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Effects of Omega-3 Fatty Acids on Child and Maternal Health

Summary

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Introduction

The purpose of this study was to conduct a systematic review of the scientific-medical literature to identify, appraise, and synthesize the human evidence for the effects of omega-3 fatty acids on child and maternal health. The review was requested and funded by the Office of Dietary Supplements, National Institutes of Health. It was undertaken as part of a consortium involving three Evidence-based Practice Centers (EPCs), which investigated the value of omega-3 fatty acid supplementation across eleven health/disease areas. The three EPCs are Southern California-RAND, Tufts-New England Medical Center, and the University of Ottawa. To ensure consistency of approach, the three EPCs collaborated on selected methodologic elements, including literature search strategies, rating of evidence, and data table design.

It has been posited that the accretion of omega-3 fatty acids within the maternal biological system has the potential to influence both maternal health during pregnancy and fetal health. Likewise, it has been hypothesized that their accumulation within the post-delivery child's biological system can affect its development and health. Birth weight is the most important factor affecting neonatal morbidity and mortality, and is thus an outcome worth monitoring.[1] Moreover, premature infants are at risk of injury to every organ system in the newborn period. Of greatest concern for infants who survive are the risks of developing permanent neurocognitive deficits that impact their lifelong health and functional capacity.[2-5]

Results of studies conducted on residents of the Faroe Islands[6,7] suggest that marine diets, which contain omega-3 fatty acids, increase birth weight either by prolonging pregnancy[8] or by increasing the fetal growth rate.[9,10] Additionally, it has been hypothesized that marine oils may lower risks of certain complications of pregnancy, in particular preterm delivery, intrauterine growth retardation, preeclampsia, and gestational hypertension,[11] given that some of omega-3 fatty acids' presumed mechanisms of action overlap with those of aspirin.[12-14]

Docosahexaenoic acid (DHA) and arachidonic acid (AA) have been identified as important structural components of the highly specialized membrane lipids of the human central nervous system, with phospholipids of brain gray matter containing high proportions of DHA.[15-17] DHA has also been observed to be the major long-chain polyunsaturated fatty acid (LC PUFA) in the outer segments of the retina's rods and cones.[15]

Based on observational studies, it has been shown that human milk fed infants have improved neurocognitive development compared to formula fed infants; it was hypothesized that one of the contributing factors may be the availability of long-chain derivatives of linoleic acid (LA) and alpha-linolenic acid (ALA) that is present only in human milk.[18,19] This difference in fatty acids intake is reflected in lower erythrocyte membrane phospholipid DHA in

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infants fed formula.[18] Until the recent availability of infant formula with added omega-3 LC PUFAs, standard infant formula was devoid of these fatty acids.

The likely significance of omega-3 fatty acids for child health is therefore suggested by the observations that (a) the human brain and retina each contain considerable amounts of omega-3 fatty acids; (b) the children delivered at term receive an important supply of omega-3 fatty acids, especially in the third trimester of pregnancy; and (c) due to a shortened gestational period, a child delivered prematurely receives less exposure to omega-3 fatty acids content than does the term child. Not surprisingly, the observation concerning preterm infants has afforded considerable empirical study of the impact of omega-3 fatty acids on the health of such infants.

Key Questions

The questions are organized by type of population (i.e., maternal/pregnancy versus child) and type of outcome data (i.e., clinical/pregnancy versus clinical/child-developmental).

Maternal population, pregnancy outcomes/biomarkers associations:

- What is the evidence that intake of omega-3 fatty acids influences
  - duration of gestation?
  - incidence of preeclampsia, eclampsia or gestational hypertension?
  - incidence of births of human infants small for gestational age (SGA)?

Child population, growth patterns, neurological, visual or cognitive developmental outcomes/biomarkers associations:

- What is the evidence that maternal intake of omega-3 fatty acids
  - during pregnancy influences any of the clinical outcomes in term or preterm human infants?
  - within maternal breast milk, infant formula, both and/or other sources (i.e., diet) influences any of the clinical outcomes in term or preterm human infants?
- What is the evidence that term or preterm human infants' clinical outcomes are associated with the omega-3 or omega-6/omega-3 fatty acids content of
  - maternal or fetal biomarkers during pregnancy?
  - child biomarkers?

