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Should women providing milk to their preterm infants take DHA supplements?

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Key points:

- Human milk globally has an average DHA content of about 0.3 % of fatty acids, with large variation primarily due to different maternal DHA intakes from fish and seafood

- Breastfeeding usually meets DHA needs of term (100 mg/d) but not the much higher requirements very low birthweight infants (VLBWI)
- To match intrauterine DHA accretion, VLBWI require a human milk DHA content of about 1% that can be achieved by maternal supplementation with 3 g/d tuna oil
- A high milk DHA supply to VLBWI may enhance early visual and cognitive development and reduce adverse events such as severe developmental delay, bronchopulmonary dysplasia, necrotizing enterocolitis and allergies
- The supply, metabolism and biological effects of the omega-3 (n3) and the omega-6 (n-6) essential polyunsaturated fatty acids (PUFA) during pregnancy, infancy and childhood has received considerable attention and has been addressed in numerous research studies, as recently reviewed (1-4). The essential fatty acids omega-6 (n-6) linoleic acid (18:2n-6, LA) and omega-3 (n-3) alpha-linolenic acid (18:3n-3, ALA) found in plants and vegetable oils are the precursors of the biologically active long-chain polyunsaturated fatty acids (LC-PUFA). The quantitatively pre-dominant LC-PUFA are n-6 arachidonic acid (ARA, 20:4n- 6), n-3 eicosapentaenoic acid (20:5n-3, EPA) and n-3 docosahexaenic acid (DHA, 22:6n-3). Both during pregnancy and infancy, n-6 and n-3 LC-PUFA are accreted in relatively large amounts in fetal and infant tissues. Particularly high concentrations are found in the brain grey matter and in the rod outer segments of the retina and have been related to functional development such as cognition and visual acuity (4). Some LC-PUFA, including n-6 dihomo-gamma-linolenic acid (20:3n-6), ARA, EPA and DHA also serve as precursors of eicosanoids and docosanoids, such as prostaglandins. prostacyclins, leukotrienes and resolvins. In low concentrations, eicosanoids and docosanoids are powerful regulators of numerous physiological processes such as cardiovascular function and the early postnatal closure of the ductus arteriosus Botalli, thrombocyte aggregation and bleeding time, inflammation and immunity, and others. In fact, the early availability of LC-PUFA has been associated with the immune functions and the likelihood of the development of allergies and infections (1).

LC-PUFA can either be provided preformed via the placenta or the dietary sources such as human milk, or they can be endogenously synthesized from the precursors LA and ALA by consecutive desaturation and chain elongation. However, in humans the conversion rates are rather low. It was estimated that only 0.1% to 10% of the precursor fatty acids are converted to LC-PUFA, with a particularly low rate of synthesis for DHA (5-7). The rates of conversion are also very variable depending on genotypes of the fatty acid desaturase (*FADS*) gene cluster. Individuals with certain genetic haplotypes have extremely low rates of ARA and DHA synthesis and thus depend even more on the supply of preformed LC-PUFA to maintain plasma and tissue levels (1, 8-12). In infants, and particularly in preterm infants, the rates of parent PUFA conversion to LC-PUFA are considered insufficient to achieve biochemical and functional normality (13, 14).

In utero, ARA and DHA are supplied preformed to the fetus by way of an active and preferential materno-fetal transport across the placenta that we have measured *in vivo* using fatty acids labelled with stable isotopes (15, 16). The underlying mechanisms of this active materno-fetal LC-PUFA transfer have been partly explored (17-19). Fatty acids from maternal lipoproteins are released by two lipases expressed in placental tissue, lipopoprotein lipase (LPL) and endothelial lipase (EL). LPL hydrolyses triglycerides, whereas EL is a phospholipase with little triacylglycerol lipase activity. EL continues to be expressed towards the end of pregnancy, while LPL is virtually absent in the trophoblast. In addition, maternal circulating NEFA can be directly taken up by placental tissue. The binding and transfer of released fatty acids is mediated by membrane-bound proteins expressed in the trophoblast, including FABPpm (fatty acid binding protein plasma membrane), p-FABPpm (placental plasma membrane fatty acid-binding protein), FAT/CD36 (fatty acid translocase) and FATP (fatty acid transport proteins) -1 to -6 (17, 19). In the cytosol, fatty acids are bound to fatty acid binding proteins (FABPs) leading to interaction with subcellular organelles, including the endoplasmic reticulum, mitochondria, lipid droplets and peroxisomes. FABPs are also likely to function in the nucleus through the delivery of specific ligands to nuclear transcription factors, such as the peroxisome proliferator-activated receptors (PPAR). This complex

