
Enteral and Parenteral Lipid Requirements of Preterm Infants

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Abstract

Lipids provide infants with most of their energy needs. The major portion of the fat in human milk is found in the form of triglycerides, the phospholipids and cholesterol contributing for only a small proportion of the total fat. Long-chain polyunsaturated fatty acids (LC-PUFAs) are crucial for normal development of the central nervous system and have potential for long-lasting effects that extend beyond the period of dietary insufficiency. Given the limited and highly variable formation of docosahexaenoic acid (DHA) from α -linolenic acid, and because DHA is critical for normal retinal and brain development in the human, DHA should be considered to be conditionally essential during early development. In early enteral studies, the amount of LC-PUFAs administered in formula was chosen to produce the same concentration of arachidonic acid and DHA as in term breast milk. Recent studies report outcome data in preterm infants fed formula with DHA content 2–3 times higher than the current concentration. Overall, these studies show that providing larger amounts of DHA supplements is associated with better neurological outcomes and may provide other health benefits. One study further suggests that the smallest babies are the most vulnerable to DHA deficiency and likely to reap the greatest benefit from high-dose DHA supplementation. Current nutritional management may not provide sufficient amounts of preformed DHA during the parenteral and enteral nutrition periods and in very preterm/very low birth weight infants until due date and higher amounts than those routinely used are likely to be necessary to compensate for intestinal malabsorption, DHA oxidation, and early deficit. Recommendations for the healthcare provider are made in order to prevent lipid and more specifically LC-PUFA deficit. Research should be continued to fill the gaps in knowledge and to further refine the adequate intake for each group of preterm infants.

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Lipids provide infants with most of their energy needs; additionally, fat stores constitute the major energy reserve at the time of birth. However, very low birth weight (VLBW) infants and extremely low birth weight (ELBW) infants have very limited fat stores and thus depend on what is provided by enteral and parenteral nutrition [1].

Recent interest has focused on the quality of dietary lipid supply in early life as a major determinant of growth, infant development, and long-term health. Long-chain polyunsaturated fatty acids (LC-PUFAs) are of special interest since n-3 and n-6 LC-PUFAs are critical for neurodevelopment and especially the retina and visual cortical maturation. Altered neurodevelopment may lead to long-lasting effects that extend beyond the period of dietary insufficiency [1]. Furthermore, LC-PUFAs also have potentially significant modulatory effects on developmental processes that affect short- and long-term health outcomes related to growth, body composition, immune and allergic responses, and the prevalence of nutrition-related chronic diseases in later life [1]. LC-PUFA status of preterm infants depends on the amount of LC-PUFAs supplied exogenously, intestinal absorption, and, finally, the capacity of the preterm infant to synthesize the C:20 and C:22 elongated products of the parent fatty acids, α -linolenic (C18:3 n-3) and linoleic (C18:2 n-6) acid.

The aim of the present work is to review the recent literature and current recommendations regarding lipids as they pertain to preterm infant nutrition. Particularly, findings that relate to fetal accretion, intestinal absorption, metabolism, effects on development, and current practices and recommendations will be used to update recommendations for healthcare providers.

Total Dietary Lipid Intake, Cholesterol, Saturated Fats, Medium-Chain Triglycerides

Fat is the major source of energy in human milk (i.e. 40–55% of the total energy provided). The average fat content is about 3.8 g/100 ml and provides a high energy density per unit volume of the feed [1]. The variability of the fat content of human milk is very large and although milk fat content increases with duration of lactation, there appears to be little difference between milk from mothers of term and preterm babies. To date there are insufficient data to determine if addition of supplemental fat to human milk may affect short- or long-term growth outcomes and neurodevelopmental outcomes [2]. The major portion of the fat in human milk is found in the form of triglycerides (98% by weight of the total milk fat), the phospholipids (0.7%) and cholesterol (0.5%) contributing for only a small proportion of the total fat. Because of their non-polar nature, the lipids are mainly present in breast milk in the form of milk fat globules.

Intestinal fat digestion and absorption is reduced in preterm infants and as much as 20–30% of the dietary lipids are excreted in the stools [3]. The possible reasons are numerous and include low enzyme secretion (gastric, pancreatic colipase-dependent triglyceride lipase, bile-salt-stimulated lipase (BSSL), pancreatic phospholipase A₂) and low luminal bile salt concentration [3]. Furthermore, pasteurization (62.5°C for 30 min), used to provide microbiological safety of human milk, alters the nutritional and biological quality of human milk compared to fresh milk by activating the milk BSSL and changing the structure of milk fat globules.

