EDITORIAL (SEE CRUME ET AL., P. 641)

Fuel-Mediated Teratogenesis and Breastfeeding

About 30 years ago, Norbert Freinkel and Boyd Metzger introduced a seminal hypothesis into developmental medicine and diabetes research. The fuel-mediated teratogenesis concept says that prenatal exposure to increased levels of "mixed nutrients," especially increased glucose, and the corresponding increase in fetal insulin have immediate as well as long-lasting deleterious consequences for the offspring of diabetic mothers (1,2). In fact, this paradigm became a kind of forerunner of today's rapidly expanding fields of "perinatal programming" and "developmental origins of health and disease." It has variously been proven to be valid and has even been extended to the case of maternal overweight during pregnancy (3). Accordingly, exposure to maternal gestational diabetes mellitus (GDM) and overweight is meanwhile one of the best proven paradigms concerning the long-term impact of perinatal programming (4,5).

It is crucial for the concept of fuel-mediated teratogenesis that altered food supply during critical periods of early development gives rise to lasting deleterious consequences. Differentiation and maturation, however, of affected organs and systems, such as pancreas, adipose tissue, and brain, are not finished at birth (2). The question therefore arises whether a prolongation of these critical exposures into the neonatal period might have similar effects.

Colostrum is already produced during the last trimester of gestation. The composition of early breast milk reflects metabolic changes that occur in GDM (6). Moreover, in a considerable number of women with GDM, glucose metabolism does not completely normalize after pregnancy (7). Studies suggest that breast milk from women with diabetes contains, for example, increased levels of glucose and insulin as compared with breast milk from healthy mothers (6,8,9). Moreover, it has been shown that not only glucose but even hormones like insulin and leptin are absorbed from milk in the immature gut of an infant (10).

Therefore, an important question is whether this continuing exposure after birth to altered fuels through breastfeeding might have consequences for child development. Here, data obtained in animal experiments are intriguing. Studies have shown that, indeed, exposure to milk from mothers with diabetes and/or obesity increases the risk of developing overweight and diabetogenic disturbances, even irrespective of or in addition to genetic diabetes susceptibility (11–14).

Against this background, the question arose whether or not breastfeeding in offspring of diabetic mothers (ODM) might have a different long-term impact on body weight, metabolic regulation, and diabetogenic risk as compared with breastfeeding in healthy mothers. In 2002, our group published first data on the consequences of breastfeeding for the development of body weight and glucose tolerance in ODM. In a population of 112 ODM born during the 1980s in East Germany, we found a quantitative relation between the volume of breast milk from diabetic mothers ingested during the first week of life and later risk of overweight: the more "diabetic" breast milk an infant ingested during the first week of life, the higher his/her risk of becoming overweight at 1–5 years of age (15). It is crucial for the interpretation of these observations, as highlighted by us on various occasions (15,16), that those infants who did not receive breast milk from their biological, diabetic mothers were instead nourished not with formula but with banked breast milk from nondiabetic donor mothers, thereby creating a different "reference exposure" than in all other studies where breastfeeding was tested against formula. In a further analysis, we confirmed that the critical period for this nonbeneficial outcome appears to be the first week of life (16).

Subsequently, a number of studies addressed the issue of breastfeeding in ODM and its long-term effect on overweight or glucose tolerance with mixed results. While one study did not find a protective effect at 1 year of age (17), a second study observed a decreased glucose tolerance in breastfed ODM (18). Three subsequent studies rather showed a decreased risk of overweight in ODM who were breastfed for at least 4 months, as compared with formula (19–21). It is important to realize that a number of variables and potential confounders exist that might have contributed to these seemingly conflicting results, most of all differences in the reference exposure (formula vs. nondiabetic banked breast milk), study design (prospective vs. retrospective), time point of exposure (early vs. late neonatal period), exposure data quality (quantitative vs. semiquantitative; exclusive vs. nonexclusive breastfeeding), ethnicity, socioeconomic status, type of maternal diabetes, age at follow-up, year of birth, and maternal body weight.

