# Lipid Needs of Preterm Infants: Updated Recommendations

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Long-chain polyunsaturated fatty acids (LCPUFAs) are of nutritional interest because they are crucial for normal development of the central nervous system and have potential long-lasting effects that extend beyond the period of dietary insufficiency. Here we review the recent literature and current recommendations regarding LCPUFAs as they pertain to preterm infant nutrition. In particular, findings that relate to fetal accretion, LCPUFA absorption and metabolism, effects on development, and current practices and recommendations have been used to update recommendations for health care providers.

The amounts of long-chain polyunsaturated fatty acids (LCPUFAs) used in early studies were chosen to produce the same concentrations as in term breast milk. This might not be a wise approach for preterm infants, however, particularly for very and extremely preterm infants, whose requirements for LCPUFAs and other nutrients exceed what is normally provided in the small volumes that they are able to tolerate. Recent studies have reported outcome data in preterm infants fed milk with a docosahexaenoic acid (DHA) content 2-3 times higher than the current concentration in infant formulas. Overall, these studies show that providing larger amounts of DHA supplements, especially to the smallest infants, is associated with better neurologic outcomes in early life. We emphasize that current nutritional management might not provide sufficient amounts of preformed DHA during the parenteral and enteral nutrition periods and in very preterm/very low birth weight infants until their due date, and that greater amounts than used routinely likely will be needed to compensate for intestinal malabsorption, DHA oxidation, and early deficit. Research should continue to address the gaps in knowledge and further refine adequate intake for each group of preterm infants. *(J Pediatr 2013;162:S37-47)*.

Preterm infants are particularly susceptible to postnatal growth failure and nutrient deficiencies. Dietary lipids provide preterm infants with most of their energy needs. Recent interest has focused on the quality of dietary lipid supply early in life as a major determinant of growth, infant development, and long-term health. In this regard, LCPUFAs are of concern because they are crucial for normal development of the central nervous system development and have the potential for long-lasting effects extending beyond the period of dietary insufficiency.[1] Furthermore, LCPUFAs also have potentially significant modulatory effects on developmental processes that affect short-term and long-term health outcomes related to growth, body composition, immune and allergic responses, and the prevalence of nutrition-related chronic diseases.[1]

Recommendations for intake of total fat, essential fatty acids (EFAs), and medium-chain triglycerides (MCTs) have not varied over the last decade, and to our knowledge, there are no new data that would cause us to modify the current recommendations.[1] This is not to say that there have been no new developments in the area of LCPUFAs. Consequently, the aim of this article is to review the recent literature and current recommendations regarding LCPUFAs as they pertain to preterm infant nutrition. In particular, findings related to fetal accretion, LCPUFA absorption and metabolism, effects on development, and current practices and recommendations are used to update recommendations for health care providers.

## LCPUFA Fetal Accretion Rate

When data on intrauterine accretion are available, the amount of nutrient required to attain the mean rate of accretion can be used to estimate the minimum nutrient requirement for preterm infants. When there are adequate bioavailability data on the relative absorption of a nutrient from human milk or infant formulas and on oxidation rate and/or losses, a recommendation can be made regarding the minimum amount for absorption that will result in a net retention rate similar to the intrauterine accretion rate.

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| ALA | $\alpha$-linolenic acid |
| ARA | Arachidonic acid |
| DHA | Docosahexaenoic acid |
| EFA | Essential fatty acid |
| EPA | Eicosapentaenoic acid |
| LA | Linoleic acid |
| LCPUFA | Long-chain polyunsaturated fatty acid |
| MCT | Medium-chain triglyceride |
| MDI | Mental Development Index |

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Attention so far has focused mainly on DHA accumulation in the central nervous system. Whether the brain is protected when availability of DHA is limited is not known, but the ease with which fetal brain DHA is altered by maternal dietary n-3 fatty acid intake suggests that the membrane lipid composition of the fetal brain is sensitive to changes in DHA supply.[2] Because most LCPUFAs accumulate in white adipose tissue and, to a lesser extent, in lean mass and the liver,[3] it is important to consider the accumulation of DHA and other LCPUFAs in all relevant organs.

Analyses of fetal autopsy tissue yielded the following estimates of intrauterine accretion of LCPUFAs during the last trimester: 106 mg/kg/day for linoleic acid (LA), 4 mg/kg/day for α-linolenic acid (ALA), 212 mg/kg/day for arachidonic acid (ARA), and 43 mg/kg/day for DHA.[3] It is likely that the accumulation of LCPUFAs is not linear over time during the last trimester of gestation. Thus, using these numbers to calculate an average daily rate of fatty acid accumulation will overestimate or underestimate tissue requirements during specific periods of growth. A more precise estimate of the fetal accretion rate cannot be determined until more data become available.