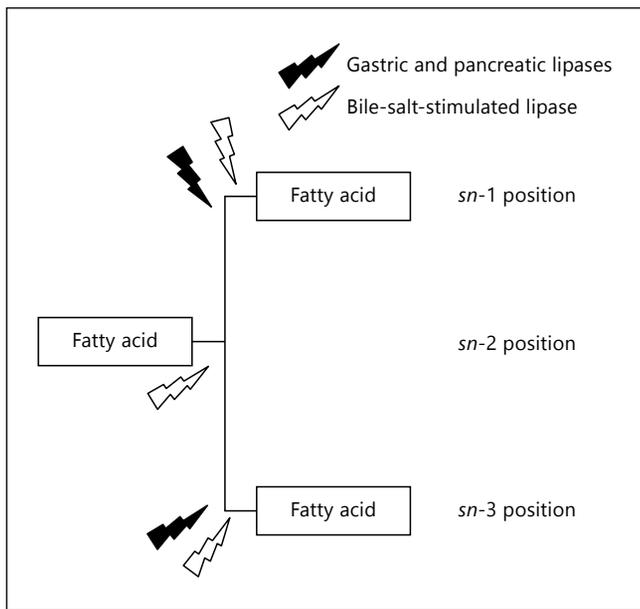


Fig. 1. Stereospecificity and chain lengths of fatty acids at the *sn*-1, *sn*-2 and *sn*-3 positions in triglycerides determine the metabolic fate of dietary fat during digestion and absorption. The enzymatic hydrolysis of dietary triglycerides is a major activity of digestion, largely occurring in the duodenum. Preferential hydrolysis by pancreatic and lipoprotein lipases target the fatty acids in the *sn*-1 and *sn*-3 positions resulting in two free fatty acids and one *sn*-2 monoglyceride which has a water solubility and is absorbed well. In human milk, palmitic acid and myristic acid are found in high proportions at the *sn*-2 position of triglycerides and is therefore well absorbed. The BSSL has no stereospecificity and equally cleaves the three fatty acids from the triglyceride.

Considerable amounts of cholesterol are deposited in tissues, including brain, during growth and dietary cholesterol contributes to the cholesterol pool in plasma and tissues. However, the major proportion of deposited cholesterol appears to be derived from endogenous synthesis and there is yet no evidence that the dietary supply of cholesterol affects nervous system development [1]. Whether or not the preterm infant would benefit from a dietary supply of cholesterol similar to that provided by the human milk (i.e. 10–20 mg/dl) is not known.

In breast milk, long-chain saturated fatty acids such as palmitic acid and myristic acid are found in high proportions (70 and 60% respectively) at the *sn*-2 position of triglycerides. The *sn*-1 and *sn*-3 positions are mainly occupied by unsaturated fatty acids such as oleic acid. The position of the fatty acid in triglycerides can affect digestibility and the metabolism because, during digestion, the gastric and pancreatic lipases prefer to release the fatty acids at the *sn*-1 and *sn*-3 positions in the proximal intestine (fig. 1). The fatty acid present at position *sn*-2 thus remains within a monoglyceride, which can then be more easily absorbed. Since the palmitic acid as free fatty acid in the lumen can form insoluble and unabsorbed calcium soaps, the *sn*-2

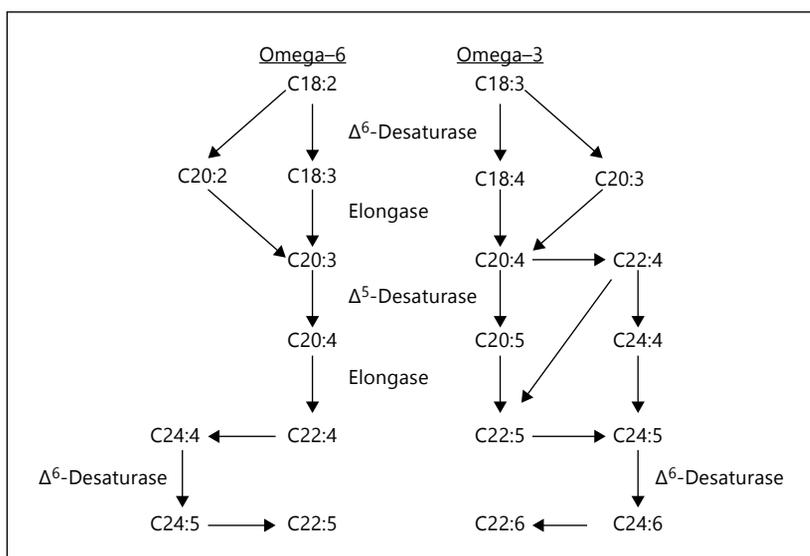


Fig. 2. Synthesis of omega-6 and omega-3 long-chain fatty acids from the parent essential fatty acids.

position of palmitic acid in breast milk ensures a maximum intestinal absorption coefficient. The use of structured lipids (synthetic β -palmitate) increases fat and mineral absorption of preterm infants [4] and may offer health benefits (improved growth, modulation of microbiota and possible immune benefits).