system achieves an active placental materno-fetal transfer of ARA and particularly of DHA. Given that intrauterine growth and body composition is generally considered the reference that postnatal care of preterm infants should match as much as feasible, it appears prudent to aim at approaching the degree of intrauterine provision of preformed LC-PUFA with postnatal nutritional regimens.

After birth, breastfed infants always receive preformed ARA and DHA with human milk lipids. The milk fatty acid composition is modified by maternal diet, lipolysis of body fat stores that markedly contribute to milk fat synthesis, maternal genotype, and stage of lactation (11, 20, 21). Around the world, human milk provides a relatively stable ARA supply around 0.5 % of milk fatty acids, whereas DHA is found at a mean level of 0.3 % but shows much more variation primarily due to differences in maternal intake of dietary DHA sources such as fish and seafood (21, 22). Full breastfeeding usually meets the recommended intakes for term born infants of 140 mg ARA/day and 100 mg DHA/day (1, 23) but not the higher recommended intakes for preterm infants. Although the milk of mothers of preterm women contains slightly higher amounts of LC-PUFA (24), the recommended DHA supply of very low birthweight infants can only be met through human milk if women obtain a markedly increased DHA intake. The human milk DHA content is linearly related to the maternal DHA intake, as we documented in a supplementation study of well-nourished mothers who fully breastfed their infants born at term (25)

LC-PUFA supply to preterm infants

Increasing DHA provision to preterm infants through DHA supplements to the lactating mother needs to be justified by indications for a benefit for clinical outcome. The recent systematic review of the Early Nutrition Academy on the roles of pre- and postnatal long-chain polyunsaturated fatty acids (LC-PUFA) included studies in preterm infants published until 2013 (1). The LC-PUFA provision to preterm infants was also evaluated in a meta-analysis of available studies (26) and in recent reviews (2, 27). Most of the available studies

in preterm infants evaluated DHA supplies with human milk or formula of about 0.2-0.3 % of fat, as often provided to healthy infants born at term. However, this level of supply is not sufficient to achieve the estimated daily intrauterine deposition of DHA of 43 mg/kg body weight, which occurs along with an even high ARA deposition of about 212 mg/kg (28). It has been estimated that the intrauterine DHA accretion rate may be matched postnatally in preterm infants by DHA provision amount to 1% of human milk or formula fat (29). This approach has been evaluated in randomized trials that studied the addition of LC-PUFA-rich oils to human milk (30) or the supplementation of mothers providing human milk with LC-PUFA-rich marine oil (31-34).

Visual and cognitive development

The Cochrane meta-analysis by Schulzke et al found no benefit of an added LC-PUFA supply to preterm infants on cognitive outcomes at the age of 12 to 18 months in 4 out of 7 studies included in this meta-analysis (26). Of interest, the three studies that found such benefits used the newer version II of the *"Bayley Scales of Infant Development"*, which raises the question whether the older version of the Bayley test or other tests might not be as sensitive to detect effects. Visual acuity was not found to be influenced by LC-PUFA supply (26).

Of particular interest are the findings of two large studies providing much higher DHA amounts with milk and hence approaching more closely the levels of intrauterine supply. Henriksen et al (2008) randomized 141 very low birthweight infants to an intervention adding an LC-PUFA-rich algal oil, mixed with soy oil and medium-chain triglyceride oil. The intervention provided an added 32 mg of DHA and 31 mg of ARA per 100 mL of human milk and started at one week after birth, with continuation until discharge from the hospital which occurred on average after nine weeks. Cognitive development was evaluated at 6 months of age by the *"Ages and Stages Questionnaire"* and event-related potentials, a measure of brain correlates related to recognition memory. At the 6-month follow-up, the authors found a

better performance of the intervention group on the problem-solving subscore, compared with the control group (53.4 vs 49.5 points). There was also a nonsignificant trend to a higher total score (221 vs 215 points). The event-related potential data revealed that infants in the intervention group had significantly lower responses after the standard image, compared with the control group (8.6 vs 13.2). Further follow-up to the age of 8 years did not indicate any significant differences at school age with regards to brain structure, cognition and behaviour (35, 36).

