

**UCLA**

**Nutrition Noteworthy**

**Title**

Finding the Magic Formula: Should Polyunsaturated Fatty Acids be Used to Supplement Infant Formula?

**Permalink**

<https://escholarship.org/uc/item/0mf457td>

**Journal**

Nutrition Noteworthy, 5(1)

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**Publication Date**

2002

Peer reviewed

## Introduction

Ever since the correlation was found between breast-feeding and higher cognitive development(1), researchers have been re-examining the composition of human breast milk in an attempt to identify the element(s) responsible for enhancing mental development in breast-fed infants. Particular attention has been paid to the long chain polyunsaturated fatty acids, docosahexaenoic acid (DHA) and arachidonic acid (AA), which are abundant in breast milk but virtually absent in infant formula. These elements are the major fatty acids found in neural tissue of the brain and retina and therefore became the most obvious choice for studying neurological development in breast-fed babies. Studies in animals have shown that infant diets lacking in these fatty acids correlate with poor visual and neural development and that these impairments are corrected if the amino acids are supplemented back into the diets.(2) Can the same results be found in humans? If so, what impact should this new knowledge have on the regulation of infant formula supplementation with fatty acids? The question of whether to supplement infant formulas with DHA and AA to increase neurological development is one of the most highly debated issues in infant nutrition today.

This paper reviews the most current data generated from studies on the role of DHA and AA on neural development. The outcome measures with respect to supplementation of formula with fatty acids DHA and AA are discussed in terms of levels of fatty acid found in the blood, visual acuity and function, and cognitive/behavioral development. Though the data fairly conclusively show positive correlations between supplemented formula feeding and plasma fatty acid levels as well as visual acuity, there is much disagreement over role of supplemented formulas in cognitive, behavioral and language development. Many believe that more research is needed before changes in federal regulations can be made regarding the addition of DHA and AA in infant formulas. Certainly, the knowledge generated from these future studies will have wide implications for parents, pediatricians, and the infant formula industry who all have vested interests in this very important issue in infant nutrition.

## Fatty Acids and Their Role in Neural Development

Docosahexaenoic acid (DHA) arachidonic acid (AA) are polyunsaturated fatty acids believed to be involved in the structural and functional development of the brain in the fetus and infant. DHA and other fatty acids are incorporated into the phospholipid bilayer of biologically active brain and retinal neural membranes in the fetus and their levels continue to increase in the months after birth. These fatty acids act to increase membrane fluidity and alter permeability and activation due to their high degree of unsaturation. (3,4)

Full-term and premature infants are able to synthesize DHA and AA from other fatty acids building blocks such as alpha-linolenic acid (ALA) and linoleic acid (LA). Interestingly, alpha-linolenic acid and linoleic acid are both present in standard infant formulas, however, some question whether these can be used by the infant to adequately synthesize the necessary amounts of DHA and AA. It is this uncertainty that has prompted the controversy over DHA and AA supplementation of infant formulas. (5)

## Research Methodologies

The studies on the role of DHA and AA in infant neural development reviewed here vary widely with respect to their sample sizes, the age of infants during the study, the composition of their infant formulas both supplemented and unsupplemented, the duration of feeding, and their outcome measures. On the whole, most of the clinical trials studied infants from their first week of life to their first birthday. They typically included a control group who received unsupplemented formula, a study group who received supplemented formula, and sometimes included a reference group of infants who were breast-fed. There are three main outcomes measures with which to evaluate the developmental effects of DHA/AA supplementation: 1.) plasma levels of DHA and AA, 2.) visual acuity, and 3.) cognitive and language development. These are discussed below.

### 1. Plasma Fatty Acids Levels and DHA/AA Supplementation

Once it was established that supplemental DHA and AA were safe for ingestion by infants(6), investigators wanted to determine if the fatty acids would be absorbed by the body and incorporated into cells as well as those found in breast milk. In 1994, it was found that infants who were fed with unsupplemented formula had lower AA and DHA concentrations in plasma, erythrocyte membranes, and cortical brain tissue than those fed human milk.(7) When a separate study measured these same levels in infants who were fed formula supplemented with DHA and AA, they found that the plasma and brain levels rose to numbers comparable to that found in breast-fed infants.(8,9) These experiments proved that the supplements were in fact being absorbed and incorporated in to the body properly, however, they revealed nothing about the effects of these compounds on neurological development.

### 2. Visual Acuity and DHA/AA Supplementation

The research studying the effects of DHA and AA on visual function, for the most part, points to a beneficial effect of DHA and AA supplementation in infant nutrition.(10,11) A meta-analysis by SanGiovanni of 5 original papers and 4 review articles revealed that DHA-supplemented formula produced a significant advantage in visual acuity resolution over non-supplemented formula in pre-term infants.(12) Visual function was assessed based on behavioral and electrophysiological measurements at the ages of 2 months and 4 months. Other studies, however, showed no significant difference in visual function.(13,14) It should be noted that these tended to use control formulas with higher levels of ALA which can be elongated to DHA, whereas studies that did report a significant difference in visual function tended to use control formulas with lower contents of ALA.

