0.47	25 ± 0.50	0.01
Type of maternal diabetes (% GDM)	25 (20)	42 (34)	44 (36)	0.009
Pregestational duration of diabetes (type 1) (years)	7.5 ± 0.75	9.9 ± 0.95	7.9 ± 0.87	0.13
Parity (1/2/≥3; *n*)	44/18/19	45/28/7	43/24/14	0.68
Parental socioeconomic/educational status (man/non-man/grad; *n*)	16/55/10	15/57/8	19/48/14	0.89
Mean maternal blood glucose (third trimester) (mmol/l)	5.2 ± 0.13	5.2 ± 0.14	5.2 ± 0.13	0.99
Gestational age (weeks)	38 ± 0.16	39 ± 0.14	39 ± 0.12	0.01
Sex (male/female)	44/37	40/40	46/35	0.75
Birth weight (g)	3,487 ± 71	3,378 ± 62	3,519 ± 59	0.27
Total milk intake (g/day)	151 ± 64	129 ± 43	182 ± 50	<0.001
Neonatal hypoglycemia	9.9 (8)	3.7 (3)	2.5 (2)	0.04
5-min Apgar score <7	6.2 (5)	5 (4)	1.2 (1)	0.12
Any Apgar score <7	36 (29)	25 (20)	14 (11)	0.001

Data are *n*, means ± SE, or % (*n*). *By ANOVA or χ^2 test for trend. Man, manual worker; non-man, nonmanual worker; grad, graduation/degree.

CONCLUSIONS — In summary, our study shows a beneficial, dose-dependent influence of breast-feeding during the 1st neonatal week on the age of achieving main psychomotor developmental milestones in ODM. In marked contrast, we observed a negative, dose-dependent impact of ingesting DBM on a main cognitive parameter, i.e., on the age at which the children started to speak. This, once again, draws further attention to possible long-term consequences of early breast-feeding in ODM.

In general, breast-feeding has beneficial influences on the psychomotor and cognitive development (3–5). However, all of these studies were performed in healthy, nondiabetic mothers and their children. ODM have delayed neuropsychological and cognitive development (7–10). Most interestingly, delayed speech development in ODM has been described (10). Such alterations have so far been found to correlate only slightly to maternal metabolic parameters during pregnancy (8). Therefore, the question

Table 3—*Age of achievement of early and late developmental milestones according to tertiles of mean daily consumption of DBM during the first 7 days of life*

	"Lifting head while prone"	"Following with eyes"	"Walking without help"	"Speaking first words"
Reference (Denver Developmental Scale)	8.0 (5.0–17.0)	8.0 (5.0–16.0)	52.0 (48.0–64.0)	44.0 (26.0–60.0)
ODM (all infants)	8.0 (1.0–28.0)/ 12/201 (6.0%)	10.0 (3.0–24.0)/ 11/188 (5.8%)	52.0 (36.0–72.0)/ 10/132 (7.6%)	48.0 (24.0–100.0)/ 13/84 (15%)
ODM according to tertiles of DBM volume				
First tertile	8.0 (1.0–24.0)/ 4/67 (6.0%)	12.0 (3.0–24.0)/ 2/63 (3.2%)	56.0 (36.0–72.0) 7/44 (16%)	44.0 (32.0–72.0)/ 4/28 (14%)
Second tertile	8.0 (2.0–28.0)/ 5/67 (7.5%)	10.0 (4.0–24.0)/ 6/62 (9.7%)	54.0 (44.0–72.0)/ 2/44 (4.5%)	46.0 (24.0–72.0)/ 2/28 (7.1%)
Third tertile	6.0 (2.0–24.0)/ 3/67 (4.5%)*	8.0 (3.0–24.0)/ 3/63 (4.8%)*	52.0 (38.0–68.0)/ 1/44 (2.3%)†	48.0 (32.0–100.0)/ 7/28 (25%)‡

Data are median (95% CI) or median (range)/delayed/total. *$P = 0.002$ across tertiles by Kruskal-Wallis test; †$P = 0.02$ by χ^2 test for trend; ‡$P = 0.036$ by Kruskall-Wallis test.

remains which pathogenetic mechanisms may contribute to a negative impact of maternal diabetes on neurodevelopment in the offspring.