Makrides and coworkers performed a very large randomized multicentre trial enrolling as many as 657 preterm infants who were provided with a conventional (0.35 %) or high (1 %) DHA supply from day 2-4 of life until term. The higher DHA provision was achieved by supplementation of women providing human milk with a daily dose of 3 g of tuna oil, or by a preterm formula with increased DHA content, along with about 0.5 % ARA (31-34). No adverse effects of supplementation were observed in the infants. The higher DHA supply improved visual acuity development at the corrected age of 4 months, with an acuity that was 1.4 cycles per degree higher than in the control group (Table 1) (37). The Bayley test of infant development (version II) was applied at an age of 18 months, corrected for gestational age. While no significant benefit of the intervention was detected in the total study population, improved cognitive development was found in girls, and in the group of smaller infants with a birthweight less than 1250 g (Table 1). Probably of even greater clinical importance, the rate of children with severe developmental retardation (Mental Development Index <70) was reduced by half (Table 1). Later follow-up to the age of 7 years did not indicate any significant differences at school age with regards to cognition, behaviour and visual function (38-40).

Effects on other outcomes

In the previously cited trial with 657 preterm infants provided with conventional (0.35 %) or high (1 %) levels of DHA in the milk supplied, the occurrence of chronic lung disease

(bronchopulmonary dysplasia, BPD), defined by the need for oxygen treatment at a postmenstrual age of 36 weeks, was reduced by high DHA supply in boys (relative risk [RR]: 0.67 [95% confidence interval (CI): 0.47-0.96]; P=.03) and in all infants with a birth weight of <1250 g (RR: 0.75 [95% CI: 0.57-0.98]; P=.04) (32). Since this was a secondary endpoint, a new trial to revisit this important effect has been initiated (41). A meta-analysis including 18 randomized controlled trials found that n-3 LC-PUFA supply was not associated with a decreased risk of BPD in all studied preterm infants, but trials that included only infants born at ≤32 weeks of found a trend toward reduced BPD (pooled RR 0.88, 95% CI 0.74-1.05, 7 studies, n = 1156 infants) along with a reduction in the risk of necrotizing enterocolitis (pooled RR 0.50, 95% CI 0.23-1.10, 5 studies, n = 900 infants (42).

The preterm trial by Makrides et al. providing either 0.3 % or 1 % of milk fatty acids as DHA also evaluated the incidence of atopic conditions up to the age of 18 months. (32). There was no effect on duration of respiratory support, admission length, or home oxygen requirement. There was a reduction in reported hay fever in all infants in the high-DHA group at either 12 or 18 months (RR: 0.41 [95% CI: 0.18-0.91]; P=.03) and at either 12 or 18 months in boys (RR: 0.15 [0.03-0.64]; P=.01), while there was no effect on asthma, eczema, or food allergy. A recent Cochrane review evaluated published data on effects of pre- or postnatal n-3 LC-PUFA supplementation to women during pregnancy or the or breastfeeding period on allergy outcomes in their children (43). Although the data were derived from a limited number of informative randomized trials, an added n-3 LC-PUFA supply reduced the risk of any medically diagnosed, IgE mediated allergy in children aged 12 to 36 months (risk ratio 0.66, 95% confidence interval 0.44 to 0.98) but not after the age of 36 months Food allergies were no different after the age of 1 year, but a clear reduction was seen for infants. Also, medically diagnosed IgE-mediated eczema was reduced by maternal n-3 LC-PUFA supply at the age of 1-3 years but not at other ages (43). These data point to possible benefits of a higher n-3 LC-PUFA supply in early life on allergic and atopic disorders.

