Effects of early infant nutrition and perinatal exposure to PCBs and dioxins on neurological development. A study of breast-fed and formula-fed infants
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Summary

In this thesis, effects of early infant nutrition and effects of perinatal exposure to PCBs and dioxins on neurological development are described.

A number of investigators have reported beneficial effects of breast-feeding on development in infants. Breast milk contains not only advantageous substances, but also toxic compounds. Since 1984, the presence of PCBs and dioxins in Dutch breast milk has been of great public concern. From animal studies, it was known that these compounds are neurotoxic. Considering the relatively high intake from breast milk as compared to formula milk, arguments have been postulated to discourage breast-feeding. Consequently, the Dutch government initiated the ‘Dutch Breast Milk Study’: a study of the possible adverse effects of placental and lactational exposure to PCBs and dioxins. This study became a cooperative effort between clinical scientists and animal experimental research workers in the Netherlands.

PCBs and dioxins cross the placenta and the developing fetus can be affected during a critical period of organ growth and development. Much larger quantities of PCBs and dioxins are transferred to the infant postnatally via breast milk. Since milk lipids in formula milk are replaced by lipids of mainly vegetable origin, the postnatal exposure of formula-fed infants is negligible.

Until now effects of fetal and postnatal exposure to PCBs and dioxins have been evaluated behaviourally or as regards mental and psychomotor development, but not with the help of an age-adequate neurological examination. In this thesis, the study group consisted of 418 Dutch Caucasian mother-infant pairs. This number consisted of 104 breast-fed and 107 formula-fed infants in Groningen, and 105 breast-fed and 102 formula-fed infants in Rotterdam. A maternal blood sample was taken in the last month of pregnancy and cord blood was collected immediately after birth. Plasma samples were analyzed for four non-planar PCB congeners 118, 138, 153, and 180. The sum of the concentrations of the four PCB congeners 118, 138, 153, and 180 in plasma (i.e. $\Sigma PCB_{\text{maternal}}$ and $\Sigma PCB_{\text{cord}}$, respectively) was used as a measure of prenatal exposure to PCBs. Prenatal and postnatal exposure to PCBs and dioxins via breast milk was reflected by the levels of these compounds in a 24-hour sample taken in the second week after delivery. The contents of seventeen 2,3,7,8-substituted polychlorinated dibenzo-\(p\)-dioxins (PCDDs) and dibenzofurans (PCDFs), three planar PCBs, and 23 non-planar PCB congeners were determined in breast milk fat as well as in formula milk fat. After adjusting for covariates, we analyzed the relationship between prenatal
exposure to PCBs and lactational exposure to PCBs and dioxins and the neurological condition in the neonatal period and at 18 months of age.

The dietary intake of the same women during pregnancy was investigated, in order to propose feasible measures to reduce the dietary intake of PCBs and dioxins. In addition, in cooperation with the Central Laboratory for Clinical Chemistry of the University Hospital Groningen, we analyzed the fatty acid composition, sterols, minor carbohydrates, and sugar alcohols of the breast milk in the Groningen subpopulation, and in 10 currently available types of formula milk to establish the differences between these compounds in breast milk versus formula milk. We also measured the dietary intake of the breast-feeding women and investigated the relation between the consumption of linoleic acid (LA; 18:2ω6) and of fish and the fatty acid composition of their breast milk. Since the mechanisms responsible for an advantageous effect of breast-feeding are as yet unknown, we evaluated whether a dose-response effect of the arachidonic acid (AA; 20:4ω6), docosahexaenoic acid (DHA; 22:6ω3) or cholesterol levels in human milk exists for the neurological outcome at 18 months.

Chapter 2 describes the relationship between perinatal background exposure to PCBs, PCDDs, and PCDFs and the neurological condition of 418 newborns. We analyzed the concentrations of PCB 118, 138, 153, and 180 in maternal as well as in cord plasma. The milk samples were analyzed for the seventeen 2,3,7,8-substituted PCDDs and PCDFs, which are usually found in biotic samples, three planar PCBs, and 23 non-planar PCB congeners. Perinatal exposure to PCBs, PCDDs, and PCDFs occurs prenatally via the placenta and postnatally via breast milk. To investigate whether such an exposure affects the neonatal neurological condition, the neurological optimality of the 418 newborns was evaluated with the Prechtl neurological examination. Of the 418 children, 394 were neurologically classified as normal, 20 newborns as suspect, and 4 newborns as abnormal. Higher levels of PCBs, PCDDs, and PCDFs in breast milk were related to reduced neonatal neurological optimality. Higher levels of planar PCBs in breast milk were associated to a higher incidence of hypotonia. Since severe neurological deviations were absent, reflexes and responses were normal, and the minor dysfunction mainly consisted of hypotonia, it is possible that the site of action is in the developing muscle.

In Chapter 3, the food intake of 418 women during pregnancy was recorded in order to investigate an association between dietary intake and PCB and dioxin levels in human milk and PCB levels in maternal and cord plasma. After adjusting for covariates, a weak association was found between the estimated dietary intake of PCBs and dioxins and their corresponding levels in breast milk. The dietary intake of PCBs and dioxins was also related to the PCB levels in maternal and cord plasma. Dairy products accounted for about half and industrial oils for about a quarter of the estimated PCB and dioxin intake.

The contribution of a pregnancy-related diet to PCB and dioxin levels in human milk and to PCB levels in maternal and cord plasma is relatively low. A decrease in
the exposure to PCBs and dioxins of the fetus and the neonate probably requires long-term reduction of the intake of these pollutants. Substitution of normal cheese by low-fat cheese and the use of vegetable oils instead of fish oils in the preparation of foodstuffs by the food industry could contribute to a reduced intake of PCBs and dioxins.