In this issue of *Diabetes Care*, a study by Crume et al. (22) further supports the notion that a long-term breastfeeding (i.e., longer than 6 months) has a protective effect on later overweight risk in ODM. Crume et al. (22) analyzed data from a population in which routine screening and treatment for GDM has long been established and performed (EPOCH). Unfortunately, however, this is not the case in many other populations, although it probably has an important impact on the outcome. Therefore, to allow a comparison with data from other populations, further analyses on the potential impact of the quality of diabetes care on the outcome in breastfed infants of mothers with GDM will be needed. Because maternal diabetes induces specific alterations in the composition of breast milk, good metabolic control during pregnancy and postpartum will necessarily prevent altered milk composition and, consequently, may also prevent potential negative consequences for the developing infant. This might explain discrepancies between the results of this and other clinical studies and those obtained in animal experiments where exposure to untreated maternal diabetes/obesity during the suckling period regularly induced obesity and diabetogenic alterations in the offspring (11–14). Furthermore, one has to keep in mind that the cut-off of 6 months used by Crume et al. was obviously chosen because it corresponds to the recommendations of the American Academy of Pediatrics (23). While in normal populations,

however, a clear dose-response relation exists between the duration of breastfeeding and overweight risk, with a 4% decrease in the risk for each month of breastfeeding from birth up to 9 months (24), such a dose-response relation was not found in ODM so far and only long-time breastfeeding was clearly related to a reduction in overweight risk (19,25). One might speculate that early breast milk (in particular colostrum) from diabetic mothers lacks a protective effect on overweight risk because of its altered composition (9). However, continued breastfeeding has positive effects on maternal glucose metabolism (26). Therefore breast milk composition in mothers with previous GDM will normalize over time, and their late breast milk will provide the same beneficial effects on overweight risk as breast milk from healthy mothers.

In essence, there is no doubt that breastfeeding should be recommended and promoted in ODM as in the general population (15,16,25,27,28). Beyond its important role for mother-child binding, breastfeeding as compared with formula feeding has a considerable number of positive short- and long-term effects on human development, such as a decreased incidence of respiratory infections (29), a lower risk of asthma (30) and atopy (31), and a decreased risk of high blood pressure (32), type 2 diabetes (33) as well as type 1 diabetes (34). Moreover, profound evidence exists that breastfeeding has the potential to decrease the long-term risk of developing obesity as shown by the results of at least four meta-analyses on this issue (24,27,35,36). Concrete reasons for that benefit, in terms of quantitative and qualitative advantages of breast milk versus formula, remain to be established and may lead in the future to a better and safer composition and use of formula also in ODM. However, it remains to be established whether or not early breastfeeding in ODM is as beneficial as in healthy mothers and whether specific milk components might lead to a different outcome. A better understanding of this paradigm of neonatal nutritional "programming" might not only improve neonatal feeding recommendations and practices in ODM but may enable better insights into fundamental mechanisms of neonatal "fuel-mediated" development.

Irrespective of that, a primary prevention of nutritionally mediated disadvantages in ODM is now clear: Population-wide detection and adequate treatment of GDM both pre- and postnatally should be performed to enhance not only the prenatal but also the neonatal nutritional environment of the offspring. This recommendation is not only in-line with the seminal scientific work on fuel-mediated teratogenesis, but it is of outstanding practical importance because universal screening and therapy of GDM have not been established in a majority of countries.

Finally, in a paradigmatic sense the impact of studies such as the one by Crume et al. reaches far beyond the issue of the impact of breastfeeding on obesity risk in ODM. Those studies address the idea that the process of fuel-mediated teratogenesis does not end at birth but extends into the neonatal period. If breastfeeding has the potential to change long-term risks in GDM offspring and, thereby, modify the consequences of exposure to a diabetic intrauterine environment, then we have to extend the historical concept of fuel-mediated teratogenesis beyond birth, opening important chances and challenges of a neonatal diabetes prevention.

ANDREAS PLAGEMANN, MD
THOMAS HARDER, MD

From the Clinic of Obstetrics, Division of "Experimental Obstetrics," Campus Virchow-Klinikum, Charité–University Medicine Berlin, Berlin, Germany.

Corresponding author: Andreas Plagemann, andreas.plagemann@charite.de.

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