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Review

Fatty acid requirements for the preterm infant

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S U M M A R Y

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

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