The placenta selectively favors the transfer of DHA over other fatty acids, including ARA, during the last trimester of pregnancy.[4] It is generally thought that the fetus does not synthesize LCPUFAs from their precursors at rates sufficient to support an adequate DHA accretion rate. However, evidence from stable isotope studies in preterm infants suggests that ARA and DHA synthesis occurs to some degree at an age when the infant would normally be dependent on placental transfer.[5] Tracer studies indicate that the rate of ARA synthesis is significantly greater than the rate of DHA synthesis, suggesting that the fetus has a greater ability to regulate ARA supply by de novo synthesis or placental reuptake compared with DHA supply.[4] Overall, these data suggest that exogenous supply of DHA may be more critical than that of ARA during the perinatal period.

## LCPUFA Absorption and Metabolism

The fetus does not accumulate appreciable amounts of fat until the last trimester of gestation. Thus, postnatally, adipose tissue cannot be a significant source of LCPUFAs for brain growth of preterm infants as it is for term infants. The LCPUFAs used for organ growth, including brain growth, depend on the amount of LCPUFAs supplied exogenously, intestinal absorption of LCPUFAs, and, finally the capacity to synthesize and oxidize LCPUFAs.

**Digestion and Absorption of LCPUFAs.** Mechanisms of fat absorption and digestion have been reviewed extensively elsewhere.[1] MCTs and structured lipids (eg, synthetic β-palmitate) do not fall within the scope of this review, even though they may affect LCPUFA absorption and improve overall fat absorption. Human milk fat is provided in the form of a milk fat globule and consists mainly of triacylglycerols (98%), phospholipids (1%), and cholesterol and cholesterol esters (0.5%). In breast milk, LCPUFAs are mainly triacylglycerols esterified at the *sn*-2 and *sn*-3 positions and can be part of the phospholipid fraction.[6] Human milk contains bile salt-stimulated lipase and palmitic acid in the β position of the triglyceride molecule. These unique components increase the bioavailability of human milk fat by improving absorption and digestion. However, human milk for preterm infants is often pasteurized to suppress viral and bacterial activity. Heat inactivates bile salt–stimulated lipase and changes the structure of the milk fat globule. These actions may be the reason why feeding pasteurized milk is associated with a 30% reduction in fat absorption and growth rate.[7] Fortification of human milk, particularly with calcium, may further impair LCPUFA absorption. Overall, only 70%-80% of ARA and DHA from pasteurized breast milk is absorbed by very preterm infants (**Table I**).

The recombinant form of human bile salt–stimulated lipase significantly increases DHA and ARA absorption when added to pasteurized human milk.[8] This approach can be potentially beneficial, but the safety, efficacy, and cost-effectiveness of using recombinant human bile salt–stimulated lipase as an additive must be fully characterized before routine use can be recommended.

LCPUFAs from fish oils or from single-cell algae are added as triacylglycerols to the fat blend of preterm formulas. DHA in algal oils has a weak positional specificity and contains equal amounts of DHA in the *sn*-1, *sn*-2, and *sn*-3 positions, unlike the DHA triacylglycerols present in breast milk. These chemical differences may reduce absorption of DHA derived from algal sources. Although fish oil provides DHA with a bond located in the *sn*-2 position, it also contains eicosapentaenoic acid (EPA), which has not yet been proven safe in preterm infants (**Table I**).

Phospholipids are not a common source of LCPUFAs in preterm formulas.[9,10] However, it can be speculated that DHA derived from phospholipids offers potential advantages because it: (1) is one of the forms found naturally in human milk; (2) provides ARA and other LCPUFAs; and (3) may be one way to promote brain DHA uptake.[11]

**LCPUFA Metabolism by Preterm Infants.** Studies using LCPUFA precursors labeled with stable isotopes have demonstrated that LCPUFA synthesis occurs even in small preterm infants.[1] Using the novel "stable isotope natural abundance" approach, the estimated mean endogenous synthesis of ARA was reported as 27 mg/kg/day at 1 month and 12 mg/kg/day at 7 months, and that of DHA was 13 mg/kg/day at 1 month and 2 mg/kg/day at 7 months.[12] Thus, endogenously synthesized LCPUFAs are insufficient to meet requirements defined by the fetal accretion rate. Whether conversion in human milk-fed preterm infants is similar to that in formula-fed preterm infants, or whether conversion is affected by the supply of dietary EFAs or LCPUFAs, remains to be established.

Recent studies in adult populations have suggested that variability in biochemical and functional central nervous system responses to changes in diet are explained in part by