Adverse effects:

- What is the evidence for the risk, in pregnant or breastfeeding women, term or preterm human infants, of short- and long-term adverse events related to their intake of omega-3 fatty acids during pregnancy or after birth?

Methods

A Technical Expert Panel (TEP) consisting of six members was convened to provide advisory support to the project, including refining the questions and highlighting key variables requiring consideration in the evidence synthesis.

Study Identification

Several electronic databases were searched: MEDLINE®, PreMEDLINE®, EMBASE, the Cochrane Library including the Cochrane Central Register of Controlled Trials, and CAB Health. Searches were not restricted by language of publication, publication type, or study design, except with respect to the MeSH term "dietary fats," which was limited by study design to increase its specificity. Search elements included scientific terms, with acronyms, as well as generic and trade names relating to the exposure and its sources (e.g., eicosapentaenoic acid [EPA], omega-3 fatty acids, infant formula) and relevant population terms (e.g., gestational hypertension). Reference lists of included studies, book chapters, and narrative or systematic reviews retrieved after having passed the first level of relevance screening were manually searched to identify additional unique references. Through contact with content experts, attempts were made to identify both published and unpublished studies. A final set of 2,049 unique references was identified and posted to an internet-based software system for review.

Studies were considered relevant if they described live, otherwise "healthy" human populations of any age. The generic term "child" was used to refer to infants (less than 12 months of age), toddlers, and children up to 18 years old. Excluded were studies whose biomarker data were solely obtained from aborted fetuses and which did not distinguish between data obtained from term and preterm births.

Interventional/exposure studies had to specifically investigate foods or supplements known to contain omega-3 fatty acids of any type, from any source, any serving size or dose, delivered in any fashion and for any length of time. No restrictions were placed on the types or doses of pre- or on-study cointerventions. While omega-6 fatty acids appear to play a key role in health and development, and their possible co-influence on outcomes is thus assessed in our review, studies exclusively investigating their impact on health outcomes were excluded.

If at least two randomized controlled trials (RCTs) were identified, no other types of design were required. Yet, if insufficient numbers of RCTs were retrieved, non-RCT (i.e., controlled clinical trials, without random allocation) and

observational studies (i.e., cohort, case-control, or cross-sectional studies) were included. Descriptive study designs were also excluded.

Any and all child developmental outcomes reflecting the four categories of the developmental arc were considered relevant. As markers of omega-3 fatty acids metabolism, the following fatty acids compositions or concentrations, from any source (e.g., red blood cell [RBC] membranes, plasma phospholipids) were considered relevant: EPA, DHA, AA/EPA, AA/DHA, AA/EPA+DHA.

Two initial levels of screening for relevance, and two reviewers per level, were employed (directed at bibliographic records, then full articles). A screening identified and excluded uncontrolled studies. Calibration exercises preceded each step of the screening process. The reasons for the unsuitability of excluded studies were noted according to a modified QUOROM format.[20] Disagreements were resolved by consensus and, when necessary, third-party intervention.

Data Abstraction

Following a calibration exercise involving two studies, eleven reviewers independently abstracted the contents of included studies using an electronic data abstraction form. A second reviewer then verified these data. Data abstracted included the characteristics of the report (e.g., publication status), study (e.g., sample size), population (e.g., preterm versus term status), intervention/exposure (e.g., omega-3 fatty acids types), and comparator(s), cointerventions (e.g., omega-6 fatty acids use), withdrawals and dropouts, including reasons, clinical outcomes, fatty acids content of biomarkers, and adverse events.

