Clinical Overview of Effects of Dietary Long-Chain Polyunsaturated Fatty Acids during the Perinatal Period

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Two long-chain polyunsaturated fatty acids (LC-PUFA) that have been studied in relation to infant and child development are considered: docosahexaenoic acid (DHA) and arachidonic acid (ARA), respectively, members of the n-3 or ω-3 and n-6 or ω-6 fatty acid families, and synthesized from linoleic and α-linolenic acids (see fig. 1). These LC-PUFA are found preformed in animal fats, including human milk. US infants fed human milk instead of infant formulas available in the late 1970s (which did not contain LC-PUFA) were observed to have a greater proportion of DHA and ARA in their red blood cell membrane phospholipids [1]. Research thereafter asked if DHA and ARA were ‘conditionally essential’ nutrients for infant development, i.e. if biochemical pathways for synthesis provided less than optimal DHA and ARA for function. Visual acuity and early cognitive development were outcome measures, because Martha Neuringer and her colleagues found reduced retinal and brain DHA, lower visual acuity and less mature attention in rhesus monkeys fed diets low in α-linolenic acid during development [2]. Their studies provided clear evidence that retinal and brain DHA were important for optimal visual acuity and a measure of early learning in n-3 deficiency. In the main, clinical studies did not limit α-linolenic acid and were designed to determine the need for LC-PUFA.

The first postnatal supplementation studies were done in the US in preterm infants, and supplementation was based on the amount of DHA in breast milk of US women. Preterm infants uniformly demonstrated higher (but probably not optimal) visual acuity with 0.2% DHA. Later, we learned that milk DHA content in the US is among the lowest in the world (~0.2% of total fatty acids). Both term and preterm infants have now been fed up to 1% of fatty acids as DHA. Preterm infants were fed approximately 0.3% compared to approximately 1% fatty acids as DHA until a corrected age of term birth had similar performance [3].
US term infants benefited from LC-PUFA with 0.32–0.96% DHA and 0.64% ARA compared to a formula without LC-PUFA, but infants fed the LC-PUFA-supplemented formulas had similar 12-month visual acuity [4] and cognitive performance to 6 years of age (fig. 2).

Challenges that I see for the future: (1) More finely grained measures of brain development are needed. These have shown benefits of LC-PUFA, whereas global measures designed to evaluate whether infants/toddlers are progressing normally generally have not [5]. (2) The effects of perinatal LC-PUFA supplementation may be easier to find later in childhood when children are able to be tested on more complex behaviors. For example, the effects of perinatal LC-PUFA supplementation emerged around 4 years of age in children subjected to tests of early cognition twice yearly between 18 months and 6 years of age (fig. 2). An exciting aspect suggested by some studies of brain development is that early LC-PUFA status may program development for later advantage. (3) Intrauterine exposure to LC-PUFA may be very important for fetal

Fig. 1. Pathways for conversion of essential fatty acids to LC-PUFA.
brain development, but transfer from mother to fetus is highly variable and the reasons are not known. Randomized trials that use ITT compare groups with a great deal of overlap in newborn DHA status. We need to determine what variables influence this transfer. (4) Single-nucleotide polymorphisms in the fatty acid desaturase genes (FADS1/2) are now recognized to influence maternal and infant LC-PUFA status, and it might be hypothesized that they influence LC-PUFA requirement, but this has not been studied.

**References**

3. Smithers LG, Collins CT, Simmonds LA, et al: Feeding preterm infants milk with a higher dose of docosahexaenoic acid than that used in current practice does not