### 3. Cognitive/Behavioral Development and DHA/AA Supplementation

Studies on the effects of supplemented DHA and AA on cognitive and behavioral development have, unfortunately, been even more inconclusive. In studies comparing the effect of supplemented formula or breast milk with unsupplemented formula, the tests used to measure cognitive and behavioral development in term infants were the Bayley mental development index (MDI) and the psychomotor developmental index (PDI). In one study, the supplemented formula group scored slightly higher than the control group on the MDI scale, but did not perform as well as the breast-fed group. Interestingly, on the PDI scale, both the supplemented group and

unsupplemented groups performed better than the reference breast-fed group. None of the differences on either scale however were statistically significant after adjustments were made for socioeconomic factors.(15) A second study also showed no statistical difference between reference, control and study groups on the MDI and PDI scales at age 12 months and 24 months except for a MDI score of the breast-fed group at age 24 months that was significantly higher than the other formula groups.(13) In another study, while the PDI scores of study and reference groups did not differ, the MDI score of the DHA/AA supplemented group fared significantly higher than the unsupplemented group and a group supplemented with only DHA fared intermediately between these two groups.(16) Finally, a recent study by Auestad with a large sample size studied multiple measures of infant development at several ages from birth to 14 months including growth, visual acuity, information processing, general development, language and temperament. They found that none of these tests could distinguish between the control formula group and the DHA/AA supplemented group. (4)

### Evaluation of the Current Data

While the data on the effects of DHA and AA on neurological development of infants look promising on the whole, many discrepancies between study findings still exist, pointing to the need for further research. Discrepancies between studies may stem from a number of sources including differing doses of AA, DHA, ALA and LA fatty acids or differing ratios of these fatty acids in both control and supplemented formulas. Sources and preparations of DHA and AA also vary among research studies as well as the ages of evaluation and duration of use. Finally, genetic and environmental differences may have also played a role in the discrepancies as the studies were carried out in different parts of the world (North America, Australia, and Europe).(4)

While supplemented groups tended to fair better than or equal to unsupplemented group, many of the differences observed were not large enough to prove a statistical significance due to an underlying problem of low sample size.(17) Additionally, many believe that the early tests for cognitive and behavioral development are poor predictors of cognition at later ages and that they may be insufficiently sensitive for detecting the effects of LCPUFA on infant cognitive function, especially since measurements were only made at a few time points.(18) Thus, the effects of formula supplementation on long-term development into later childhood, adolescence, or adulthood are still unknown. In order to derive meaningful information from clinical trials of this nature, future studies will have to be designed with standardized dosages, outcome measures, and length of evaluation using an appropriately large sample size.

### Implications for Policy Changes

In the United States as well as abroad, scientists, health professionals, and regulation officials all differ on whether DHA and AA should be added to infant formula. Some Asian and European countries have allowed but not required the inclusion of DHA and AA in infant formulas since the late 1990's, based on current scientific evidence and the support of a number of international organizations including the European Society for Pediatric Gastroenterology and Nutrition, the British Nutrition Foundation, and the WHO/FAO Expert Committee on Fats and Oils in Human Nutrition. The United States Food and Drug Administration, however, has been much slower to embrace the approval of fatty acid supplementation of infant formula because of the conflicting results of current studies. According to Abbott Laboratories and Mead Johnson Nutritionals, the

FDA granted approval in late 2001 to these two U.S. companies to develop a line of DHA/AA supplemented formulas that should be available to the public in the early months of 2002. Like the European countries, the supplementation will be allowed but not required of formula makers who will likely market their products at a 15%-20% higher cost compared to unsupplemented formulas. Obviously, the approvals were a great victory for the infant formula companies who had been financially supporting some of the research. (6)

Despite the FDA approval, many still fear that the current knowledge on DHA and AA is still too premature to warrant their widespread use. The American Council on Science and Health believes that “the current data has not consistently shown that supplementation of formulas with DHA and AA has a lasting beneficial effect on infant development” nor does it “adequately establish the safety of adding these fatty acids to formulas.”(6) Others are concerned about the safety of DHA and AA supplementation in sick children since many of the clinical trials studying safety did not include very sick infants in their study population. Additionally, there has been no reports on the long-term benefits or harms of DHA and AA in later life. Lastly, because the formulas with DHA and AA will only be available at a higher price, infants who do not have access to these formulas for economic reasons will not be able to benefit from the potential health benefits. (19)

### Conclusion

The question of whether DHA and AA should be included in infant formula is highly controversial. Some suspect that these fatty acids are responsible for higher neural development for several reasons. Firstly, DHA and AA are major components of cortical and retinal neural tissue and are incorporated into phospholipid membranes both pre- and post-gestation. Additionally, breast-fed infants perform better on cognitive standardized tests than formula fed infants. Because DHA and AA levels are higher in breast milk than in formula and because breast-fed infants have higher levels of DHA and AA in their plasma, erythrocyte membranes and cortical tissue than formula-fed infants, many believe that DHA and AA are likely players in neural development.

