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Review

Fatty acid requirements for the preterm infant

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SUMMARY

Fatty acids are critical nutrient regulators of intracellular signaling and influence key pathways including inflammatory responses, hemostasis as well as central nervous system development and function. Preterm birth interrupts the maternal–fetal transfer of essential fatty acids including docosahexaenoic and arachidonic acids, which occurs during the third trimester. Postnatal deficits of these nutrients accrue in preterm infants during the first week and they remain throughout the first months. Due to the regulatory roles of these fatty acids, such deficits contribute an increased risk of developing prematurity-related morbidities including impaired growth and neurodevelopment. The fatty acid contents of parenteral and enteral nutrition are insufficient to meet current recommendations. This chapter summarizes the regulatory roles of fatty acids, current recommendations and limitations of parenteral and enteral nutrition in meeting these recommendations in preterm infants. Suggested areas for research on the roles of fatty acids in preterm infant health are also provided.

1. Introduction

Dietary fat intake from parenteral and enteral lipids contributes to an appropriate balance of macronutrients; its energy density and composition optimize protein and carbohydrate metabolism. This high energy density constitutes a relatively higher calorie release from oxidation of fat as compared to protein and carbohydrate. The provision of essential and critical long chain fatty acids support optimal growth, development, and health in preterm infants. The quality and quantity of parenteral and enteral lipids continue to evolve with improved understanding of the regulatory mechanisms of the building blocks of complex lipids and their role in infant health. Dietary lipid components, including fatty acids and their metabolites, serve not only as energy sources but also as regulators of developmental, immune and metabolic pathways. Improved delivery of dietary lipids to preterm infants will contribute a critical nutritional influence on infant health. These lipid delivery strategies must coordinate optimal aspects of timing, mode of delivery as well as quantity and quality of lipid subclasses.

2. Placental transfer and fetal acquisition of long chain polyunsaturated fatty acids (LC-PUFAs)

Lipolysis in maternal circulation releases non-esterified fatty acids for transfer [1]. Lipoprotein lipases and endothelial lipases act at the maternal placental surface to free fatty acids for transfer. Mechanisms of fatty acid transfer across the placenta involve simple diffusion and transport mechanisms such as fatty acid-binding proteins and fatty acid translocases.

LC-PUFA accretion during the third trimester by the fetus coincides with a period of substantial growth and continued organ development. Targeted trafficking sends these essential nutrients to concentrate in the brain and retina as well as skeletal muscle and adipose tissue. The fat stored in adipose tissue acts as a depot and source for fatty acids through early infancy.

Preferential transfer occurs for essential fatty acids over non-essential, and a distinct pattern occurs such that arachidonic acid (AA, 20:4n-6) and docosahexaenoic acid (DHA, 22:6n-3) are preferentially transferred over linoleic acid (LA, 18:2n-6) and alpha-linolenic acid (ALA, 18:3n-3). The concept of biomagnification refers to the finding that fetal circulation contains higher levels of AA and DHA as compared to maternal levels [1]. Multiple lipid classes show this pattern, as measured in umbilical cord blood versus maternal blood, including triglycerides, cholesterol esters and phospholipids [2]. This phenomenon highlights the biological

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importance of these nutrients. Although the fetal liver shows Δ5- and Δ6-desaturase activities, the activity level appears insufficient to produce needed amounts of the longer chain PUFA [3], also emphasizing the importance of placental transport.

Estimated daily fetal accrual rates during the third trimester for AA are 212 mg/kg/day and estimated rates for DHA accretion range between 43 and 60 mg/kg/day [4,5]. Roles for AA in fetal development include cell growth and differentiation, and its heavy concentrations in the central nervous system reflect its role in neurodevelopmental processes [6]. DHA is key for central nervous system development and function, and is most highly concentrated in the retinal photoreceptor rod cell [7]. It helps mediate neuronal development. Maternal DHA status and thus fetal DHA accretion impact later cognitive function in childhood [8].

Disorders during pregnancy may impair fetal LC-PUFA accrual. Pregnancies complicated by intrauterine growth restriction show altered endothelial lipase expression (decreased) as well as altered lipoprotein lipase expression (increased) [9,10]. Altered fatty acid transport appears to be multi-factorial in pregnancies complicated by pre-eclampsia; reasons include lower maternal stores of these LC-PUFA, impaired placental perfusion, as well as placental dysfunction [11]. Decreased DHA transfer has been shown in some but not all pregnancies complicated by gestational diabetes [12,13], which likely reflects the complex disordered metabolism involving both insulin resistance and altered estrogen regulation [12].

3. Infant fatty acid status after preterm delivery

Interrupted gestation and incomplete adipose stores of fatty acids make the preterm infant especially reliant on exogenous sources of fatty acid delivery and vulnerable to rapid changes in fatty acid levels and relative balance to one another [2]. Within the first postnatal week, the use of Intralipid® results in a deficit of DHA and AA, and an excess of LA, the primary fatty acid in this soybean oil-based emulsion [14]. The deficit in DHA was associated with the risk of chronic lung disease, whereas the reduction in AA was associated with the risk of nosocomial sepsis. Prolonged Intralipid use, for more than a month, contributes to a prolonged lower DHA status lasting into the second postnatal month [15]. Of concern, this lower DHA status remained for weeks, even after establishment of full enteral feedings in infants with longer Intralipid exposure [16]. Cumulatively, these findings suggest that early deficits are lasting and will not be reversed by enteral feedings alone. Although insufficient to prevent early postnatal deficits in DHA and AA, human milk feedings compared with formula feedings mitigate DHA, and AA declines in extremely preterm infants [16]. This emphasizes the benefits of human milk feedings and the importance in supporting lactation in women who deliver preterm.