Chapter 4 describes the neurological optimality of all 418 children at the age of 18 months in relation to the prenatal and breast milk mediated exposure to PCBs and dioxins. On the basis of the neurological examination, 408 toddlers were classified as neurologically normal. Nine children were categorized as 'mildly abnormal' and one toddler had a hypertonic syndrome which was diagnosed as abnormal. After adjusting for covariates, transplacental PCB exposure was negatively related to the neurological optimality at 18 months. Although greater amounts of PCBs and dioxins are transferred via nursing than via placental passage, an effect of lactational exposure to PCBs and dioxins could not be detected. On the contrary, we found a beneficial effect of breast-feeding on the fluency of movements.

Chapter 5 describes the concentrations of triglycerides, sterols, di- and monosaccharides, and sugar alcohols, as well as the fatty acid composition of 10 currently available types of formula milk for term babies. The results were compared with mature human milk from 99 exclusively breast-feeding women, living in the Groningen region. These women collected 24-hour samples in the second week (n=99), sixth week (n=99), and 3 months (n=25) after delivery. The triglyceride concentrations in human milk were lower than those of the formula milk. Formula milks tended towards a higher proportion of medium-chain fatty acids and contained lower proportions of long-chain polyunsaturated fatty acids. Formulas had cholesterol concentrations 3-35 times lower, and much higher phytosterol concentrations, compared with the human milk. In the formula milk types the glucose, sorbitol, and myoinositol concentrations were generally lower, whereas the fucose and erythreitol concentrations were in the lower mean ± 2SD human milk range. The galactose concentrations in the formulas were generally higher. It is concluded that formula milk and human milk differ considerably in fatty acid composition and concentrations of cholesterol, phytosterols, monosaccharides, and sugar alcohols. The biological consequences of these differences in composition are uncertain.

Chapter 6 describes a study of the influence of maternal diet on (long-chain) polyunsaturated fatty acids in mature human milk. Since long-chain polyunsaturated fatty acids (LCPUFA’s; \( \geq C_{20} \)) are considered essential in the perinatal period, LCPUFA addition to infant formulas is advised, especially those for premature babies. Human milk may serve as reference. Milk fatty acid composition depends on maternal diet, however. We investigated (LC)PUFA balance in 24-hour milk from 99 lactating women, collected on postnatal days 14 (n=99), 42 (n=99), and 89 (n=25). To estimate the influence of maternal diet, food intakes were recorded on postnatal days
Summary and conclusions

12-14, 40-42, and 87-89. The data revealed that linoleic acid (18:2ω6) comprised 85% of daily PUFA intake. Sixty-one percent of the women did not consume fish, resulting in a median (range) daily fish intake of 0 (0-56.8) g. Distributions of milk dihomo-γ-linolenic (20:3ω6) and arachidonic (20:4ω6) acids were Gaussian, but those of eicosapentaenoic (20:5ω3) and docosahexaenoic (22:6ω3) acids were skewed to the right. There was a significant linear relationship between milk 20:5ω3 and 22:6ω3. High milk 20:5ω3 (>0.1 g/100 g) and 22:6ω3 (>0.4 g/100 g) were related to recent fish consumption, rather than to their precursor α-linolenic acid (18:3ω3). Milk 20:3ω6 and 20:4ω6 were not related to their precursor 18:2ω6 either. Literature data show that high formula 18:3ω3/18:2ω6 combined with addition of 20:5ω3 and 22:6ω3 causes retarded growth, probably because of low infant 20:4ω6 status. However, milk from Inuit women and women following fish oil supplementation contains much higher 20:5ω3 and 22:6ω3 contents. The milk of these women may prevent low neonatal 20:4ω6 status due to low-normal 20:4ω6 contents and normal 18:3ω3/18:2ω6 ratios. We hypothesise that formula 18:3ω3/18:2ω6 and long-chain polyunsaturated fatty acid contents may have to be balanced to prevent low 20:4ω6 status. From an evolutionary point of view, milk of mothers on diets with high 18:2ω6 and low LCPUFAω3 may not be the ideal reference for a balanced addition of LCPUFA to formula milk.

In Chapter 7, we analyzed arachidonic acid, docosahexaenoic acid, and cholesterol in breast milk and formula milk and investigated the influence of these components on the neurological outcome in 104 breast-fed toddlers at the age of 18 months. In Chapter 4, we reported a beneficial effect of breast-feeding on neurological development at 18 months of age. The neurochemical mechanisms responsible for this effect are not clear. Many studies point towards the possible role of AA and DHA, as they are structural lipids and present in neural membranes throughout the brain. Most formula milks do not contain AA and DHA, and the cholesterol content of human milk is markedly higher than that of formula milk (see Chapter 5). Cholesterol is an essential component of cell membranes and the major component of nerve cell membrane lipids. The difference between the neurological outcome of breast-fed and formula-fed infants could be partially due to higher AA, DHA, and cholesterol levels in breast milk: in that case, a dose-response effect of the AA, DHA or cholesterol levels in the breast-feeding group would have been expected.

No dose-response effect of the intake of AA and DHA, and cholesterol via breast milk was found on the neurological condition of 18-month-old toddlers. The dietary supplies of AA, DHA and cholesterol through human milk could be amply sufficient to cover the minimum needs for adequate brain development. Future research should concentrate on randomized enriched formula milk trials.