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Toward optimizing vision and cognition in term infants by dietary docosahexaenoic and arachidonic acid supplementation: A review of randomized controlled trials

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ABSTRACT

The question of whether a dietary supply of docosahexaenoic acid (DHA) and arachidonic acid (ARA) imparts advantages to visual or cognitive development in term infants has been debated for many years. DHA and ARA are present in human milk, and nursing infants consume these fatty acids needed for rapid synthesis of cell membranes, particularly neural cells. The reported mean DHA and ARA levels of human milk worldwide are 0.32% and 0.47% of total fatty acids, respectively. Prior to 2002 in the US, formula-fed infants did not receive these fatty acids and relied solely on endogenous conversion of the dietary essential omega-3 (n-3) and omega-6 (n-6) fatty acids, α-linolenic and linoleic acids, to DHA and ARA, respectively. Formula-fed infants were found to have significantly less accretion of DHA in brain cortex after death than breastfed infants. Numerous studies have found positive correlations between blood DHA levels and improvements in cognitive or visual function outcomes of breastfed and formula-fed infants. Results of randomized controlled clinical trials of term formula-fed infants evaluating functional benefits of dietary DHA and ARA have been mixed, likely due to study design heterogeneity. A comparison of visual and cognitive outcomes in these trials suggests that dietary DHA level is particularly relevant. Trials with formulas providing close to the worldwide human milk mean of 0.32% DHA were more likely to yield functional benefits attributable to DHA. We agree with several expert groups in recommending that infants receive at least 0.3% DHA, with at least 0.3% ARA, in infant feedings; in addition, some clinical evidence suggests that an ARA:DHA ratio greater than 1:1 is associated with improved cognitive outcomes.

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1. Introduction

The potential roles of the long-chain polyunsaturated fatty acids (LCPUFA) docosahexaenoic acid (DHA; 22:6n-3 or 22:6ω3) and arachidonic acid (ARA; 20:4n-6 or 20:4ω6) in infant growth, development, and health have been the subject of intense research for several decades. Almost 30 years ago, Clandinin et al. [1] quantified the marked accretion of these fatty acids in human brain during the last trimester of pregnancy. Concurrently, other investigators reported significantly lower levels of DHA and ARA in blood of formula-fed term infants in comparison with breastfed infants [2,3] and animal studies demonstrated that n-3 PUFA were essential for normal development of vision [4,5]. This convergence of data raised questions regarding the need for adequate delivery of these fatty acids to the neonate to support appropriate neural development, and led to the first clinical trials of DHA-supplemented formula for preterm infants [6,7]. Several early studies found lower growth of preterm infants fed formula with n-3 LCPUFA but no ARA [8–10], raising the concern of negative consequences from imbalances in these two essential families of PUFA. The beneficial effects of LCPUFA supplementation in preterm infants brought into question the potential needs for DHA and ARA in the term infant diet.

2. The term infant's need for LCPUFA

The importance of providing an appropriate supply of DHA and ARA is relevant throughout infancy, as both fatty acids continue to accumulate rapidly in brain gray matter through at least the first 2 years of life [11]. During late gestation and early post-natal life, the neonate's brain experiences a tremendous increase in growth and cellular proliferation termed the "brain growth spurt." Dobbing and Sands [12] reported that brain weights increased 60-fold, from approximately 20 g in the second trimester to nearly 1200 g by age 2. During this time of hyperplastic growth,

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synaptogenesis and myelination occur at a rapid pace in the infant's neural network [13]. Concurrently, the content of DHA and ARA in the human forebrain increases by nearly 30-fold [11], reflecting an active placental transfer of these LCPUFA prenatally and subsequently placing a considerable demand for a post-natal supply of LCPUFA. For the rapidly growing infant, there is a high demand for complex lipids to form vital cell membrane structures; thus, the availability of pre-formed substrates, such as DHA and ARA, as integral neural membrane components is at a premium.

The role of DHA in visual development is of key interest because of the uniquely high concentration of DHA in photoreceptor cell membranes of the retina [14]. Since the retina and brain are both tissues derived embryologically from neuroectoderm [15], measuring functional outcomes in the visual system provides a readily accessible index to neurodevelopmental milestones. Assessment of visual acuity, in particular, has been used extensively in evaluating clinical effects of DHA because of the availability of visual-evoked potential (VEP), a sensitive, non-invasive method that can be used to quantify changes in an aspect of neurodevelopment that is developing rapidly early in life [16].

While all human milk contains both DHA and ARA [17], these fatty acids were not specifically added to infant formulas available in the US prior to 2002. Humans, including infants, are capable of endogenous synthesis of DHA and ARA from the precursor essential fatty acids α-linolenic acid (ALA; 18:3n-3) and linoleic acid (18:2n-6), respectively. Endogenous synthesis, particularly of DHA from ALA, however, is limited and can vary widely among individuals, approaching zero for some infants [18]. Many studies have demonstrated that the concentration of DHA in infant blood is responsive to the amount provided in the diet [19,20] and, regardless of levels of ALA, formula-fed infants who do not receive an exogenous supply of DHA do not achieve blood DHA levels equivalent to those of breastfed infants [21–23]. Autopsy studies found that brain accumulation of DHA, but not ARA, was greater in breastfed infants than infants fed formula with no added LCPUFA [24,25].

