Perinatal Supply and Metabolism of Long-Chain Polyunsaturated Fatty Acids
Importance for the Early Development of the Nervous System

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ABSTRACT: The long-chain polyunsaturated fatty acids, arachidonic (AA) and docosahexaenoic acid (DHA), are essential structural lipid components of biomembranes. During pregnancy, long-chain polyunsaturated fatty acids (LC-PUFA) are preferentially transferred from mother to fetus across the placenta. This placental transfer is mediated by specific fatty acid binding and transfer proteins. After birth, preterm and full-term babies are capable of converting linoleic and α-linolenic acids into AA and DHA, respectively, as demonstrated by studies using stable isotopes, but the activity of this endogenous LC-PUFA synthesis is very low. Breast milk provides preformed LC-PUFA, and breast-fed infants have higher LC-PUFA levels in plasma and tissue phospholipids than infants fed conventional formulas. Supplementation of formulas with different sources of LC-PUFA can normalize LC-PUFA status in the recipient infants relative to reference groups fed human milk. Some, but not all, randomized, double-masked placebo-controlled clinical trials in preterm and healthy full-term infants demonstrated benefits of formula supplementation with DHA and AA for development of visual acuity up to 1 year of age and of complex neural and cognitive functions. From the available data, we conclude that LC-PUFA are conditionally essential substrates during early life that are related to the quality of growth and development. Therefore, a dietary supply during pregnancy, lactation, and early childhood that avoids the occurrence of LC-PUFA depletion is desirable, as was recently recommended by an expert consensus workshop of the Child Health Foundation.

KEYWORDS: arachidonic acid; docosahexaenoic acid; infant nutrition; dietary requirements; long-chain polyunsaturated fatty acids

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INTRODUCTION

The potential of the early diet for modulation of the normal trajectory of brain development is of great interest. Long-chain polyunsaturated fatty acids (LC-PUFA), especially arachidonic acid (AA) and docosahexaenoic acid (DHA), are preferentially deposited in relatively high concentrations in developing neural cells and they modulate the structure, fluidity, and function of brain membranes.\(^1,2\)

DHA acyl chains promote the function of the G protein-coupled system in membranes of photoreceptor cells and enhance the signaling pathways of metarhodopsin II.\(^3\) The prenatal and postnatal accretion of LC-PUFA determine myelination and synaptogenesis during the postnatal brain growth spurt.\(^4\) Recent studies have also provided evidence that DHA is involved in dopamine and serotonin metabolism.\(^5\) In preterm babies, the availability of AA has been associated with weight at birth\(^6\) and growth during the first year of life.\(^6\)

This article discusses the potential roles of LC-PUFA during early human growth and development, under the perspective of preventive nutrition. The metabolism of essential fatty acids and their LC-PUFA metabolites, their transfer from mothers to their babies before and after birth, and differences between breast-fed and formula-fed infants are addressed. Available information on the influence of LC-PUFA on the development of visual and other neural functions in preterm and in healthy infants is reviewed.

FIGURE 1. Simplified scheme of the conversion of the precursor essential fatty acids to their long-chain polyunsaturated metabolites.
LONG-CHAIN POLYUNSATURATED FATTY ACID METABOLISM

The liver is the major site for the metabolism of PUFA, both for synthesis of hepatic membrane phospholipids as well as for export and uptake by most other cells. AA and DHA can be synthesized by desaturation and elongation of the essential fatty acids, linoleic acid (LA, C18:2 n-6) and α-linolenic acid (ALA, C18:3 n-3), respectively. The metabolism of LA and ALA uses the same enzymes, resulting in competition between n-6 and n-3 fatty acids (Fig. 1).7,8

In the central nervous system, neurons appear unable to carry out fatty acid desaturation. By contrast, glial cells, astrocytes, and cerebral endothelium can elongate and desaturate precursors of LC-PUFA and accumulate DHA for maintaining a brain environment enriched in LC-PUFA.9 However, the accumulation of preformed DHA and AA in the brain is far more efficient than the desaturation and elongation of the precursors.10 In humans, the fetal and infant brain DHA content is relatively more affected by the diet than AA content, suggesting that endogenous metabolic regulation of AA content is more effective.11