4. Health consequences of suboptimal LC-PUFA status

The relevance of LC-PUFA to the health of preterm infants stems from their regulatory effects on cell receptor signaling and gene expression as well as their conversion to metabolites which regulate inflammatory processes and organogenesis. Common morbidities associated with prematurity often involve elements of uncontrolled inflammation, and laboratory and clinical evidence suggests that alterations in LC-PUFA delivery to preterm infants will have implications on the risk of these diseases.

4.1. Chronic lung disease

Preterm infants born prior to 30 weeks of gestation had increased odds of chronic lung disease associated with decreasing DHA levels during the first postnatal week [14]. Infants born <1250 g who were fed human milk from mothers randomized to take DHA supplements during lactation showed lower rates of chronic lung disease compared to infants fed milk from their mothers assigned to placebo [17]. Murine models of hyperoxia-induced lung injury suggest that DHA and downstream products of AA and DHA mitigate alveolar damage [18,19]. Forthcoming results from supplementation trials are expected to shed light on respiratory outcomes in preterm infants resulting from LC-PUFA supplementation [20].

4.2. Necrotizing enterocolitis

The clinical suggestion of a role for LC-PUFA in necrotizing enterocolitis (NEC) prevention in preterm infants was identified in a clinical trial of LC-PUFA supplementation using egg phospholipids to provide AA, DHA as well as choline [21]. This intervention significantly reduced the incidence of NEC in preterm infants fed formula, although the study was not primarily designed to evaluate NEC. Support for a protective mechanism has been found in animal models evaluating LC-PUFA effects on rates of NEC and severity of disease. AA and DHA supplementation in rats exposed to a model of NEC induction showed a reduced incidence by 30–50% [22]. LC-PUFA supplementation reduced gene expression of toll-like receptor 4, which activates immune inflammatory responses. Inflammatory bowel disease may be a relevant intestinal disease with similar pathophysiological mechanisms through which regulatory roles of LC-PUFA and their metabolites may be understood [23,24]. Common dysregulated targets of interest include toll-like receptor 4 expression, nuclear factor B regulation, peroxisome proliferator-activated receptor, as well as targets of eicosanoids and specialized pro-resolving mediators [23,24].

4.3. Retinopathy of prematurity

Impaired n-3 fatty acid status likely contributes to the aberrant retinal vascularization observed in retinopathy of prematurity [25]. Decreased severity of retinopathy occurred in preterm infants born <1250 g when exposed to a standard lipid emulsion supplemented with an additional emulsion containing fish oil compared with infants receiving only the standard lipid emulsion without fish oil [26]. Mechanisms of protection remain to be determined but animal models suggest direct regulatory effects from DHA and eicosapentaenoic acid (EPA, 20:5n-3) as well their metabolites (resolvins, neuroprotectins), and n-3 fatty acid regulation of adiponectin [25,27].

4.4. Neurodevelopment

The evidence elucidating the precise role and impact of LC-PUFA supplementation, primarily DHA and AA, on neurodevelopmental outcomes in preterm infants has been inconsistent [28–31]. This has remained a conundrum given the high concentrations of LC-PUFA in the central nervous system as well as the responsiveness of the CNS to deprivation or supplementation based on non-human primate and human studies [32,33]. A recent and unique association bridged evaluations of red blood cell LC-PUFA levels, brain imaging and developmental testing in preterm infants [34]. Higher DHA levels were associated with reduced severity of intraventricular hemorrhage, improved markers of brain structure on MRI and improved language and motor scores with no effect on cognitive scores. Questions such as the role of gender and genetic differences in fatty acid metabolism, variability of dosing and timing of regimens, as well as appropriateness of developmental tests administered in clinical trials to detect the effects of these nutrients have been raised [35].

Although most investigations focus on directly increasing central nervous system concentrations of LC-PUFA, indirect

mechanisms of preserving development should also be considered. Sepsis remains an independent risk factor for neurodevelopmental impairment [36]. Low AA levels in the first week are associated with an increased risk of sepsis [14]. As with sepsis, similar analogies can be made for NEC, another risk for neurodevelopmental impairment [37]. Accumulating data in animal models suggest a role of LC-PUFA in brain development as factors necessary for reducing inflammation-related neuronal injury as well as ischemic injury. Multiple mechanisms are implicated including pathways regulated by brain-derived neurotropin factor (BDNF) and pathways altered by oxidative stress which ultimately impact regulation of neuronal homeostasis and repair [38,39]. Common nutritional practices which delay provision of sufficient LC-PUFA may exacerbate the homeostasis of these important protective mechanisms.

4.5. Targets in LC-PUFA delivery

Recommended LC-PUFA intake must account for estimated fetal accretion, rates of endogenous production and expected bioavailability which is potentially altered by the following factors: impaired hydrolysis, malabsorption secondary to immaturity, fatty acid oxidation especially in states of insufficient total energy delivery and/or increased utilization mediated by illness severity.

Current recommended nutritional practices for optimal lipid and fatty acid delivery include:

- Initiation of intravenous lipids after birth to avoid fatty acid deficiency, and then advancement to 3–4 g/kg/d in order to optimize total energy delivery and carbohydrate and protein metabolism. Currently, the benefits of providing intravenous lipids outweigh risks of lipid-free diets.
- The preferred infant diet is mother's own milk when not contraindicated despite the possibility of lower DHA provisions. Initiation of human milk feedings promptly after birth is recommended.
- Current recommended LC-PUFA intake for preterm infants [40,41] include:
  - LA: 385–1540 mg/kg/d.
  - ALA: >50 mg/kg/d.
  - AA + DHA: When providing 55–60 mg/kg/day of DHA, AA should ideally be provided at doses of 35–45 mg/kg/day, although an accepted range for AA intake is 18–45 mg/kg/d. There is no evidence to support the provision of DHA without AA in preterm infants.
  - EPA: ≤20 mg/kg/d. EPA requirements are not well defined and are based on estimated intake for human milk-fed preterm infants. Excessive intakes should be avoided.