Since the coefficient of fat absorption decreases with increasing chain length and increases with increasing number of double bonds of the fatty acid, high concentrations of medium-chain triglycerides (MCTs) have been used in some preterm formulas to increase the coefficient of fat absorption of preterm infants [3]. Beside their good absorption even in the presence of low intraluminal bile salts and pancreatic lipases, further arguments for the use of MCTs include their carnitine-independent transport into the mitochondria and subsequent oxidation that is more rapid than for longer-chain fatty acids. Therefore, other substrates such as glucose and essential fatty acids (EFAs) can be spared from oxidation. Finally, there was no evidence of difference in short-term growth parameters when high and low MCT formulas were compared [5].

Overall, there are only few relevant new data compared to the previous edition [1] and the recent ESPGHAN recommendations for enteral nutrition of the preterm infant [6] that would support a significant modification of current recommendations.

PUFA Fetal Accretion Rate and Metabolism

LC-PUFA of the omega-6 (n-6) and omega-3 (n-3) series are derived from the EFA precursors linoleic acid (n-6) and α -linolenic acid (n-3) by consecutive enzymatic desaturation and chain elongation (fig. 2). LC-PUFAs are incorporated in practically

all tissues of the fetus and infant, and they are the predominant PUFA in mammalian brain and neuronal tissues. In humans, most brain LC-PUFAs are accumulated during the phase of rapid brain growth in the last trimester of gestation and the first 2 years after birth.

Lipids are transferred across the placenta to meet fetal demands, including the EFAs linoleic acid (LA, C18:2 n-6) and α -linolenic acid (ALA, C18:3 n-3), as well as LC-PUFA. The placenta selectively favors the transfer of the fatty acids arachidonic acid (ARA) and docosahexaenoic acid (DHA) at all stages during pregnancy. Analyses of fetal autopsy tissue yield estimates of intrauterine accretion of LC-PUFAs and show that the accumulation of LC-PUFAs is not linear during the last trimester [7]. Recent estimates suggest that the fetal accretion rates are lower than previously estimated; transfer for ARA and DHA respectively was estimated at 26.4 and 9.5 mg/kg/day between 25 and 35 weeks of gestation and 31.6 and 13.8 mg/kg/day respectively between 35 and 40 weeks of gestation [7]. In term infants, most ARAs and DHAs are stored in adipose tissue (44 and 50%, respectively), substantial amounts of ARA are in skeletal muscle (40%) and brain (11%); for DHA, brain (23%) and skeletal muscle (21%) represent the most relevant tissue pools [7].

Evidence from stable isotope studies in premature infants demonstrates that ARA and DHA synthesis occurs to some degree at an early age when the infant would mostly depend on placental transfer [8]. Using the 'stable isotope natural abundance' approach in formula-fed preterm infants, mean endogenous synthesis of ARA has been estimated to be 27 and 12 mg/kg/day at 1 and 7 months of age, respectively, and that of DHA to be 13 and 2 mg/kg/day, respectively [9]. Whether conversion in human milk-fed preterm infants is similar to that in formula-fed preterm infants or if conversion is affected by the supply of dietary EFAs or LC-PUFAs remains to be established but this study demonstrates that endogenously synthesized LC-PUFAs are likely insufficient to meet requirements based on the fetal accretion rate.

Recent studies also suggest that variability in biochemical and functional central nervous system responses to changes in diet are partly explained by single nucleotide polymorphisms in genes responsible for EFA desaturation. This adds complexity to defining LC-PUFA needs and to establish the effect of other nutrients (i.e. LC-PUFA precursors, n-3/n-6 fatty acid ratio), which affect endogenous LC-PUFA synthesis [10].

Essential PUFA can be converted into long-chain derivatives (LC-PUFAs) or stored in tissues in the form of triglycerides or phospholipids, but they can also undergo total or partial β -oxidation, and hence supply energy or acetate units for the neosynthesis of saturated or monounsaturated fatty acids (fig. 3). ALA, and LA to a much lower extent, is particularly sensitive to oxidation and it is estimated that 75% of ingested ALA is either partially or completely oxidized. To date, none of the estimated accretion estimates have considered the balance between DHA oxidation and endogenous biosynthesis. Present evidence has shown that human adults oxidize DHA to a greater extent than previously thought [11]. DHA oxidation is likely to also occur in preterm infants, especially when energy intake does not meet requirements.