SOURCES OF ESSENTIAL AND LONG-CHAIN POLYUNSATURATED FATTY ACIDS IN THE PERINATAL PERIOD

Fetal Essential Fatty Acid and LC-PUFA Supply

During pregnancy, the fetus is supplied with preformed LC-PUFA by placental transfer. The biochemical mechanisms involved in the underlying transport processes are not fully understood and it is unknown to which extent maternal dietary intakes can affect the LC-PUFA transfer from the mother to the fetus. Plasma lipids of mothers at birth contain higher levels of the essential fatty acid precursors, ALA and LA, than the cord blood lipids of their healthy term infants.12 By contrast, percentage values for LC-PUFA are clearly and significantly higher in infants than in their mothers. These results point to a preferential and selective materno-fetal LC-PUFA transfer.13

Maternal triacylglycerols are hydrolyzed by lipoprotein lipase before they are transferred by the placenta.14 Several proteins have been reported or proposed to be involved in the fatty acid movement across the placenta (Table 1).15-18 The presence in placental tissue of plasma membrane fatty acid binding protein (FABPpm), fatty acid translocase (FAT), fatty acid transport protein (FATP), and recently a new fatty acid binding protein located exclusively on the maternal-facing membranes, named placental plasma membrane fatty acid binding protein (p-FABPpm), has been reported. FABPpm, FAT, and FATP have not shown any specificity for particular types of free fatty acids.19 However, pretreatment of human placental choriocarcinoma (Bewo) cells with antibodies against p-FABPpm inhibited most of the uptake of DHA (64%) and AA (68%), whereas oleic acid uptake was inhibited only 32% compared with the controls treated with preimmune serum.20 Thus, p-FABPpm may be involved in the preferential uptake of LC-PUFA by these cells. p-FABPpm and classic FABPpm are both peripherally membrane-bound proteins of similar size (~40 kDa), but they differ in amino acid composition, pl value, and aspartate aminotransferase activity. Definitive evidence about the structure and function of p-FABPpm must await analysis of its complete amino acid and/or cDNA sequence.
TABLE 1. Plasma membrane fatty acid binding/transport proteins in the human placenta

<table>
<thead>
<tr>
<th>Year</th>
<th>Research group</th>
<th>Name</th>
<th>Size (kDa)</th>
<th>Similarities</th>
<th>Proof of function</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985</td>
<td>Berk</td>
<td>FABPpm</td>
<td>43</td>
<td>MAspAT</td>
<td>Antibody inhibition, gene expression</td>
<td>15</td>
</tr>
<tr>
<td>1993</td>
<td>Abumrad</td>
<td>FAT</td>
<td>88</td>
<td>CD36</td>
<td>Inhibition by protein labeling</td>
<td>17</td>
</tr>
<tr>
<td>1994</td>
<td>Lodish</td>
<td>FATP</td>
<td>63</td>
<td></td>
<td>Gene expression</td>
<td>18</td>
</tr>
<tr>
<td>1994</td>
<td>Dutta-Roy</td>
<td>p-FABPpm</td>
<td>40</td>
<td></td>
<td>Antibody inhibition</td>
<td>16</td>
</tr>
</tbody>
</table>

Note: Plasma membrane fatty acid binding protein = FABPpm; fatty acid translocase = FAT; fatty acid transport protein = FATP; placental FABPpm = p-FABPpm.

Essential Fatty Acid and LC-PUFA Supply with Breast-Feeding

After birth, breast-fed infants receive appreciable amounts of preformed AA and DHA with human milk lipids that meet LC-PUFA accretion rates in membrane-rich tissues. The fatty acid concentration of milk is related to the maternal diet, maternal plasma fatty acid composition, length of breast-feeding, and other factors. While LA values appear to be related to maternal dietary LA intake, AA values in milk are within a rather very narrow range. By contrast, there are more than four-fold differences between the lowest and highest ALA and DHA values, respectively, which indicates a larger relative variability of n-3 than of n-6 fatty acid content in human milk.