DHA recommendations are estimated from fetal accretion rates, AA intakes are estimated to support growth and prevent declines [42], whereas EPA recommendations are extrapolated from normative intake in human milk-fed preterm infants [42]. Current nutritional practices should assume that deficits in DHA and AA accumulate immediately after birth. Compared to the ideal DHA accretion rate, a deficit of about 50% of the DHA is established by the end of the first month [4]. Recommended amounts for these critical fatty acids should continue through 40 weeks of postmenstrual age. It is not yet determined whether continuing these amounts beyond this time period would be of benefit.

5. Unique challenges in nutritional delivery of fatty acids in preterm infants

Nutritional provisions in the first postnatal month involve a transition from parenteral nutrition to enteral nutrition. The metabolic capacities of preterm infants create challenges to providing what is considered optimal amounts of lipids and fatty acids. The quality and quantity of fatty acids in current parenteral formulations and enteral nutrition are not optimal for the needs of preterm infants, whether they are in the acute phase of illness or in a phase of recovery and growth.

5.1. Parenteral delivery of fatty acids

Nutritional practices surrounding the provisions of parenteral lipids vary considerably [43]. Starting doses reportedly range from 0.5 g/kg/d to 3 g/kg/d. Recent findings in very low birth weight infants show that intravenous lipid administration from birth, with amino acids, improved early nitrogen retention without improved growth compared with infants who did not receive lipids [44]. In this same study, infants receiving early lipids had higher triglyceride and glucose levels. The lipids used were either 100% soybean or a combination of soy, medium chain triglycerides (MCTs), olive and fish oils.

The postnatal declines in systemic AA and DHA levels described earlier with the use of Intralipid are not entirely mitigated by early provision of fish oil-containing emulsions [45]. Emulsions containing fish oil in combination with other oil sources will raise DHA and EPA levels; however, the early postnatal deficit in DHA is not eliminated and the increase in n-3 fatty acid delivery results in a further decline in AA, even more so than what is observed with Intralipid [46]. Documented changes in EPA levels have been extreme, with increases as much as 25% from baseline after infusion of a 100% fish oil-based emulsion; the consequences of this substantial increase in the preterm infant are unknown [47]. The concomitant changes in AA and EPA levels with increased n-3 fatty acid delivery are important considerations given their unique bioactive roles in human physiology. Further deprivation in AA may impact growth, organogenesis and immune function, and an increased risk of bleeding may occur under circumstances of either low AA or high EPA status [48]. Monitoring for extremes in biochemical changes are important outcome measures in addition to correlated clinical findings as optimization of lipids and fatty acids moves forward. It is important to note that different formulations uniquely impact fatty acid bioavailability and that genetic polymorphisms in desaturase enzymes will also contribute to a portion of this variation from infant to infant [49].

5.2. Enteral delivery of fatty acids

5.2.1. Mechanisms of digestion and absorption

Hydrolysis of the triglyceride molecule present in enterally fed fats is necessary to release fatty acids for absorption. Lipases are the cleavage enzymes and multiple forms exist. These forms have specificity to their site of action in the enteric system, have conditions for optimal function and show specificity to sites of action on lipid compounds [50]. Lingual and gastric lipases, the two that act pre-duodenum, are active in preterm infants and perform as much as one-third of lipid digestion when infants are orally fed. The intestinal lumen is the site of activity for the pancreatic and bile salt-stimulated lipases. Lipase action occurs after bile salts emulsify fats. The emulsified droplets are hydrolyzed by the lipases, releasing non-esterified fatty acids and monoglycerides. Small micelles, formed from bile salts and the free fatty acid and monoglycerides, undergo absorption by enteric epithelial cells. Repackaging of the free fatty acids and monoglycerides to form triglycerides occurs within the intestinal epithelial cell, and then further packaging to form chylomicrons occurs. Chylomicrons are ultimately secreted into the lymphatic system.

Chylomicrons traverse through lymphatics to the circulatory system where local processing can occur adjacent to specific tissues. Chylomicrons become coupled to apoproteins and are hydrolyzed by lipases (hepatic, lipoprotein or endothelial). Free fatty acids released by lipase activity may be incorporated into cell membrane phospholipids at the sn-1 or sn-2 position, may enter cells and undergo β-oxidation for energy production in mitochondria and peroxisomes, or they may re-enter circulation where ultimately they will be stored in an esterified form in sites including adipose, liver and muscle tissues. Carnitine facilitates fatty acyl-coA transfer across mitochondrial membranes for β-oxidation and is sufficient in both human milk and infant formula.

5.2.2. Impaired digestion and malabsorption in the preterm infant

The preterm infant's developmental deficiencies in enteral fat digestion and absorption lead to a malabsorptive state. Bile salt and pancreatic lipase deficiencies impair absorption of total fat and specific fatty acids [51]. Losses of total fat and/or specific fatty acids including DHA and AA may reach rates of 20–30% [52,53]. Absorption is generally worse with formula feedings. In addition to malabsorption causing energy loss, the accumulation of undigested fats may also cause intestinal inflammation and injury [54]. Preterm infants failed to demonstrate improved absorption with age based on longitudinal monitoring of coefficients of fatty acid absorption during the first two months [53]. Safe mechanisms to improve lipid absorption and fatty acid bioavailability in the preterm infant are needed.