Conclusion

Based on the available data, a high milk DHA supply to very low birthweight infants and to extremely low birthweight infants at levels that support tissue accretion rates similar to the high rates of intrauterine deposition has the potential to enhance the early visual and cognitive development, and to reduce the occurrence of adverse events such as severe developmental delay, bronchopulmonary dysplasia, necrotizing enterocolitis and allergic manifestations in infancy and early childhood. Lapillonne described the dose-response relationship between the level of DHA in the milk provided to preterm infants and the achieved mental development (Figure 2) and concluded that a DHA intake near 1 % of fatty acid supply is desirable (44). Based on current knowledge, DHA should always be supplied along with ARA, which human milk always provides (45).

Current recommendations stipulate for very low birthweight infants a daily DHA supply of at least 18 mg but preferably 55-60 mg/kg bodyweight (≈1 % of total fatty acid supply) and a daily ARA supply of at least 18 mg but preferably 35-45 mg/kg (≈0.6-0.75 %) (1, 27). It is possible that subgroups of preterm infants achieve greater benefits, for example more immature infants or those with lower birthweights, as well as infants with genotypes predicting a low rate of endogenous LC-PUFA formation. Women providing milk to their very low or extremely birthweight infants can achieve the desirable DHA content in their milk by taking a supplement of 3 g tuna oil per day (≈1% of total fatty acid supply) (29).

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Table 1: Providing preterm infants with milk with a higher DHA dose (about 1% of fatty acids, compared to 0.3%) improved early visual function and reduced markedly abnormal developmental outcomes at age 18 months (29). Later follow-up did not indicate any significant developmental differences at school age.

	High DHA (≈1%)	**Standard DHA** (≈0.3%)	Significance
Visual acuity (cycles per degree, cpd)), age 4 months (corrected for gestational age)			
	9.6 (3.7)	8.2 (1.8)	P=0.025
Mental development index (MDI), age 18 months (corrected for gestational age)			
Girls	99.1(13.9)	94.4 (17.5)	P=0.03
Boys	91.3 (14.0)	91.9 (17.2)	n.s.
Markedly abnormal development index (MDI) , age 18 months (corrected for gestational age)			
MDI <70	17 (5%)	35 (11%)	P=0.03
MDI <85	64 (20%)	90 (27%)	P=0.08

Figure 2: The DHA content in mature human milk is linearly related to the DHA intake of the breastfeeding mother. Data from a randomized supplementation trial, redrawn from (25).