Although milk LC-PUFA content is influenced by the maternal diet, studies investigating milk composition indicate some metabolic control of milk PUFA content. We studied PUFA turnover in lactating women using LA uniformly labeled with the stable isotope 13C. The collection of milk and breath samples over a period of 5 days after the tracer application revealed that about 30% of milk LA is directly transferred from the diet, whereas about 11% of milk dihomoy-linolenic acid and 1.2% of milk AA originate from direct endogenous conversion of dietary LA. Thus, the major portion of PUFA in human milk lipids is derived from maternal body stores and not directly from the maternal diet. This results in a relatively constant milk PUFA supply to the recipient infant, which might be of biological benefit (FIG. 2).

In a more recent study, we evaluated the contribution of dietary and endogenously synthesized AA to its milk secretion in 10 Mexican women on a habitual diet with a very low fat content. The accumulated 72-h recovery of 13C-LA in milk was 16.3±6.4% of the dose, but only 0.01% of the label was found as 13C-AA. The AA stemming from conversion of dietary LA contributed only 1.1% to the total milk AA secreted. In this population, 70% of LA and almost 90% of AA secreted in milk were not derived from direct intestinal absorption. Thus, only a minor fraction of milk AA stemmed from conversion of LA, and maternal body stores are the major source of human milk LA and AA. We also studied supplementation of lactating women with n-3 LC-PUFA and found that this intervention can effectively prevent the postnatal decline of milk DHA without changing the percentage utilization of DHA.
FIGURE 2. Schematic depiction of linoleic acid turnover in human lactation. Stable isotope studies with oral intake of $^{13}$C-labeled linoleic acid indicate that 12.5% of dietary linoleic acid is transferred into milk, 20% is oxidized, and about 67% is deposited in maternal stores with slow turnover, such as adipose tissue. Only 30% of the infant linoleic acid supply with human milk is derived directly from the maternal diet, but 70% originates from maternal body depots with slow turnover. Thus, breast-fed infants receive a relatively constant PUFAs supply, even if there are short-term changes of maternal dietary intake.

**Fatty Acid Status in Infants Fed Human Milk or Formula without and with LC-PUFA**

In contrast to human milk, conventional milk formulas with fat derived from vegetable oils do not provide appreciable amounts of LC-PUFA. Infants fed such formulas depend on the utilization of body stores or on endogenous LC-PUFA synthesis for tissue deposition. A number of studies have evaluated the fatty acid composition of plasma and erythrocyte membrane lipid classes in full-term infants fed human milk or formula without LC-PUFA in order to estimate their LC-PUFA status. A marked decrease in plasma and red blood cell AA and DHA in formula-fed as compared with breast-fed infants was observed in the absence of dietary supplementation at different ages. Moreover, not only plasma and red blood cell, but also tissue LC-PUFA contents appear to be affected. The proportion of DHA in the brain cortex of breast-fed infants was higher compared to those fed formula without LC-PUFA.

Although infantile LC-PUFA synthesis has been demonstrated in newborns during the first week of life with refined stable isotope techniques, a limited δ6-desaturase activity and a high utilization of LC-PUFA for deposition, oxidation, and metabolic conversion to eicosanoids seem to result in an inadequacy of endogenous n-6 and n-3 LC-PUFA synthesis to prevent LC-PUFA depletion in infants fed conventional formulas without preformed LC-PUFA.

Therefore, LC-PUFA supplementation of infant formulas has been proposed to achieve similar levels of LC-PUFA in the plasma and cells of formula-fed infants as found in breast-fed babies. Carlson et al. supplemented preterm formulas with
marine oils rich in eicosapentaenoic acid (EPA) and DHA, which resulted in a reduction of AA plasma levels associated with lower growth rate in preterm babies. This effect was attributed to the presence of high EPA content in the supplemented formula, which might have inhibited AA synthesis or displaced AA from phospholipids. Further studies were carried out with other fat supplements, such as a fish oil with low EPA content, fractionated egg yolk phospholipids, evening primrose oil, and single cell oils from algae and fungi. The studies showed that a balanced supplementation with both DHA and AA can normalize LC-PUFA status in infants relative to reference groups fed human milk. Incorporation of AA in formulas supplemented with DHA appears desirable to avoid subnormal plasma levels of AA.