The clinical trials reviewed here study the effects of DHA/AA supplemented formulas on DHA/AA plasma levels, visual function, and cognitive/behavioral development in relation to unsupplemented formula-fed and breast-fed infants. While the first two measures show positive correlations with supplemented DHA and AA, the latter outcome measure has produced conflicting results. Because of this, some are concerned that the addition of these fatty acids to infant formula has not been adequately proven to be useful or even safe and are therefore wary of policy changes that endorse this practice before more research is done. However, if it can be shown that DHA/AA supplementation is both safe and beneficial for infants in the long term, the resulting changes in infant formula may represent one of the biggest breakthroughs in infant nutrition.

### REFERENCES

1. Morrow-Tlucak M, Haude RH, Enhart CB. Breastfeeding and cognitive development in the first two years of life. *Soc Sci Med* 1998, 26:635-639.
2. Neuringer M, Conne WE, Van Petten C et al. Dietary omega-3 fatty acid deficiency and visual loss in infant rhesus monkeys. *J Clin Invest* 1984, 73:272-276.

3. Meisner, K. Should Long-Chain Polyunsaturated Fatty Acids be Added to Infant Formula? March 2000. Booklet published by American Council on Science and Health, Inc.
4. Heird The role of polyunsaturated fatty acids in term and preterm infants and breastfeeding mothers. *Pediatr Clin North Am* - 01-Feb-2001; 48(1): 173-88
5. Motil KJ. Infant feeding: a critical look at infant formulas. *Curr Op Pediatrics* 2000, 12:469-476.
6. Meisner.
7. Carlson SE et al. Docosahexanoic acid status of preterm infants at birth and following feeding with human milk or formula. *Am J Clin Nutr* 1986, 44:798-804.
8. Bondia-Martinez E, Lopez-Sabater MC, Castellote-Bargallo AI, Rodriguez-Palmero M, Gonzalez-Corbella MJ, Rivero-Urgell M, Campoy-Folgoso C, Bayes-Garcia R, Fatty acid composition of plasma and erythrocytes in term infants fed human milk and formulae with and without docosahexaenoic and arachidonic acids from egg yolk lecithin, *Early Hum Dev* 1998;53:S109-S119.
9. Savino F et al. Arachidonic (AA) and docosahexaenoic (DHA) acid content in healthy infants fed with an HA milk formula supplemented with LCPUFA and in breast fed infants. *Adv Exp Med Biol.* 2000;478:411-2.
10. Birch EE, Hoffman DR, Uauy R, Birch DG, Prestidge C, Visual acuity and the essentiality of docosahexaenoic acid and arachidonic acid in the diet of term infants, *Pediatr Res* 1998;44:201-209.
11. Simmer K. Longchain polyunsaturated fatty acid supplementation in preterm infants. *Cochrane Database Syst Rev.* 2000;(2)
12. San-Giovanni JP et al. Meta-analysis of dietary fatty acids and long-chain polyunsaturated fatty acids as they relate to visual resolution acuity in healthy preterm infants. *Pediatrics* 2000. 105:
13. Makrides M, Neumann MA, Simmer K, Gibson RA, A critical appraisal of the role of dietary long-chain polyunsaturated fatty acids on neural indices of term infants: a randomized, controlled trial, *Pediatrics* 2000;105:32-38.
14. Neuringer M. Infant vision and retinal function in studies of dietary long-chain polyunsaturated fatty acids: methods, results, and implications. *Am J Clin Nutr* 2000; 71(1 Suppl): 256S-67S
15. Lucas A, Stafford M, Morley R, Abbott R, Stephenson T, MacFadyen U, Elias-Jones A, Clements H, Efficacy and safety of long-chain polyunsaturated fatty acid supplementation of infant-formula milk: a randomised trial, *Lancet* 1999;354:1948-1954.
16. Birch EE. A randomized controlled trial of early dietary supply of long-chain polyunsaturated fatty acids and mental development in term infants. *Devel Med Child Neurol* 2000. 42:174-181.
17. Auestad N et al. Growth and development in term infants fed long-chain polyunsaturated fatty acids: a double-masked, randomized, parallel, prospective, multivariate study. *Pediatrics* 2001, 108(2): 372-81.
18. Lucas A. Efficacy and safety of long-chain polyunsaturated fatty acid supplementation of infant-formula milk: a randomised trial. *Lancet* - 4-Dec-1999; 354(9194): 1948-54
19. Gibson RA, Makrides M. Long-chain polyunsaturated fatty acids in breast milk: are they essential? *Adv Exp Med Biol.* 2001;501:375-83.