As judged by the medians, at least two developmental milestones showed a retardation in the entire cohort, in accordance with a general neurodevelopmental delay in ODM (7–10). Our findings show that early neonatal ingestion of DBM may promote aspects of early psychomotor development in ODM. ODM who had ingested larger volumes of DBM performed an early psychomotor parameter ("lifting head while prone") earlier than those who had ingested smaller volumes of DBM. Remarkably, for the parameter "following with eyes," with regard to the Denver Developmental Scale (16), ingestion of larger volumes obviously resulted in a normalization of the age of achieving this milestone compared with those infants who had ingested smaller volumes of DBM. For late psychomotor development (e.g., "walking without help"), a clear tendency was observed in the same direction. These data indicate a beneficial influence of early neonatal ingestion of breast milk in ODM on psychomotor development. This is in agreement with studies from the general population on positive effects of breast-feeding on psychomotor parameters. Moreover, our data indicate that early neonatal ingestion of DBM can help to reduce the delay in psychomotor development in ODM.

In general, breast-feeding also promotes the development of cognitive processes during childhood, such as speaking. Remarkably, however, this was not the case here. Instead, higher intake of DBM was associated with delayed onset of speaking. This observation further supports the interpretation that ingestion of larger volumes of DBM in the early neonatal period may induce negative effects in development.

For all four developmental milestones investigated, we additionally calculated the number of delayed children, i.e., of those who achieved the respective devel-

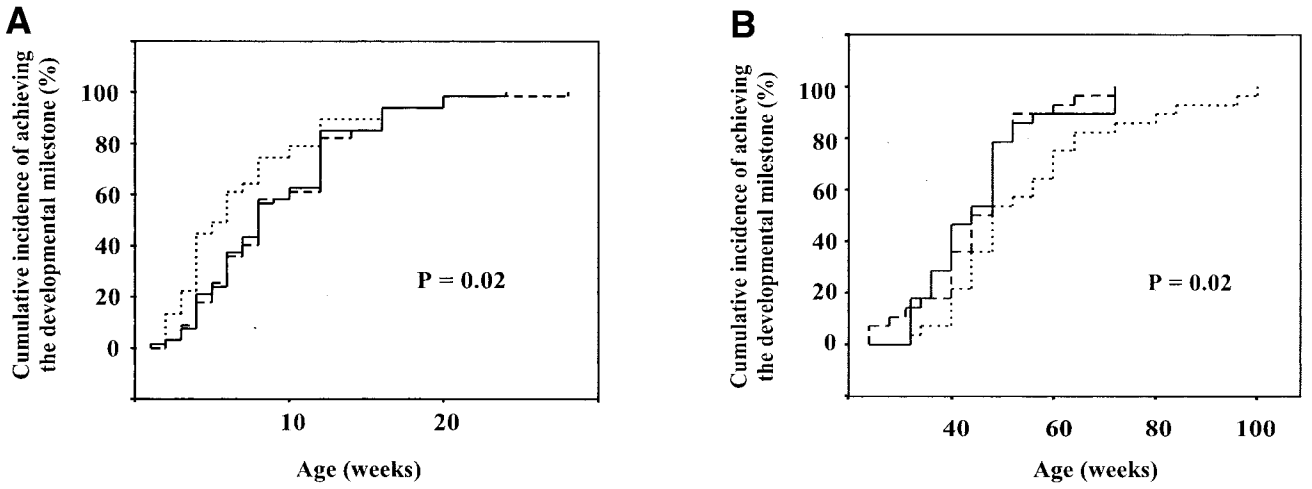

Figure 1—*Kaplan-Meier curves for cumulative incidence of achieving the developmental milestones "lifting head while prone" (A) and "speaking first words" (B) according to first (solid line), second (broken line), and third (dotted line) tertile of mean daily consumption of DBM during the first 7 days of life. Significance by log-rank test.*

opmental milestone at an age that was behind the upper limit of the 95% CI of the Denver Developmental Scale. This kind of analysis showed the size of the effect of early neonatal intake of DBM on neurodevelopmental outcome as being relatively small, at least for three of the developmental milestones. For "lifting head while prone" or "following with eyes" or "speaking first words," we did not observe a significant relation between neonatally ingested volume of DBM and the number of delayed infants. However, for the late psychomotor developmental milestone "walking without help," we observed that early neonatal ingestion of larger volumes of DBM was associated with a significantly smaller number of delayed infants, thereby showing a dose-dependent relationship. This finding is in agreement with data from normal populations, which show a beneficial effect of breast-feeding on psychomotor development (3). Moreover, this finding further supports the suggestion that even in the case that breast milk composition is altered by maternal diabetes, its ingestion by the infant may have beneficial effects, e.g., like those on psychomotor development, which have to be carefully weighed up against possible harms.