EFFECT OF DHA STATUS ON VISUAL FUNCTION IN PRETERM INFANTS

Since loss of DHA in brain due to dietary restrictions of n-3 fatty acids modifies neuronal function, many studies have been carried out to assess whether improving LC-PUFA status affects visual and cognitive functions in preterm and full-term infants. These are difficult studies since neuronal processes are complex and multifactorial. Potentially confounding factors, such as birth weight, parental education and socioeconomic status, smoking, variability in the infant’s DHA status at birth, different PUFAs ratios among the formulas studied, sample size, and different test methodology may influence the results and obscure potential effects of dietary LC-PUFA supply.

In spite of these difficulties, five prospective, randomized clinical trials have been published reporting an effect of the addition of DHA to formulas on the development of visual function in preterm infants. Uauy and coworkers studied infants born at 27–33 weeks, with an average birth weight of about 1300 g. The infants were randomized to feeding formulas with corn oil (devoid of n-3 PUFA), soy oil (containing the n-3 precursor, ALA), and soy and marine oils (containing both ALA and n-3 LC-PUFA, including 0.35% of fatty acids as DHA) or were part of a nonrandomized reference group fed human milk. At 36 weeks postconceptional age (PCA), the group fed soy and marine oils had lower rod electroretinogram thresholds and higher amplitudes than the corn oil–fed group, similar to the human milk group. Soy oil alone showed a slightly better response than corn oil, but did not match the result of human milk or marine oil. Furthermore, at 57 weeks PCA, transient visual evoked potentials (VEPs) and Teller card tests showed visual acuity to be significantly better in infants fed human milk or marine oil formula than infants fed the other formulas.

Carlson and coworkers randomized infants born with an average gestational age of 29 weeks and a weight of 1100 g to conventional formula or formula enriched with marine oil (0.2% DHA), which were fed up to 79 weeks PCA. Teller card acuity was significantly better in marine oil–supplemented babies at 2 and 4 months of age (corrected for expected term birth).

In a further trial, Carlson and coworkers studied infants with a mean gestational age of 28.5 weeks and a birth weight of 1100 g fed for a shorter time period with a marine oil–supplemented formula providing 0.2% DHA. In comparison to a control formula, they had an improved Teller card visual acuity at 2 months corrected age,
but not thereafter. Interestingly, the subgroup of infants with chronic lung disease did not show an improvement of visual function with n-3 LC-PUFA.

Faldella and coworkers\(^\text{42}\) studied flash VEPs at 52 weeks PCA in 58 preterm infants with an average gestational age of 31 weeks and a birth weight of 1500 g. The infants were fed breast milk or were randomized to a preterm formula supplemented with LC-PUFA (with 0.23% DHA) or a control formula. Breast milk and an LC-PUFA-supplemented formula resulted in similar VEP latencies, while the control formula group showed significantly delayed VEP latencies.

In a multicenter trial, O'Connor and coworkers\(^\text{43}\) studied 470 preterm infants with birth weights of 750–1800 g and fed, in addition to varying amounts of human milk, with one of three formulas without LC-PUFA, a formula with 0.43% of fatty acids as AA and 0.27% DHA from fish and fungal oils, or a formula with 0.41% AA and 0.24% DHA from fish and egg oils. At term, the infants were switched to formulas with the same oil sources, but only 0.15–0.16% DHA. No adverse effects of any formula on growth or other side effects were found. Visual acuity measured by behavioral methods by different investigators in the various centers was not different. However, VEPs measured in three of the participating centers indicated an advantage of 3–4 cycles/degree at 6 months in the two groups fed enriched formulas relative to controls.

In summary, these trials support the efficacy of n-3 LC-PUFA intake on the early development of the visual system, which was not achieved to a similar extent with formulas providing the n-3 precursor PUFA, ALA. In a meta-analysis of the previously published results, SanGiovanni and coworkers concluded that DHA-supplemented formula versus DHA-free formula showed significant differences in visual resolution acuity at 2 and 4 months of age, with combined estimates of behaviorally based visual resolution acuity differences at these ages of 0.47±0.14 and 0.28±0.08 octaves, respectively, at 2 and 4 months. A 1-octave difference equals a reduction in the width of the stimulus elements by 50%. Similarly, a Cochrane review concluded that there is evidence that n-3 LC-PUFA supplementation of formula increases the early rate of visual maturation in preterm infants.\(^\text{44}\)