Numerous studies [26–40] have found significant positive correlations between red blood cell (RBC) or plasma levels of DHA and improvements in cognitive or visual outcomes in breastfed and formula-fed infants (Tables 1 and 2), lending further support for a link between DHA status early in life and neurodevelopment. Some studies, however, have found no relationship [41–44] or a negative relationship [43,45] between blood DHA status and neurodevelopmental outcomes.

3. Human milk model for infant nutrition

Human milk is the "gold standard" model for infant formula, both in composition and in the physiologic effects closely tied to the composition. It is recognized as the ideal food for term infants and is recommended as the sole source of nutrition for the vast majority of infants for approximately the first 6 months of life [46,47]. With few exceptions, nutrient intake recommendations for term infants from birth to 6 months of age are based on the nutrient composition of mature human milk from healthy, well-nourished mothers [48]. Unlike many nutrients in mature human milk, however, the amounts of most fatty acids, and particularly DHA, can vary considerably in human milk, largely depending on the mother's diet. Brenna et al. [17] conducted a comprehensive, critical review of published research on human milk levels of DHA and ARA from around the world. They reported the mean level (% fatty acids $\pm$ SD) of DHA in mature human milk worldwide as $0.32 \pm 0.22\%$, with greater than a 20-fold range of means from individual populations or countries, from 0.06% to 1.4%. The worldwide mean for ARA was $0.47 \pm 0.13\%$, with a much smaller range of 0.24–1.0%. The highest DHA levels were found in coastal or island populations with high marine food intake. The lowest levels were found in inland populations and developed countries, both of which are associated with low fish intake. Mean values from studies conducted in the United States ranged from 0.15% to 0.37% for DHA and 0.40% to 0.67% for ARA.

4. Studies of LCPUFA and neurodevelopment of breastfed infants

Studies of breastfed infants indicate that the DHA level in human milk may influence visual and cognitive outcomes,

Table 1
Studies reporting correlations between DHA levels in blood and cognitive outcomes in breastfed and formula-fed infants.

Author [Ref.]	Blood DHA[a] (type of feeding)	Cognitive outcome
Agostoni et al. [26]	↑ at 4 mo (breastfed and formula-fed)	↑ Brunet-Lézine DQ at 4 mo, $p = 0.01$ ($n = 55$)
Agostoni et al. [27]	↑ at 24 mo (RBC-PC) (breastfed and formula-fed)	↑ Brunet-Lézine DQ at 24 mo, $p = 0.03$ ($n = 20$)
Gibson et al. [28]	↑ at 3 mo (breastfed)	↑ MDI at 12 mo, $p = 0.02$ ($n = 51$)
Scott et al. [45]	↑ at 4 mo (RBC, plasma phospholipid) (breastfed and formula-fed)	↓ MacArthur CDI Vocabulary Production and Comprehension at 14 mo, $p < 0.05$ (n's not specified)
Birch et al. [29]	↑ at 4 mo (RBC and plasma) (formula-fed)	↑ MDI at 18 mo, $p = 0.03$ ($n = 56$)
Innis et al. [30]	↑ at 2 mo (RBC-PE and plasma phospholipid) (breastfed)	↑ Speech perception by conditioned head-turn at 9 mo, $p = 0.02$ ($n = 53$)
Innis [31]	↑ at 2 mo (RBC-PE, RBC-PC and plasma phospholipid) (breastfed)	↑ MacArthur CDI Vocabulary Production and Comprehension at 18 mo, $p \leq 0.05$ (n's not specified)
Helland et al. [32]	↑ at 1 mo (plasma phospholipid) (breastfed)	↑ K-ABC at 4 years [Sequential Processing ($p = 0.05$), Simultaneous Processing ($p = 0.03$), Mental Processing Composite ($p = 0.01$)]($n = 84$)
Jensen et al. [42]	4 mo (plasma phospholipid) (breastfed)	No correlation with any measure of neurodevelopment at 12 or 30 mo (n's not specified)
Lauritzen et al. [43]	4 mo (breastfed)	No correlation with Intention Scores on means-end problem solving test at 9 mo or with MacArthur CDI at 2 years; ↓ MacArthur CDI Vocabulary Comprehension at 12 mo, $p = 0.016$ ($n = 69$)
Helland et al. [44]	1 and 3 mo (plasma phospholipid) (breastfed)	No correlation with K-ABC Sequential Processing Scale and Mental Processing Composite Scale at 7 years (n's not specified)

DHA, docosahexaenoic acid; mo, months; DQ, Developmental Quotient; RBC, red blood cell; PC, phosphatidylcholine; MDI, Bayley Scales of Infant Development Mental Development Index; CDI, Communicative Development Inventories; PE, phosphatidylethanolamine; K-ABC, Kaufman Assessment Battery for Children.

[a] DHA level in total red blood cells unless otherwise noted. ↑ Indicates higher level of DHA and improvement in cognitive outcome.

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