In addition to the kind of neonatal nutrition, gestational age, neonatal hypoglycemia, and asphyxia are known to particularly influence psychomotor and neuropsychological development (17,18). Theoretically, these factors could also be linked to neurodevelopment in ODM, more so because neonates of diabetic mothers show increased prevalences of hypoglycemia and low Apgar scores (19), especially when maternal diabetes is undetected and untreated, respectively. The adverse effect of intake of DBM on speech development was not confounded by other factors. Low gestational age, high prevalence of neonatal hypoglycemia, and high prevalence of low Apgar score occurred in the lowest tertile of neonatal DBM intake and vice versa. Thereby, children in the highest tertile of neonatal intake of DBM had even fewer other risk factors that might have impaired speech development. Furthermore, the only parameters differing between mothers with type 1 diabetes and those with GDM or their infants were maternal age, BMI, and parity. However, these parameters did not differ between tertiles of DBM exposure, thereby also justifying the combined analysis of offspring of women with type 1 diabetes and those with GDM. Importantly, we can also exclude that the effects of early neonatal ingestion of DBM were confounded by the total amount of milk intake (DBM plus other types of milk) because no relation was observed.

In addition to perinatal risk factors, parental socioeconomic/educational status influences neurodevelopment in childhood (20). We observed a beneficial effect of a higher parental socioeconomic/educational status on the age of achieving developmental milestones only for one of the four evaluated. However, this parameter ("following with eyes") was an early developmental milestone and reflected psychomotor rather than neuropsychological outcome. Therefore, one might conclude that parental socioeconomic/educational status had only a transient and minor influence on the neurodevelopment in our cohort of ODM in former East Germany. Importantly, however, parental socioeconomic/educational status was not significantly associated with the kind of neonatal nutrition here, making it unlikely to be a confounder of the relationship between neonatal nutrition and neurodevelopment in our cohort.

The question remains regarding which pathophysiologic mechanisms may be responsible for the relationship between early neonatal ingestion of DBM and delayed development of the ability to speak in ODM, indicating a delayed cognitive development. The composition of DBM shows profound alterations, such as a decreased amount of polyunsaturated fatty acids, elevated glucose, and increased insulin concentrations (21,22). Insulin is able to cross the immature intestinal mucose-blood barrier and blood-brain barrier neonatally (23,24); therefore, breast-fed ODM may be exposed to increased insulin neonatally, even in the developing brain. Increased insulin levels during the critical period of perinatal development are suggested to be capable of inducing central nervous insulin resistance, as it was demonstrated for hypothalamic neurons regulating food intake, body weight, and metabolism (25–27). It is noteworthy that in both animal models and humans, central nervous insulin resistance is known to be associated with impaired cognitive functions, but remarkably, insulin resistance does not impair psychomotor functions (28).

Furthermore, supplementation of formula milk with polyunsaturated fatty acids improves neurodevelopment in infancy (6). Remarkably, more detailed analysis showed that neonatal intake of polyunsaturated fatty acids significantly enhanced mental development but had no impact on psychomotor function in infancy (6). Polyunsaturated fatty acids, however, are decreased in DBM (21). Taken together, increased insulin and decreased polyunsaturated fatty acids in DBM could be considered possible contributing causal factors for a negative impact of DBM on cognitive but, simultaneously, not psychomotor development in ODM.

We are convinced that breast-feeding is the best way to promote a newborn's development and should, therefore, be recommended rigorously, in general. We are aware that our data might offer a dilemma to women with diabetes during pregnancy. Therefore, before any practical conclusions and recommendations can be considered, additional studies are needed, of course, to confirm or reject our observations and hypothesis. Meanwhile, in our opinion, breast-feeding should remain the preferred and recommended type of infant feeding, also in ODM.

In conclusion, our results show that early neonatal breast-feeding by diabetic mothers has beneficial effects on early psychomotor development in their offspring. However, it simultaneously delays the onset of speaking, indicating a negative impact on cognitive development. Therefore, further studies are urgently recommended to clarify possible benefits and harms of early intake of DBM on development and programming of lasting functions and fundamental processes of life in ODM, as well as on consequences of feeding DBM in later neonatal life.

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