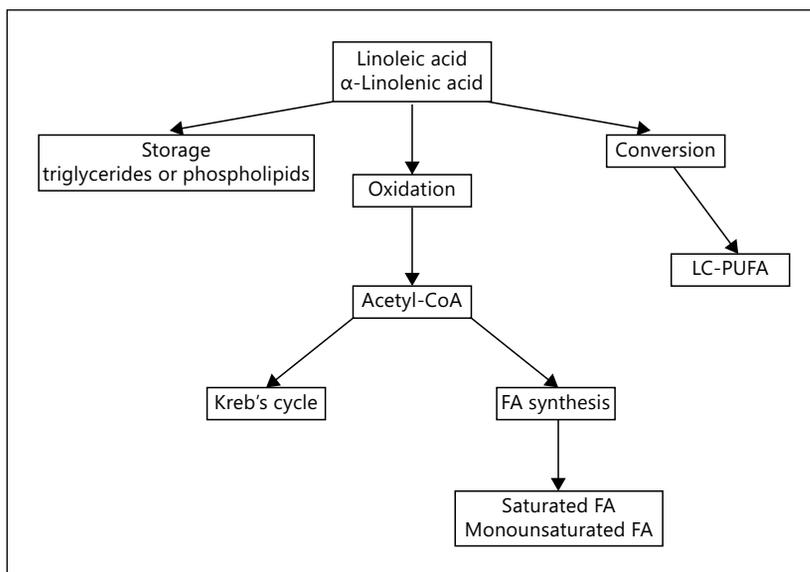


Fig. 3. Metabolic pathways of the essential fatty acids, linoleic acid and alpha-linolenic acid.

Overall these data demonstrate that exogenous supply of DHA, and to a lesser extent that of ARA, is critical in preterm infants and that both fatty acids are conditional essential nutrients in preterm infants.

Digestion and Absorption of LC-PUFAs

Human milk fat is provided in the form of milk fat globules mainly consisting of triglycerides (98%), phospholipids (1%), and cholesterol and cholesterol esters (0.5%). Breast milk supplies the two EFAs, LA and ALA, as well as their long-chain derivatives, ARA and DHA (table 1). In breast milk, LC-PUFAs are mainly triglycerides esterified at the *sn*-2 and *sn*-3 positions and can be part of the phospholipid fraction [12]. Human milk contains BSSL and palmitic acid in the β position of the triglycerides molecule. These unique components increase bioavailability of human milk fat by improving absorption and digestion. Heat inactivates BSSL and changes the structure of milk fat globules. These actions may be the reason why feeding pasteurized milk is associated with a 30% reduction in fat absorption and growth rate [13]. Fortification of human milk, particularly with calcium, may further impair LC-PUFA absorption. Overall, only 70–80% of ARA and DHA from pasteurized breast milk are absorbed by very preterm infants [14].

LC-PUFAs from fish oils or from single-cell algae are added as triglycerides 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

Table 1. Composition of LC-PUFA in milk from mothers of preterm infants

Ref.	Site	Age, weeks	n	% total fatty acids		Sample time point(s)
				DHA	ARA	
[50]	USA	26–36	46	0.22	0.56	M (day of life 42)
[21]	Australia	<33	61	0.3	0.5	Pooled; 2-week intervals; 26–40 weeks
[51]	Netherlands	27–33	20	0.26	0.48	M (day of life 28)
[52]	Hungary	23–33	8	0.27	0.66	Mean 5 sample times over 3 weeks
[53]	Canada	28–34	25	0.3	0.54	<42 days of life
[54]	Netherlands	26–36	65	0.32	0.49	Mean C, T & M
[55]	Germany	24–33	19	0.32	0.59	Mean 4 sample times over 1 month
[56]	Netherlands	30–35	5	0.4	0.6	M (3rd week of life)
[57]	Finland	25–33	23	0.4	0.44	Mean 5 sample times over 3 months
[58]	Spain	33–36	6	0.55	0.69	Mean C, T & M
[19]	Norway	26–30	141	0.7	0.5	M (4 weeks of life)
[21]	Australia	<33	60 ^a	1	0.5	Pooled; 2-week intervals; 26–40 weeks

C = Colostrum (week 1); T = transitional (week 2); M = mature (>2 weeks).

^a Mothers were supplemented with 3 g of tuna oil per day.

triglycerides present in breast milk. These chemical differences may reduce absorption of DHA derived from algal sources. In contrast, fish oils provide DHA with a bond located in the *sn*-2 position which improves absorption; it also contains eicosa-pentaenoic acid (EPA), which is well absorbed but has not yet been proven to be safe in preterm infants when provided at a high amount [14].

Timing and Amount of Enteral Lipid Administration

The possible effects of enteral LC-PUFA supplementation which include improving neurological and visual development altering growth and modulation of immune functions and are extensively reviewed elsewhere [14–16]. In experimental studies, LC-PUFAs have been shown to play important roles in central nervous system development. Poor accumulation of retinal and brain DHA leads to abnormal retinal physiology, poor visual acuity, increased duration of visual fixation, and increased stereotyped behaviors and locomotor activity. The evidence most relevant to the issue of causality showed that control performance levels were restored when DHA was added to the diets of animals in which brain DHA concentration had been severely reduced. Nevertheless, the magnitude of these effects is not large, despite the fact that the studies were conducted under profound dietary restriction. The relevance of these findings to human development is unclear.