Aggravating the problem of malabsorption are ongoing challenges in delivering appropriate amounts of LC-PUFA at the appropriate time. Delayed provisions of enteral nutrition withhold delivery of LC-PUFA when newer generation lipid emulsions are not available [55]. The LC-PUFA content of human milk and preterm infant formulas does not match estimated accrual rates by the fetus [4,42,56]. Maternal DHA supplementation does not consistently increase human milk DHA concentrations [57] and when breast milk concentrations are increased delivery is delayed, unable to mitigate the early postnatal deficits alone. The best mechanisms of supplementation are not yet defined and likely require multiple approaches which change as the infant feeding status changes throughout hospitalization.

5.2.3. Human milk – mother's own and donor

Human milk fat provides 50–60% of total energy in milk. High inter-individual variability exists; fat concentrations vary up to five-fold between individual women [58,59] and some women show variability in expressions from each breast [60]. A 3-fold increase in fat concentration can be seen when sampling foremilk (milk from the beginning of an expression) versus hind milk [60]. As growth is influenced by energy intake, this variability raises concerns for preterm infants as the total energy in milk, based on fat variability, is impossible to predict in usual clinical circumstances. Routine methods for measuring fat and total energy concentrations in any individual's breast milk will help account for this variability in routine clinical care.

The primary structures of milk lipids are milk fat globules with a surrounding milk fat globule membrane containing phospholipids, specific proteins and cholesterol [61]. The membrane contains a core of triacylglycerols, the largest lipid component of milk [61]. The sn-2 position of glycerol is most frequently esterified with palmitic acid (16:0) which minimizes palmitic acid cleavage from the glycerol backbone. This protects against the formation of soaps in the intestinal lumen which may result from free palmitic acid binding with calcium and other minerals [62]. Bile salt-stimulated lipase is present in milk and enhances milk fat absorption [63]. Heating processes during handling and storage of milk, including pasteurization, will eliminate milk's lipase activity with a resulting reduction in fat absorption [63,64].

The triacylglycerol structure of infant formulas is not similar to that of human milk and formulas do not contain lipases. The MCT content of infant formula compensates for structural differences and the absence of lipase [63]. Medium chain-fatty acids constitute less than 10% of fatty acids in human milk and up to 50% in formula. MCTs are easily absorbed, which may be beneficial, but these classes of lipids do not contain the critical and essential polyunsaturated fatty acids. Formulas contain palmitic acid primarily in the sn-1 and sn-3 positions, a suboptimal configuration [62,65]. A formula with structured placement of palmitic acid in the sn-2 resulted in intestinal microbial patterns that were more similar to that of human milk [66,67].

Sufficient LA and ALA are present in human milk. A major determinant of human milk fatty acid content is maternal dietary intake [68]. Human milk AA is similar across populations [56]. By contrast, different populations show marked variability in milk DHA content. Milk from women living in coastal regions contains the highest DHA concentrations [56]. Even within a specific geographic area there is considerable variation in milk DHA [15]. Despite its presence in human milk, DHA deficits accrue in preterm infants. Metabolizable DHA resulting from intake of preterm human milk may only be 14–16 mg/kg/day compared with substantially higher estimated fetal accretion rates mentioned above [42]. This is attributed to the insufficient amounts present which is compounded by frequent delays and interruptions to feedings in preterm infants [69]. Recent evidence suggests that intake as high as 120 mg/kg/d may be necessary to prevent declines in red blood cell DHA [70]. With increasing use of pasteurized human donor milk for preterm infants [71], it is noteworthy that DHA levels in donated milk can be markedly low and reflect the geographic region of the donor mothers [72]. This situation is aggravated by the elimination of functional bile salt-stimulated lipase by the pasteurization process.

5.2.4. Human milk fortifiers

Standard human milk fortifiers are used routinely to increase protein, total energy, vitamin and mineral provisions for human milk-fed preterm infants. Formulations have recently changed, including the addition of LC-PUFA to fortifiers. Both AA and DHA status is increased through the use of newer fortifiers [73] yet no clinical associations have been reported. The use of MCT oil additives in feedings is widely reported [43]. Although these supplements provide easily absorbed fat which can be rapidly oxidized for energy, there is no proven benefit to MCT oil supplements.

5.2.5. Formula

Preterm infant formulas have always contained sufficient LA and ALA. However, they initially did not contain the longer chain fatty acids until studies showed short-term improvements in growth and neurodevelopment [28,74]. Amounts contained in formulas reflect levels found in breast milk. They do not mimic estimated fetal accretion rates or account for the absence of lipase in formulas. Some question has been raised regarding the necessity of AA's inclusion in conjunction with DHA [75]. The roles of AA in vascular and immune regulation, among other processes including growth, allow it to be considered an essential nutrient, and current consensus is that it should be included in preterm infant formulas [75,76].

Recombinant human bile salt-stimulated lipase (rhBSSL) has been tested as an intervention to improve fat absorption for formula-fed infants and those fed pasteurized donor human milk. In preterm infants born prior to 32 weeks of gestation who were predominantly fed formula, rhBSSL did not improve growth [77]. Its

use was associated with an increase in significant adverse events, including infection and gastrointestinal complications [77]. The need to provide functional lipase safely appears worthy of further investigation.