**EFFECT OF DHA STATUS ON VISUAL FUNCTION IN FULL-TERM INFANTS**

For full-term infants, the published results are less clear. Makrides et al.\(^\text{25}\) investigated full-term infants fed an experimental formula with 0.36% DHA (% weight/weight), 0.58% EPA, and 0.27% \(\gamma\)-linolenic acid (18:3 n-6), or a control formula without DHA, both at the ages of 16 and 30 weeks. Infants fed the formula with DHA exhibited significantly better VEP acuity than infants fed the control formula at both ages, while there was no difference of visual acuity between infants fed formula with DHA and breast-fed infants. Carlson et al.\(^\text{26}\) in another controlled clinical trial with full-term infants, randomized to formula either without or with a relatively low DHA content of only 0.1% and 0.43% AA, reported that, at the age of 2 months, infants fed the DHA-supplemented formula had a significantly better grating visual acuity measured according to the Teller acuity card procedure. However, there was no difference in visual acuity at later time points, despite a persistent significant difference of DHA levels in plasma and red blood cell lipids. The low
concentration of DHA in this study might have caused the lack of a long-term effect in visual acuity.

In a multicenter trial, Auestad et al.\textsuperscript{27} investigated infants receiving formula supplemented with DHA alone (0.23\%) or with DHA and AA (0.12\% and 0.43\%, respectively), as well as infants fed formula without LC-PUFA and nonrandomized breast-fed reference infants. Using a somewhat different methodology at the four study sites, visual acuity was assessed with either an acuity card procedure or a VEP methodology from the ages of 2 to 12 months; the authors reported no group differences in visual functions. Since the study formula used was the same as the one used by Carlson et al.,\textsuperscript{26} who found an effect on visual function at 2 months, it appears possible that the differences in results between the two studies are related to the methodologies applied.

Birch et al.\textsuperscript{28} evaluated another infant formula with a higher DHA content either alone (0.35\% DHA) or in combination with AA (0.36\% DHA and 0.72\% AA). They reported that children who received one of the two DHA-containing formulas had significantly better sweep VEP acuity at the ages of 6, 17, and 52 weeks; the provision of DHA improved visual function up to 1 year of age. By contrast, Jørgensen et al.\textsuperscript{29} did not detect significant differences in swept steady-state VEP values of term infants, at the age of 4 months, fed infant formulas supplemented with DHA or not. However, these authors reported a nonsignificant improvement of visual acuity by the addition of DHA to the formula.

Hoffman et al.\textsuperscript{30}, using similar supplemented formulas in healthy term infants as previously used by Birch et al.,\textsuperscript{28} confirmed again more mature electoretinographic responses and VEPs in infants fed supplemented formulas than in infants fed conventional formulas in the first year of life. Makrides et al.\textsuperscript{31} conducted a clinical trial with infants fed placebo, DHA-supplemented formula (0.35\%) with only 0.1\% EPA, DHA plus AA–supplemented formula (0.34\% AA, 0.34\% DHA), and breast-fed infants. There were no significant differences in measures of visual function at 16 or 34 weeks of age.

Auestad et al.\textsuperscript{32} performed a double-masked, randomized, parallel trial in 239 term infants fed formulas without or with 0.46\% AA and only 0.14\% DHA for 1 year, and in 165 breast-fed infants weaned to formulas with and without AA plus DHA. No effects of this rather low dose of DHA on growth, visual acuity, information processing, general development, language, and temperament were detected.

In conclusion, some of the controlled trials in healthy term infants showed that DHA improved visual acuity during the first year of life, but others found no significant effect. None of the trials reported negative effects on visual acuity. Differences among the results of various studies may be due to differences in methodology and in strategies of supplementation. The dose and form of DHA supply may well be important causative factors for the differences between studies. Lauritzen et al.\textsuperscript{45} recently reported a close dose-response relationship between DHA content in milk and VEP visual acuity in infants at 4 months of age.