Studies in preterm humans indicate possible benefits for retinal and cognitive development, as suggested by greater retinal sensitivity to photic stimulation assessed by electroretinography, more mature visual acuity, and short-term effects on global

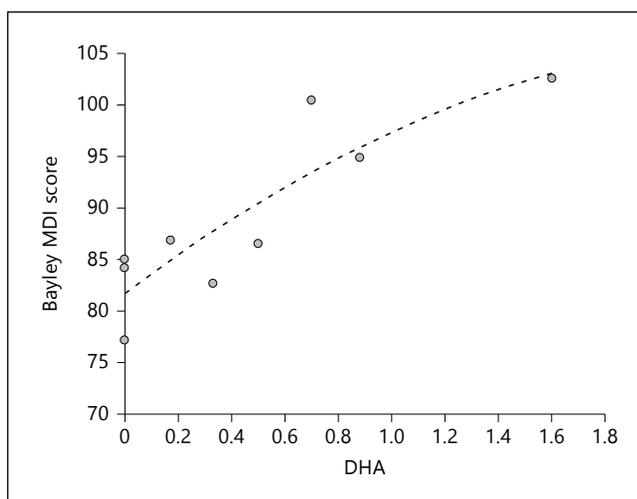
developmental outcomes at 6–18 months after DHA supplementation of preterm infant formula in controlled clinical studies. With regard to neurodevelopment in preterm infants, recent meta-analyses suggest that benefits of formula supplementation with LC-PUFA are less clear [17]. This is somewhat surprising because many studies indicate that LC-PUFAs play an important role during development. Among many possible explanations for the difficulty in demonstrating clinical benefits of LC-PUFA supplementation in preterm formulas by meta-analysis are the extreme variability in study design of studies and the selection of relatively mature and healthy preterm infants which are likely less DHA-deficient than VLBW infants [14].

Interestingly, the amount of LC-PUFAs used in early studies was chosen to produce the same concentration of ARA and DHA in formula as in term breast milk (i.e. 0.2–0.4% fatty acids). This may not be a wise approach for preterm infants and, particularly, for very and extremely preterm infants because the amount of DHA provided by ingesting breast milk is below the in utero accretion rate. Three studies report outcome data in preterm infants fed milk with a higher DHA content of 0.5–1.7% of total fatty acids [18–22]. The first study, which examined the effect of providing DHA supplementation (0.50% of total fatty acids) for up to 9 months after term, showed that DHA improved growth in the whole cohort of preterm infants and improved mental development in boys [18].

In a more recent study, the effects of the supplementation of human milk with oils that provided an extra 32 mg of DHA and ARA per 100 ml was assessed [19]. This intervention started when 100 ml/kg of enteral feeding was tolerated and lasted until hospital discharge. Combined with the LC-PUFAs in human milk, the supplementation provided infants with a mean intake of 59 mg/kg/day of DHA and 48 mg mg/kg/day of ARA [17]. At the 6-month follow-up evaluation, the intervention group performed better than the control group in the problem-solving subscore of the Ages and Stages Questionnaire, and in the electrophysiologic assessment of event-related potentials suggesting better recognition memory. At 20 months' postnatal age, no differences in the mental and motor development scores of the Ages and Stages Questionnaire or in the Mental Development Index (MDI) score of the Bayley Scales of Infant Development were observed, but the intervention group had better results at 20 months at the free-play sessions, suggesting positive effects from supplementation on functions related to attention. Finally, plasma DHA concentration at discharge was positively correlated with the Bayley MDI and with 'sustained attention' [23].

The third study was designed to compare the effects of a high versus standard DHA intake (i.e. 1 vs. 0.35% total fatty acids as DHA) while ARA intake was kept constant (0.5% total fatty acids). This study included both breast-fed and formula-fed infants. Mothers who provided breast milk took capsules containing 3 g of either tuna oil (900 mg DHA) or soy oil (no DHA), which resulted in milk with either high or standard DHA content. A formula with matching high versus standard DHA concentrations was used for infants who required supplementary feeds. The feeding regimen was

Fig. 4. Relationship of DHA intake (expressed as % of total fatty acid in milk during hospitalization) and Bayley MDI score at 18–20 months' corrected age of preterm infants [adapted from 12, 15, 34].



started between days 2 and 5 after birth and maintained until expected term. All infants received a standard term formula with DHA after the expected term. Visual acuity was improved significantly at 4 months' corrected age [22]. At 18 months there were no overall differences in MDI or in the Psychomotor Developmental Index (PDI) of the Bayley Scales, but fewer infants were classified as having an MDI score <70 [20]. Infants who weighed <1,250 g and were fed the high-DHA diet had a higher MDI score than controls (mean difference 4.6; 5% CI 0.1, 9.0; $p < 0.05$), but the difference was not significant when gestational age at delivery, sex, maternal education, and birth order were taken into account. Girls, but not boys, fed a high-DHA diet had higher MDI scores and were less likely to have mild or significant developmental delay than control girls. Finally, the early advantage seen on visual and cognitive functions did not translate into any clinically meaningful change in language development or behavior when assessed in early childhood [24]. Supplementation of VLBW infants with larger doses of DHA may be beneficial for functions beyond development since this trial did demonstrate a reduction in the incidence of oxygen treatment at 36 weeks (boys or infants with a birth weight of <1,250 g only) fed the high versus standard DHA intake, and a lower incidence of hay fever (boys only) at either 12 and 18 months [20, 25].