6. Current knowledge gaps and areas for research

Many questions remain that need to be addressed to inform optimal lipid and fatty acid delivery practices for the preterm infant. Select questions include, but are not limited to, the following:

1. Should target doses of LC-PUFA supplementation mimic in-utero estimates of fetal acquisition, or be even higher to compensate for impaired absorption as well as the consideration that some LC-PUFAs may be oxidized for energy use, reducing amounts available for functional purposes? Does a target dose, or target biochemical measure, change throughout hospitalization for the preterm infant?
2. What consensus biochemical measure of fatty acid status should be used across clinical investigations to allow for comparison of associations between fatty acid status and clinical outcomes?
3. What are best mechanisms for achieving target LC-PUFA intake and which aspects of a multi-pronged approach contribute the most to providing metabolizable LC-PUFA?
4. What fatty acid composition in intravenous lipid emulsions is ideal for the preterm infant?
5. What are the clinical implications of both extreme alterations of LC-PUFA levels as well as altered ratios of lipid classes induced by parenteral formulations?
6. What interventions during pregnancy might optimize perinatal lipid status for the preterm infant?

7. Conclusions

Dietary lipids and fatty acids are key regulators of developmental processes in preterm infants. This includes regulation of immune responses, vascular tone, organogenesis and central nervous system development. To meet the specific needs of the preterm infant, new parenteral and enteral formulations and methods of delivery are needed.

Current lipid emulsions, regardless of formulation, induce extremes of fatty acid profiles in preterm infants. Their compositions differ from estimated fetal exposures as well as amounts provided in human milk feedings. A lipid emulsion composition with a complex blend including n-3 fatty acids comes closer to the preterm infant's needs, yet more work is needed to find the correctly balanced solution that maintains levels of fatty acids that the preterm infant would have been exposed to if the infant had remained in utero. The 100% fish oil emulsions are not ideal for routine parenteral lipid delivery in preterm infants; however, there may be benefit as a therapeutic intervention when considering modifying immune or inflammatory processes through nutritional interventions. Such applications are being considered for parenteral nutrition-associated liver disease and brain injury of varying etiologies [78–80] with ongoing work needed to define safe dosing that will minimize risk.

Increasing metabolizable fatty acids via enteral provisions likely requires a multi-faceted approach. The pancreatic insufficient state of the preterm must be compensated for especially when providing formula and/or pasteurized human milk. In addition, the different diets currently provided must meet the new recommended targets and this may require modification of existing formulas as well as routine supplementation of mothers providing breast milk. Finally, enteral strategies must be developed in tandem with parenteral delivery of nutrition such that the transition from parenteral to full enteral nutrition does not result in the loss of accrual of these critical fatty acids. Attention to improving these aspects as well as improved understanding of the time-sensitive needs of LC-PUFA delivery will improve long chain fatty acid status and infant outcomes.

Future clinical trials in the neonatal intensive care unit intended to improve long chain fatty acid status and outcomes must consider recommended intakes in the continuum across the transition from parenteral to enteral nutrition. Ideally, standardized collection and analysis of clinical data and biological samples will allow for study comparisons and aggregation of information to implement practices supported by evidence.

Practice points

- In consideration of recommended intakes of LC-PUFAs, fortified human milk feedings are to be considered the optimal form of nutrition for preterm infants.
- Delaying the introduction and advancement of enteral feedings contributes to the lasting deficits in AA and DHA.
- The clinical implications of parenteral feedings using intravenous lipid emulsions containing fish oil are currently unknown.

Conflict of interest statement

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References

[1] Haggarty P. Fatty acid supply to the human fetus. Annu Rev Nutr 2010;30:237–55.
[2] Innis SM. Essential fatty acid transfer and fetal development. Placenta 2005;26(Suppl. A):S70–5.
[3] Chambaz J, Ravel D, Manier MC, Pepin D, Mulliez N, Bereziat G. Essential fatty acids interconversion in the human fetal liver. Biol Neonate 1985;47:136–40.
[4] Lapillonne A, Jensen CL. Reevaluation of the DHA requirement for the premature infant. Prostaglandins Leukot Essent Fatty Acids 2009;81:143–50.
[5] Georgieff MK, Innis SM. Controversial nutrients that potentially affect preterm neurodevelopment: essential fatty acids and iron. Pediatr Res 2005;57:99R–103R.
[6] Su HM, Corso TN, Nathanielsz PW, Brenna JT. Linoleic acid kinetics and conversion to arachidonic acid in the pregnant and fetal baboon. J Lipid Res 1999;40:1304–12.
[7] Giusto NM, Pasquare SJ, Salvador GA, Castagnet PI, Roque ME, Ilincheta de Boschero MG. Lipid metabolism in vertebrate retinal rod outer segments. Prog Lipid Res 2000;39:315–91.
[8] Jacques C, Levy E, Muckle G, Jacobson SW, Bastien C, Dewailly E, et al. Long-term effects of prenatal omega-3 fatty acid intake on visual function in school-age children. J Pediatr 2011;158:83–90. e1.
[9] Gauster M, Hiden U, Blaschitz A, Frank S, Lang U, Alvino G, et al. Dysregulation of placental endothelial lipase and lipoprotein lipase in intrauterine growth-restricted pregnancies. J Clin Endocrinol Metab 2007;92:2256–63.
[10] Tabano S, Alvino G, Antonazzo P, Grati FR, Miozzo M, Cetin I. Placental LPL gene expression is increased in severe intrauterine growth-restricted pregnancies. Pediatr Res 2006;59:250–3.
[11] Wadhwani N, Patil V, Pisal H, Joshi A, Mehendale S, Gupte S, et al. Altered maternal proportions of long chain polyunsaturated fatty acids and their transport leads to disturbed fetal stores in preeclampsia. Prostaglandins Leukot Essent Fatty Acids 2014;91:21–30.
[12] Herrera E, Desoye G. Maternal and fetal lipid metabolism under normal and gestational diabetic conditions. Horm Mol Biol Clin Investig 2016;26:109–27.
[13] Ortega-Senovilla H, Alvino G, Taricco E, Cetin I, Herrera E. Gestational diabetes mellitus upsets the proportion of fatty acids in umbilical arterial but not venous plasma. Diabetes Care 2009;32:120–2.