Data Synthesis

A summary table provided a question-specific overview of included studies' relevant data, which is presented in greater detail in evidence tables. A question-specific summary matrix described each study in terms of its quality and applicability ratings. Question-specific qualitative syntheses of the evidence were derived. Meta-analysis was performed if the following criteria were met: at least two RCTs, same population characteristics (mean age, health status, gender), same co-interventions, same intervention based on the type of omega-3 fatty acids supplemented (DHA+AA vs. DHA vs. DHA+EPA, etc.) regardless of the daily dose in the child population, same comparator based on source of placebo (e.g., olive oil, unsupplemented formula), outcomes relevant to respond to the key-questions: percentage (n) of premature deliveries, incidence of gestational hypertension (GHT), pre-eclampsia or eclampsia, incidence of IUGR or SGA infants, weight, length, and head circumference of infants (means), neurological and cognitive development measured by validated scales (e.g., Bayley's Developmental Scale score), and visual acuity or visual function of infants measured by appropriate tests (Teller's Card test, etc.).

Results

Literature Search

Of the 2,049 records entered into the initial screening for relevance, 1,579 were excluded. Of the 191 reports that made it to this level of screening, 74 were excluded. Hence, in total, 117 reports, describing 89 unique studies, were deemed relevant for the systematic review, with 20 studies each described by more than one report and three reports describing more than one unique study. There were 63 randomized controlled trials (RCTs) and 26 observational studies across all the key questions. Only one study required translation from German to English.[21] No studies were identified across all the child outcomes (i.e., growth patterns, neurocognitive development, and visual function) regarding the influence of the intake of omega-3 fatty acids from sources other than human milk, or infant formula, as well as the association between omega-3 or omega-6/omega-3 fatty acids content of fetal biomarkers and any of the clinical outcomes. Synopses of evidence are presented according to the clinical outcomes by population.

Safety Issues

Overall, omega-3 fatty acids supplementation in pregnant women, breastfeeding mothers, and preterm and term infants, was very well tolerated and did not generate any serious adverse events across the included RCTs. The safety data was reported in 21 RCTs. In pregnant women, the adverse events related to the omega-3 fatty acids intake were mild and transient, with nausea and gastrointestinal discomfort being the most commonly reported.[22,23] For both term and preterm populations, change in number of stools and flatulence were the most common adverse events related to the omega-3 supplemented formulas. However, most of the serious harms were related to the fact that the infants were premature with low birth weights, which increases the occurrence of necrotizing enterocolitis (NEC), bleeding problems, infections and respiratory failure, among others in the case of preterm infants.[24-43] None of the withdrawals were due to the interventional formula.

Pregnancy Outcomes

Duration of gestation-intake during pregnancy: Fifteen poor quality RCTs addressed this question.[11,44-51,59] Seven trials included otherwise healthy pregnant women,[52-58] the remaining eight studies included a high-risk population of pregnant

women. Ten studies did not find a significant difference between intervention groups in the duration of gestation measured as mean of gestational age at delivery.[22,23,53-58] Four poor quality studies observed that the omega-3 fatty acids group had a significantly greater duration of gestation after treatment compared with the unsupplemented group.[22,52]

Omega-3 fatty acids did not have a significant effect on the proportion of premature deliveries in ten studies.[11,23,52,55,59] Fish consumption in the background diet was used as a covariate in only one trial.[52] Other covariates used to control the results were: the compliance with the intervention,[52] current smoking status,[23,55] maternal BMI, and number of prior pregnancies.[55] The only variable that had an impact on the results was the smoking status in Smuts et al.'s study.[55] The duration of gestation was significantly longer in the high-DHA group in the nonsmokers.[55]

Meta-analysis of the incidence of premature deliveries was performed from eight RCTs that used capsules containing DHA+EPA (OR: 0.88 [95% CI: 0.62-1.25]),[11,44,49] and two trials using high DHA eggs (OR: 0.53 [95% CI: 0.13-2.29])[47,50] or control group. There is inconsistent evidence of the use of omega-3 fatty acids supplements during the second or third trimester of pregnancy to reduce the incidence of premature pregnancies in high- and low-risk populations. Nevertheless, the overall effect does not show a significant difference between study arms.