Overall, these studies show that providing larger amounts of DHA supplements is associated with better neurological outcomes (fig. 4) and possibly better respiratory outcomes. One study suggested that the smallest babies are the most vulnerable to DHA deficiency and likely to reap the greatest benefit from high-dose DHA supplementation [20]. The observation that a non-significant difference in mean MDI translated to fewer infants with a low MDI score suggests that a high dose of DHA is more efficient, or is only efficient, in certain subgroups of infants, probably those at high risk of DHA deficiency. It should also be noted that none of the studies prevented the

early DHA deficit due to parenteral nutrition [26]. This early DHA deficit may explain, at least in part, why development assessed at 18 months remained below the normal range observed in term infants.

Practical Consideration with Regard to Enteral LC-PUFA Supplementation

The fat and fatty acid content of human milk is known to be highly variable. For example, fatty acid composition varies among countries, between specific women, by length of gestation and stage of lactation, throughout the day, and within a feeding. Variability is greater for ALA and DHA than for LA and ARA [27, 28]. The worldwide mean (\pm SD) concentration of DHA in breast milk (by weight) is $0.32 \pm 0.22\%$ (range 0.06–1.4%) and of ARA is $0.47 \pm 0.13\%$ (range 0.24–1%) [29]. When viewed as a percentage contribution to total fatty acids, DHA is often slightly higher in preterm than full-term milk [30]. The LC-PUFA content of banked human milk appears to be similar to mature milk [14].

Preterm infant formulas are currently supplemented routinely with commercially available sources of LC-PUFA so that the fatty acid composition resembles that of human milk. Most of the LC-PUFA oils added to infant formulas are derived from microorganisms. Some, however, are derived from a combination of low-EPA fish oil as a source of DHA and oil from microorganisms as a source of ARA. The usual DHA content of preterm formulas ranges between 0.2 and 0.4% of total fatty acids but the infants fed these formulas have constantly exhibited a reduced DHA status at time of discharge of hospital or expected term [14] (table 2).

Human milk responds to changes in the maternal diet, and LC-PUFA supplementation of mother increases DHA concentration in milk. Mothers who live in coastal areas or on islands produce milk with the highest DHA levels. At milk DHA contents above 0.8% of fatty acids (~ 45 mg/kg/day), none of the infants have an erythrocyte DHA concentration below 6% at expected term, but at milk DHA content of 1% (~ 55 mg/kg/day), the erythrocyte DHA concentration ranges between 6.5 and 9%, which are values expected to be seen in term infants at birth (table 2). Preterm infants receiving 59 mg DHA/kg/day exhibit increased plasma DHA concentration by 12% during time from study inclusion to hospital discharge [19].

Three of the six reports of preterm infants fed preterm formula supplemented with omega-3, but not omega-6 LC-PUFAs showed some indices of lower growth [31]. Since then, all trials have investigated the effects of omega-3 LC-PUFA supplementation in preterm formulas together with ARA supplementation and none have demonstrated a negative effect of supplementation on indices of growth [31]. Furthermore, supplementing lactating mothers with fish oil to increase the DHA content of human milk to approximately 1% dietary fatty acids had no effect on weight or head circumference up to 18 months' corrected age compared with standard feeding practice (0.2–0.3% DHA) [20]. In fact, preterm infants fed higher DHA were 0.7 cm longer at 18

Table 2. One approach, when feeding preterm infants, would be to match the concentrations of DHA in the fetal blood in utero. In that case, the DHA status of preterm infants should increase during hospitalization in order to reach, at expected term, a level comparable to that of term infants at birth [34]. Many studies have used LC-PUFA concentrations in plasma (PPL) or red blood cell (RBC) phospholipids in an attempt to describe the LC-PUFA status at expected term. DHA status of preterm infants fed current preterm formulas containing 0.2–0.37% fatty acids as DHA, which translates into 14 to 30 mg/kg/day, or breast milk exhibit a decline in their DHA status between birth and expected term (or hospital discharge). Those fed a DHA dose >45 mg/kg/day exhibit a DHA status that either increases during hospitalization or reach a level comparable to that of term infants

Reference	DHA, mg/kg/day	Effects on DHA status
Current DHA intake, see [14]	14–30	Decline in DHA status
[19]	32	Decline in DHA status (PPL)
[21]	45 ^a	RBC DHA at expected term <6% ^d
[21]	54 ^b	RBC DHA at expected term = 6.5–9% ^d
[19]	59 ^c	Increase in DHA status by 12% (PPL)

^a Human milk from Danish mothers likely consuming fish.