[14] Martin CR, Dasilva DA, Cluette-Brown JE, Dimonda C, Hamill A, Bhutta AQ, et al. Decreased postnatal docosahexaenoic and arachidonic acid blood levels in premature infants are associated with neonatal morbidities. J Pediatr 2011;159:743–9. e1–2.

[15] Robinson DT, Carlson SE, Murthy K, Frost B, Li S, Caplan M. Docosahexaenoic and arachidonic acid levels in extremely low birth weight infants with prolonged exposure to intravenous lipids. J Pediatr 2013;162:56–61.

[16] Robinson DT, Caplan M, Carlson SE, Yoder R, Murthy K, Frost B. Early docosahexaenoic and arachidonic acid supplementation in extremely-low-birth-weight infants. Pediatr Res 2016 [Epub ahead of print].

[17] Manley BJ, Makrides M, Collins CT, McPhee AJ, Gibson RA, Ryan P, et al. High-dose docosahexaenoic acid supplementation of preterm infants: respiratory and allergy outcomes. Pediatrics 2011;128:e71–7.

[18] Martin CR, Zaman MM, Gilkey C, Salguero MV, Hasturk H, Kantarci A, et al. Resolvin D1 and lipoxin A4 improve alveolarization and normalize septal wall thickness in a neonatal murine model of hyperoxia-induced lung injury. PLoS One 2014;9:e98773.

[19] Rogers LK, Valentine CJ, Pennell M, Velten M, Britt RD, Dingess K, et al. Maternal docosahexaenoic acid supplementation decreases lung inflammation in hyperoxia-exposed newborn mice. J Nutr 2011;141:214–22.

[20] Collins CT, Gibson RA, Makrides M, McPhee AJ, Sullivan TR, Davis PG, et al. The N3RO trial: a randomised controlled trial of docosahexaenoic acid to reduce bronchopulmonary dysplasia in preterm infants < 29 weeks' gestation. BMC Pediatr 2016;16:72.

[21] Carlson SE, Montalto MB, Ponder DL, Werkman SH, Korones SB. Lower incidence of necrotizing enterocolitis in infants fed a preterm formula with egg phospholipids. Pediatr Res 1998;44:491–8.

[22] Lu J, Jilling T, Li D, Caplan MS. Polyunsaturated fatty acid supplementation alters proinflammatory gene expression and reduces the incidence of necrotizing enterocolitis in a neonatal rat model. Pediatr Res 2007;61:427–32.

[23] Marion-Letellier R, Dechelotte P, Iacucci M, Ghosh S. Dietary modulation of peroxisome proliferator-activated receptor gamma. Gut 2009;58:586–93.

[24] Marion-Letellier R, Savoye G, Beck PL, Panaccione R, Ghosh S. Polyunsaturated fatty acids in inflammatory bowel diseases: a reappraisal of effects and therapeutic approaches. Inflamm Bowel Dis 2013;19:650–61.

[25] Fu Z, Lofqvist CA, Shao Z, Sun Y, Joyal JS, Hurst CG, et al. Dietary omega-3 polyunsaturated fatty acids decrease retinal neovascularization by adipose-endoplasmic reticulum stress reduction to increase adiponectin. Am J Clin Nutr 2015;101:879–88.

[26] Pawlik D, Lauterbach R, Walczak M, Hurkala J, Sherman MP. Fish-oil fat emulsion supplementation reduces the risk of retinopathy in very low birth weight infants: a prospective, randomized study. JPEN J Parenter Enteral Nutr 2014;38:711–6.

[27] Connor KM, SanGiovanni JP, Lofqvist C, Aderman CM, Chen J, Higuchi A, et al. Increased dietary intake of omega-3-polyunsaturated fatty acids reduces pathological retinal angiogenesis. Nat Med 2007;13:868–73.

[28] Carlson SE, Werkman SH, Rhodes PG, Tolley EA. Visual-acuity development in healthy preterm infants: effect of marine-oil supplementation. Am J Clin Nutr 1993;58:35–42.

[29] Makrides M, Gibson RA, McPhee AJ, Collins CT, Davis PG, Doyle LW, et al. Neurodevelopmental outcomes of preterm infants fed high-dose docosahexaenoic acid: a randomized controlled trial. JAMA 2009;301:175–82.

[30] Alshweki A, Munuzuri AP, Bana AM, de Castro MJ, Andrade F, Aldamiz-Echevarria L, et al. Effects of different arachidonic acid supplementation on psychomotor development in very preterm infants; a randomized controlled trial. Nutr J 2015;14:101.

[31] Molloy CS, Stokes S, Makrides M, Collins CT, Anderson PJ, Doyle LW. Long-term effect of high-dose supplementation with DHA on visual function at school age in children born at <33 wk gestational age: results from a follow-up of a randomized controlled trial. Am J Clin Nutr 2016;103:268–75.

[32] Makrides M, Neumann MA, Byard RW, Simmer K, Gibson RA. Fatty acid composition of brain, retina, and erythrocytes in breast- and formula-fed infants. Am J Clin Nutr 1994;60:189–94.