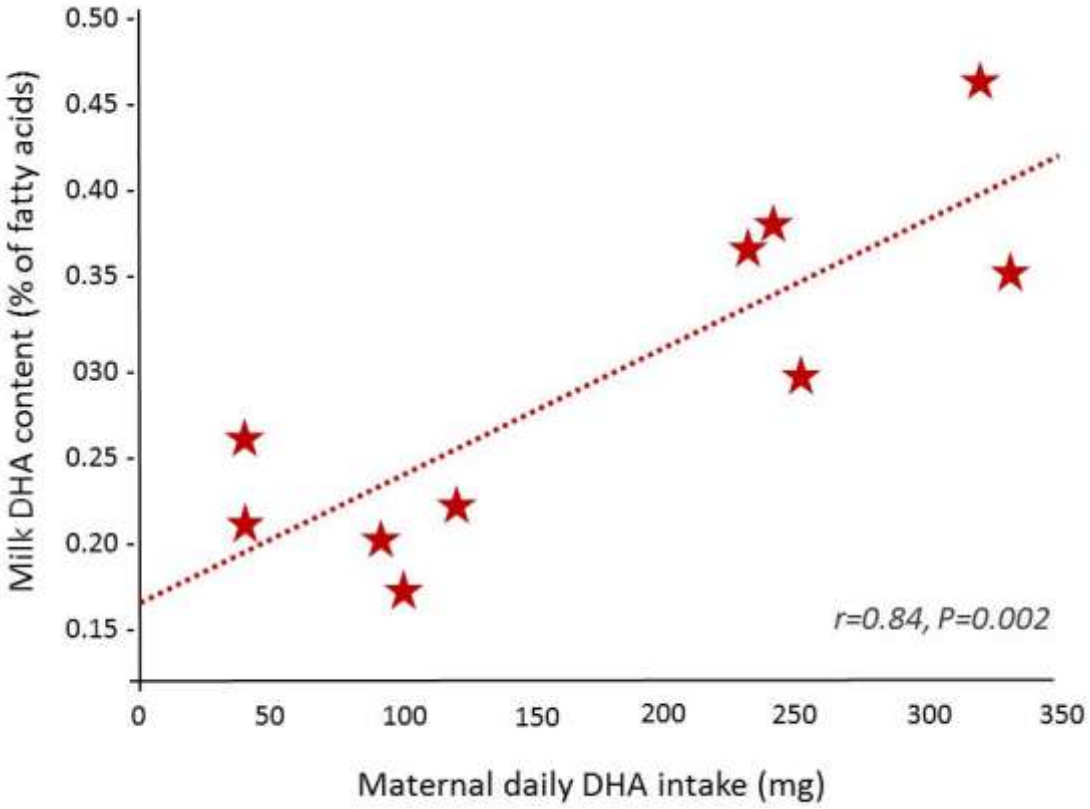
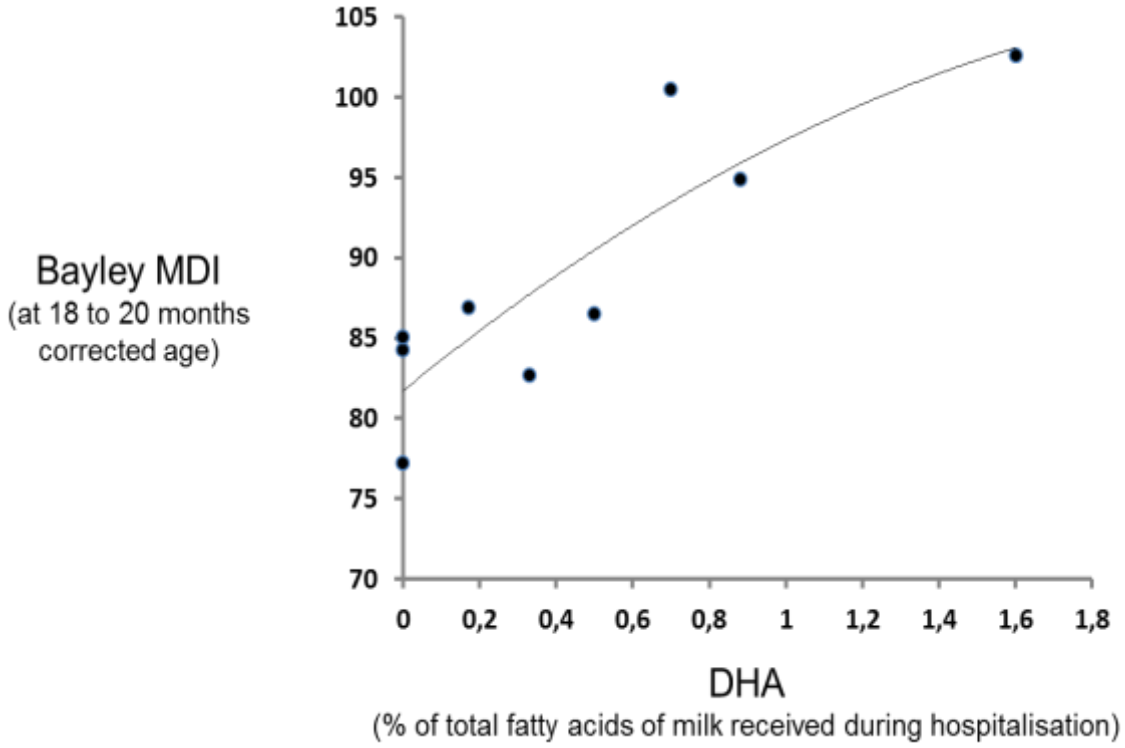


Figure 1: Dose-response relationship between milk DHA supply to preterm infants and the Mayley Mental Development Index (Baley MDI) at age 18-20 months, corrected for gestational age. Reproduced from (44), with permission (currently being requested).



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