**EFFECTS OF LC-PUFA ON BEHAVIORAL DEVELOPMENT**

While a large number of studies have evaluated visual acuity in infants, only few randomized studies have examined the effects of postnatal dietary LC-PUFA on
neurodevelopment. Different tests have been used: the Brunet-Lézine test and Bayley scales measure global neurodevelopment and provide indices of mental and motor skills relative to group norms. More specific tests of cognitive functions, information processing, and learning ability are the Fagan Test of Infant Intelligence (FTII), tests on problem solving and delayed-response tasks, and the MacArthur Communicative Development Inventory. At present, it remains unclear which tests are most sensitive to detect potential effects of LC-PUFA on nervous system development in infants.

In the aforementioned trial of O'Connor and coworkers, preterm infants fed formulas with LC-PUFA showed advantages in novelty preference in the Fagan test at 6 months, but not at 9 months. At 12 months, there was no difference in the Bayley mental development index, but there was an improvement in the Bayley motor development index.

In term infants, Agostoni et al. compared the psychomotor development of term infants randomly assigned to receive formulas with or without LC-PUFA (0.30% DHA and 0.44% AA). At the age of 4 months, Brunet-Lézine test results were significantly lower in infants fed formula without LC-PUFA than in those receiving the LC-PUFA-supplemented formula or human milk. The majority of the infants could be followed up to the age of 24 months, but at this time no differences were found with this test. However, the developmental quotients at the age of 2 years were still significantly and positively correlated to both AA and DHA contents of red blood cell phosphatidylcholine lipids at the age of 4 months.

Infant cognitive behavior was also assayed by Willats et al. using a battery of problem-solving tests at the age of 10 months. In this study, infants at term were randomly assigned in a double-blind fashion in groups receiving during the first postnatal months a formula without or with both DHA and AA from egg phospholipids, providing 0.15–0.25% DHA and 0.30–0.40% AA, respectively. Infants who received preformed dietary LC-PUFA during early infancy achieved significantly more intentional solutions and better intention scores than infants whose formulas was devoid of LC-PUFA. Since higher problem-solving scores in infancy are related to higher childhood IQ scores, this study suggested a possible beneficial role of LC-PUFA supplementation on development.

By contrast, Makrides et al. found no differences in Bayley developmental scores in term infants fed supplemented LC-PUFA formulas at the ages of 16 and 34 weeks of age. Also, Auestad et al. reported the absence of significant effects of AA plus DHA formulas on multiple measures of general development, information processing, language, and temperament over the first 14 months after birth. Further studies are needed to clarify the effect of LC-PUFA availability, the dose and type of supplement, and other influencing factors on the performance in developmental tests in healthy full-term babies.

In relation to the maternal dietary habits, recent evidence describes that breastfed infants whose mothers ate oily fish during pregnancy were more likely to achieve high-grade stereopsis than were children whose mothers did not eat oily fish (adjusted odds ratio: 1.57; 95% CI 1.00–2.45). Also, Jorgensen et al. suggest a cause-effect relationship between infant milk DHA intake and visual acuity. Further research is needed to determine the functional benefits of the supplementation of LC-PUFA for pregnant and lactating women for infants and to define whether there is a minimum DHA requirement for mothers during pregnancy.
CONCLUSIONS

There is accumulating evidence for effects of perinatal PUFA supply and metabolism on early nervous system development, which is most fascinating. Although some studies could not detect effects of DHA provision on visual function in healthy infants, other trials have clearly documented that the addition of preformed DHA to infant formulas may improve visual acuity in preterm and term infants, with advantages reported up to the age of 1 year in some studies. Recommendations for the dietary requirements of n-6 and n-3 fatty acids for brain development are complex and involve both the amounts and balance of the precursors, LA and ALA, and the amounts and balance of AA and DHA. Variability of human milk fatty acid composition highlights the need for caution in using such data as the basis to define infant substrate requirements. The Child Health Foundation Expert Consensus Workshop on the role of LC-PUFA in maternal and child health recently recommended that infant formulas for term infants should contain at least 0.2% of total fatty acids as DHA and 0.35% as AA. Since preterm infants are born with much less total body DHA and AA, they suggest that preterm formulas should include at least 0.35% DHA and 0.4% AA. It is possible that even higher levels might confer additional benefits. The relationship between dose and effect and the influence of other factors need to be further investigated since optimal dietary intakes for term and preterm infants remain to be defined.

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