[33] Neuringer M, Connor WE, Lin DS, Barstad L, Luck S. Biochemical and functional effects of prenatal and postnatal omega 3 fatty acid deficiency on retina and brain in rhesus monkeys. Proc Natl Acad Sci U S A 1986;83:4021–5.

[34] Tam EW, Chau V, Barkovich AJ, Ferriero DM, Miller SP, Rogers EE, et al. Early postnatal docosahexaenoic acid levels and improved preterm brain development. Pediatr Res 2016;79:723–30.

[35] Colombo J, Carlson SE. Is the measure the message: the BSID and nutritional interventions. Pediatrics 2012;129:1166–7.

[36] Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA 2004;292:2357–65.

[37] Martin CR, Dammann O, Allred EN, Patel S, O'Shea TM, Kuban KC, et al. Neurodevelopment of extremely preterm infants who had necrotizing enterocolitis with or without late bacteremia. J Pediatr 2010;157:751–6. e1.

[38] Malamitsi-Puchner A, Economou E, Rigopoulou O, Boutsikou T. Perinatal changes of brain-derived neurotrophic factor in pre- and fullterm neonates. Early Hum Dev 2004;76:17–22.

[39] Antonietta Ajmone-Cat M, Lavinia Salvatori M, De Simone R, Mancini M, Biagioni S, Bernardo A, et al. Docosahexaenoic acid modulates inflammatory and antineurogenic functions of activated microglial cells. J Neurosci Res 2012;90:575–87.

[40] Agostoni C, Buonocore G, Carnielli VP, De Curtis M, Darmaun D, Decsi T, et al. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. J Pediatr Gastroenterol Nutr 2010;50:85–91.

[41] Koletzko B, Poindexter B, Uauy R. Recommended nutrient intake levels for stable, fully enterally fed very low birth weight infants. In: Koletzko B, Poindexter B, Uauy R, editors. Nutritional care of preterm infants: scientific basis and practical guidelines. Karger; 2014. p. 297–9.

[42] Lapillonne A, Groh-Wargo S, Gonzalez CH, Uauy R. Lipid needs of preterm infants: updated recommendations. J Pediatr 2013;162:S37–47.

[43] Hans DM, Pylipow M, Long JD, Thureen PJ, Georgieff MK. Nutritional practices in the neonatal intensive care unit: analysis of a 2006 neonatal nutrition survey. Pediatrics 2009;123:51–7.

[44] Vlaardingerbroek H, Vermeulen MJ, Rook D, van den Akker CH, Dorst K, Wattimena JL, et al. Safety and efficacy of early parenteral lipid and high-dose amino acid administration to very low birth weight infants. J Pediatr 2013;163:638–44. e1–5.

[45] D'Ascenzo R, D'Egidio S, Angelini L, Bellagamba MP, Manna M, Pompilio A, et al. Parenteral nutrition of preterm infants with a lipid emulsion containing 10% fish oil: effect on plasma lipids and long-chain polyunsaturated fatty acids. J Pediatr 2011;159:33–8. e1.

[46] Zhao Y, Wu Y, Pei J, Chen Z, Wang Q, Xiang B. Safety and efficacy of parenteral fish oil-containing lipid emulsions in premature neonates. J Pediatr Gastroenterol Nutr 2015;60:708–16.

[47] Klein CJ, Havranek TG, Revenis ME, Hassanali Z, Scavo LM. Plasma fatty acids in premature infants with hyperbilirubinemia: before-and-after nutrition support with fish oil emulsion. Nutr Clin Pract 2013;28:87–94.

[48] Dicken BJ, Bruce A, Samuel TM, Wales PW, Nahirniak S, Turner JM. Bedside to bench: the risk of bleeding with parenteral omega-3 lipid emulsion therapy. J Pediatr 2014;164:652–4.

[49] Harslof LB, Larsen LH, Ritz C, Hellgren LI, Michaelsen KF, Vogel U, et al. FADS genotype and diet are important determinants of DHA status: a cross-sectional study in Danish infants. Am J Clin Nutr 2013;97:1403–10.

[50] Mukherjee M. Human digestive and metabolic lipases – a brief review. J Mol Catal B-Enzym 2003;22:369–76.

[51] Lindquist S, Hernell O. Lipid digestion and absorption in early life: an update. Curr Opin Clin Nutr Metab Care 2010;13:314–20.

[52] Carnielli VP, Verlato G, Pederzini F, Luijendijk I, Boerlage A, Pedrotti D, et al. Intestinal absorption of long-chain polyunsaturated fatty acids in preterm infants fed breast milk or formula. Am J Clin Nutr 1998;67:97–103.

[53] Martin CR, Cheesman A, Brown J, Makda M, Kutner AJ, DaSilva D, et al. Factors determining optimal fatty acid absorption in preterm infants. J Pediatr Gastroenterol Nutr 2016;62:130–6.

[54] Howles PN, Stemmerman GN, Fenoglio-Preiser CM, Hui DY. Carboxyl ester lipase activity in milk prevents fat-derived intestinal injury in neonatal mice. Am J Physiol 1999;277:G653–61.

[55] Viswanathan S, McNelis K, Super D, Einstadter D, Groh-Wargo S, Collin M. Standardized slow enteral feeding protocol and the incidence of necrotizing enterocolitis in extremely low birth weight infants. J Parenter Enteral Nutr 2015;39:644–54.

[56] Brenna JT, Varamini B, Jensen RG, Diersen-Schade DA, Boettcher JA, Arterburn LM. Docosahexaenoic and arachidonic acid concentrations in human breast milk worldwide. Am J Clin Nutr 2007;85:1457–64.