^b Human milk supplemented with a DHA supplement.

^c Mother's milk of women receiving 3 g of tuna oil per day.

^d Values observed for RBC DHA in term infants at birth is ~8%.

months' corrected age despite a decline in preterm infant ARA status was observed [20]. It should be noted that the diet received by the preterm was not deprived in preformed ARA since the supplementation of the mother with fish oil did not alter the milk ARA content (i.e. $0.5 \pm 0.1\%$ of total fatty acids).

Strategies to increase DHA intake of preterm infants by supplementing lactating mothers with fish oil is very efficient to induce changes in milk DHA content but it leads to a large variation in the DHA content of the human milk with values as low as 0.3% and as high as 2.5% [21]. Therefore, adding DHA \pm ARA directly into the feeding is likely the most reliable method for delivering adequate amount of LC-PUFAs to preterm infants [19].

Recommendations

- We strongly endorse human milk feeding as the preferred method of feeding preterm infants. Because of the variation of its DHA content due to the mother's diet, nutritional counseling during the lactation period is recommended.
- Nutrient recommendations for LC-PUFAs should be expressed as absolute amount per kg/day, not as a proportion of total fatty acids because the latter applies only if full enteral feeding is reached.
- DHA and ARA should be considered conditionally essential during early development and both should be provided during enteral feeding of preterm infants.
- A reasonable range of intake for DHA is to 18–60 mg/kg/day (approx. 0.3–1.0% of fatty acids). Intakes of 55–60 mg/kg/day (approx. 1.0%) of DHA from the

time of preterm birth to expected term have been tested, appear to be safe, promote normal DHA status, and appear to improve visual and neurocognitive functions and, therefore, are likely to be the estimated average requirement for very preterm infants.

- A reasonable range of intake for ARA is to 18–45 mg/kg/day. ARA should be provided during the DHA supplementation period but limited data are available to define the optimal dose of ARA. When a dose of DHA of 55–60 mg/kg/day is provided, the estimated average requirement for ARA is 35–45 mg/kg/day as this level has been shown to support growth.
- Limited data are available to define if there is any benefit for including EPA in the diet of preterm infants. Therefore, we recommend not exceeding 20 mg/kg/day of EPA, which is the mean amount of EPA provided daily by human milk + 1 SD when fed at 180 ml/kg/day.
- Limited data are available to define requirements of LC-PUFAs in subgroups of preterm infants, but it is likely that the infants with a birth weight <1,250 g will benefit the most of the higher intake.
- The recommendations for DHA, ARA, and EPA specified above should be continued until the infant reaches expected due date. After the expected due date, recommendations for term infants should be applied [32].

Timing and Amount of Parenteral Lipid Administration

Lipid emulsions are used in pediatric parenteral nutrition as a non-carbohydrate source of energy in a low volume and with low osmolarity. They also provide EFAs to prevent EFA deficiency [8]. Evidence has accumulated that in addition to their nutritional role as a source of energy and EFAs, lipid emulsions can influence numerous physiopathological processes including oxidative stress, immune responses and inflammation [33]. It has also become clear that preterm infants have special nutritional needs in early life and there is now a considerable body of evidence to suggest that lipids administered at this age may determine various outcomes in later life, including both physical growth and intellectual development [34].

Lipid emulsions contain various oils with egg yolk phospholipids as the emulsifier and glycerol to make the emulsion isotonic. For pediatric patients including preterm infants, the use of the standard 20% emulsions, which contain a lower ratio of phospholipid emulsifier/triglycerides than standard 10% lipid emulsions, is recommended since it allows more efficient triglyceride clearance, even at a higher triglyceride intake [8].

The initiation of lipids within the first 2 days of life in very preterm infants appears to be safe and well tolerated but few data support the early initiation of parenteral administration of lipids as a means to improve growth or decrease long-term morbidity [35, 36]. In contrast, a positive effect of early parenteral lipids on nitrogen balance has

been shown in two separated studies [37, 38]. In the larger one, the efficacy of the introduction of a high dose of parenteral lipids (i.e. 2–3 g/kg/day) combined with 2.4 g/kg/day of amino acids (AA) from birth onwards was compared to a group receiving a similar amount of AA but no lipids [38]. The nitrogen balance on day 2 was significantly greater and plasma urea levels were significantly lower, suggesting that administration of parenteral lipids combined with AA from birth onwards improves conditions for anabolism. On the other hand, triglycerides and glucose concentrations were significantly greater in the AA + lipid group compared with the control group and more infants required insulin therapy. There were no benefits on growth, hospital clinical outcomes or total duration of hospital stay and, therefore, the clinical benefits of such a strategy remain to be proven.

Despite the limited available data, there are concerns that lipid emulsions might have potential adverse effects, including chronic lung disease, increases in pulmonary vascular resistance, impaired pulmonary gas exchange, bilirubin toxicity, sepsis and free radical stress [8]. Furthermore, it is a matter of debate as to what extent lipid emulsions are involved in the development of cholestasis [8, 39]. Also, questions arise on long-term detrimental effects of lipid emulsion since aortic stiffness and myocardial function in young adulthood has been shown to be associated with the fact of being exposed to soybean lipid emulsion during neonatal life [40]. Guidelines with regard to side effects or use in special disease conditions are therefore prudent and it is recommended to avoid the supply of lipid emulsions in high dosages and to adjust the delivery of intravenous lipids to plasma triglyceride concentrations [8].

Practical Implication with Regard to Parenteral LC-PUFA Administration

The adequacy of historical soybean lipid emulsions for the nutritional needs of newborn and premature infants might be questioned. Although an intake of PUFA is required to prevent any EFA deficiency, it is known that excessive intake, particularly of LA, has detrimental effects which include a decrease in the formation of DHA acid from its parent precursor. A reduction in the amounts of potentially pro-inflammatory n–6 fatty acids from soybean oil may be indicated, for example in premature infants with compromised lung function given their influence on pulmonary vasculature [41, 42].

The provision of alternative emulsions containing oil mixtures which are less inflammatory, such as those rich in n–9 fatty acids, may be better for redox status. Despite a lower PUFA content in olive oil/soybean oil emulsion, higher levels of n–6 PUFA intermediates were observed, suggesting a higher degree of endogenous LA conversion [43].

The MCT-containing lipid emulsions contain equal proportions of long- and medium-chain triglycerides. These emulsions are of possible interest since they may, to

some extent, protect LC-PUFAs from β -oxidation, confer some benefit with regard to fat oxidation in preterm infants, and increase the incorporation of EFAs and LC-PUFAs into circulating lipids [39].

Whether carnitine supplementation of parenterally fed neonates is required to improve long-chain fatty acid oxidation, lipid tolerance and ketogenesis are still a matter of debate, but to date, there is no evidence to support the routine supplementation of parenterally fed neonates with carnitine [44].

Finally, the use of fish oil in lipid emulsions, which has specific anti-inflammatory effects via n-3 fatty acids, might offer additional benefits. There is a theoretical advantage to use lipid emulsions containing fish oil to maintain adequate DHA status. Since it has been shown that cord plasma and red blood cell DHA content increases with gestational age, it may be expected that infants receiving parenteral lipids exhibit similar pattern of circulating DHA. The few data published to date show that providing lipid emulsion containing 10% fish oil at a dose of ≤ 2 g/kg/day fail to demonstrate an increase in circulating DHA [45] whereas providing a target dose of 3–3.5 g/kg/day of a lipid emulsion containing 15% of fish oil beneficially modulates the DHA profile [46].

Although these alternative lipid emulsions appear promising, the clinical benefits of lipid emulsions that are not purely soybean-based (e.g. MCT-soybean, olive-soybean, and soybean-MCT-olive-fish emulsions) remain to be demonstrated. In a recent meta-analysis, only a weak association of such lipid emulsions with fewer episodes of sepsis has been demonstrated, with no beneficial effects on bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy of prematurity, patent ductus arteriosus, intraventricular hemorrhage, significant jaundice, hypertriglycerolemia, or hyperglycemia [36]. Other studies demonstrated that lipid emulsions containing fish oil lower plasma lipids [45], bilirubinemia [46] or plasma γ -glutamyl transferase [47] but have no preventive effect on cholestasis [48]. Finally, a randomized but not blinded study suggests that emulsions containing fish oil may reduce the risk of severe retinopathy [49, 59–61]. Overall, lipid emulsion containing fish oil appears to have potential beneficial effects in preterm infants. However, these lipid emulsions, primarily designed for adult care, provide as much EPA as DHA and no ARA, and it remains to be demonstrated that such intakes are safe in preterm infants.

Recommendations

- The initiation of lipids within the first 2 days of life in very preterm infants appears to be safe and well tolerated. When infused at a similar amount (g/kg/day) than that of amino acid, a dose of 2–3 g/kg/day of parenteral lipids can safely be used from birth onwards.
- Lipid emulsions that are not purely soybean-based should be preferred over the soybean or soybean/sunflower-based emulsion since they reduce the risk of sepsis and promote more favorable LC-PUFA profile.

- Lipid emulsions containing fish oil are potentially useful to favor better DHA status and improve various health outcomes. Their routine use is not recommended since their clinical benefits and safety have not yet been fully demonstrated in preterm infants.

Disclosure Statement

The author has no conflicts of interest to disclose.

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