[57] Smithers LG, Gibson RA, McPhee A, Makrides M. Effect of two doses of docosahexaenoic acid (DHA) in the diet of preterm infants on infant fatty acid status: results from the DINO trial. Prostagl Leukot Essent Fatty Acids 2008;79:141–6.

[58] Michaelsen KF, Skafte L, Badsberg JH, Jorgensen M. Variation in macronutrients in human bank milk: influencing factors and implications for human milk banking. J Pediatr Gastroenterol Nutr 1990;11:229–39.

[59] Stoltz Sjostrom E, Ohlund I, Tornevi A, Domellof M. Intake and macronutrient content of human milk given to extremely preterm infants. J Hum Lact 2014;30:442–9.

[60] Neville MC, Keller RP, Seacat J, Casey CE, Allen JC, Archer P. Studies on human lactation. I. Within-feed and between-breast variation in selected components of human milk. Am J Clin Nutr 1984;40:635–46.

[61] Lopez C, Menard O. Human milk fat globules: polar lipid composition and in situ structural investigations revealing the heterogeneous distribution of proteins and the lateral segregation of sphingomyelin in the biological membrane. Colloids Surf B Biointerfaces 2011;83:29–41.

[62] Lopez-Lopez A, Castellote-Bargallo AI, Campoy-Folgoso C, Rivero-Urgel M, Tormo-Carnice R, Infante-Pina D, et al. The influence of dietary palmitic acid triacylglyceride position on the fatty acid, calcium and magnesium contents of at term newborn faeces. Early Hum Dev 2001;65(Suppl.):S83–94.

[63] Jensen RG, Ferris AM, Lammi-Keefe CJ. Lipids in human milk and infant formulas. Annu Rev Nutr 1992;12:417–41.

[64] Andersson Y, Savman K, Blackberg L, Hernell O. Pasteurization of mother's own milk reduces fat absorption and growth in preterm infants. Acta Paediatr 2007;96:1445–9.

[65] Lu P, Bar-Yoseph F, Levi L, Lifshitz Y, Witte-Bouma J, de Bruijn AC, et al. High beta-palmitate fat controls the intestinal inflammatory response and limits intestinal damage in mucin Muc2 deficient mice. PLoS One 2013;8:e65878.

[66] Bar-Yoseph F, Lifshitz Y, Cohen T. Review of sn-2 palmitate oil implications for infant health. Prostagl Leukot Essent Fatty Acids 2013;89:139–43.

[67] Yaron S, Shachar D, Abramas L, Riskin A, Bader D, Litmanovitz I, et al. Effect of high beta-palmitate content in infant formula on the intestinal microbiota of term infants. J Pediatr Gastroenterol Nutr 2013;56:376–81.
[68] Insull Jr W, Hirsch J, James T, Ahrens Jr EH. The fatty acids of human milk. II. Alterations produced by manipulation of caloric balance and exchange of dietary fats. J Clin Invest 1959;38:443–50.
[69] Lapillonne A, Eleni dit Trolli S, Kermorvant-Duchemin E. Postnatal docosahexaenoic acid deficiency is an inevitable consequence of current recommendations and practice in preterm infants. Neonatology 2010;98:397–403.
[70] Collins CT, Sullivan TR, McPhee AJ, Stark MJ, Makrides M, Gibson RA. A dose response randomised controlled trial of docosahexaenoic acid (DHA) in preterm infants. Prostagl Leukot Essent Fatty Acids 2015;99:1–6.
[71] Breastfeeding and the use of human milk. Pediatrics 2012;129:e827–41.
[72] Valentine CJ, Morrow G, Fernandez S, Gulati P, Bartholomew D, Long D, et al. Docosahexaenoic acid and amino acid contents in pasteurized donor milk are low for preterm infants. J Pediatr 2010;157:906–10.
[73] Berseth CL, Harris CL, Wampler JL, Hoffman DR, Diersen-Schade DA. Liquid human milk fortifier significantly improves docosahexaenoic and arachidonic acid status in preterm infants. Prostagl Leukot Essent Fatty Acids 2014;91:97–103.
[74] O'Connor DL, Hall R, Adamkin D, Auestad N, Castillo M, Connor WE, et al. Growth and development in preterm infants fed long-chain polyunsaturated fatty acids: a prospective, randomized controlled trial. Pediatrics 2001;108:359–71.
[75] Brenna JT. Arachidonic acid needed in infant formula when docosahexaenoic acid is present. Nutr Rev 2016;74:329–36.
[76] Hadley KB, Ryan AS, Forsyth S, Gautier S, Salem N. The essentiality of arachidonic acid in infant development. Nutrients 2016:8.
[77] Casper C, Hascoet JM, Ertl T, Gadzinowski JS, Carnielli V, Rigo J, et al. Recombinant bile salt-stimulated lipase in preterm infant feeding: a randomized phase 3 study. PLoS One 2016;11:e0156071.
[78] de Meijer VE, Gura KM, Le HD, Meisel JA, Puder M. Fish oil-based lipid emulsions prevent and reverse parenteral nutrition-associated liver disease: the Boston experience. J Parenter Enteral Nutr 2009;33:541–7.
[79] Williams JJ, Mayurasakorn K, Vannucci SJ, Mastropietro C, Bazan NG, Ten VS, et al. N-3 fatty acid rich triglyceride emulsions are neuroprotective after cerebral hypoxic-ischemic injury in neonatal mice. PLoS One 2013;8:e56233.
[80] Barrett EC, McBurney MI, Ciappio ED. Omega-3 fatty acid supplementation as a potential therapeutic aid for the recovery from mild traumatic brain injury/concussion. Adv Nutr 2014;5:268–77.