Duration of gestation-maternal biomarkers: Nothing conclusive can be drawn from four studies that assessed this association.[55,60-62]

Incidence of gestational hypertension (GHT), preeclampsia, or eclampsia-intake during pregnancy: Of eight RCTs with a quality score approaching good internal validity,[22,23,52,63,64] six trials compared the use of fish oil supplements containing DHA and EPA with placebo. The population included healthy or high-risk pregnant women (i.e., twin pregnancy).[22,23,63,64] The incidence of GHT in these populations, after the use of omega-3 fatty acids or placebo did not differ in six studies.[22,23,52,59,63] Regarding the incidence of preeclampsia (hypertension, edema, and proteinuria), six studies showed that compared with placebo, supplementation with omega-3 fatty acids did not have a significant effect.[22,23,55,59,63] Meta-analysis of the incidence of gestational hypertension from two studies revealed a nonsignificant difference between groups (OR: 1.07, CI 95%: 0.75; 1.51).[22,23] These findings were not adjusted for the potential covariates or confounders, such as background diet, grade of risk for GHT or preeclampsia in the current pregnancy, smoking status, and age.

Incidence of preeclampsia-eclampsia or gestational hypertension-maternal biomarkers: Five observational studies were identified,[21,65-68] of which four selected preeclamptic women and normal pregnant women as controls.[21,66-68] The results are very inconsistent across the studies.

Incidence of SGA infants- intake during pregnancy: Fourteen poor quality score RCTs showed that in the majority of the studies, the mean birth weight was not influenced by the intervention. None of the trials adjusted their results for the maternal background diet, which can be an important effect modifier.

Meta-analysis of the birth weight (mean) was combined in two studies that were comparable in terms of type of intervention and population (weight mean difference: -61.51, CI 95%: -256.21; 133.18) showing a nonsignificantly difference between groups.[23] The incidence of infants with IUGR showed a nonsignificant effect (OR: 1.14, CI 95%: 0.79; 1.64)[22,23,59] of supplementation during pregnancy.

Incidence of SGA infants-maternal biomarker: Six studies addressed this question.[58,60,61,69-71] de Groot et al.'s RCT found a significantly positive correlation between the maternal plasma and RBC DHA content and birth weight; however, this relationship was nonsignificant when measured at delivery.[58] Two observational studies found that the women with IUGR fetuses had a significantly lower content of LA (omega-6) in the plasma.[69,71] The content of DHA, EPA, AA, total omega-3 and omega-6 fatty acids, however, did not show a constant pattern across the studies. Two observational studies did not observe a correlation between maternal plasma biomarkers and birth weight,[61,69] consistent with the result in the RCT.[58]

Growth Pattern Outcomes

Maternal intake during pregnancy: One good quality RCT addressed this question,[54] showing no statistical difference between infants (n=590 enrolled, 341 completers) from mothers that were taking the supplementation with omega-3 and omega-6, or omega-6 fatty acids predominantly, on the weight, length, and head circumference (HC) from birth to 12 months of age.[54]

Maternal breast milk: One good quality RCT evaluating omega-3 supplementation in Norwegian mothers,[54] one poor quality RCT,[72] and two observational studies were identified.[73,74] Both RCTs showed no apparent effects of breast milk, with maternal intake of omega-3 (DHA) or omega-6 fatty acids (AA), on the growth patterns at any time point.[54,72] The single prospective cohort of Swedish mother/term infant pairs showed a positive correlation between the maternal mother's breast milk content of AA/DHA and the infant's rate of increase of HC at 1 and 3 months of age.[74] A cross-sectional

study from Africa showed that the differences in weight-for-age and weight-for-height z-scores and weight gain (g) were significantly lower in infants from Ouagadougou (low omega-3 fatty acids intake) compared with infants from Brazzaville (high omega-3 intake).[73]

Formula intake, preterm infants: Twenty RCTs of poor quality were identified,[25-32,34,75-85] of which eighteen failed to find an effect of the omega-3 supplementation in preterm formulas on the growth parameters at any time point.[25-30,32,34,75-84] The outcomes measured were the mean (SD) and gain in weight, length, and HC and the normalized z-score of weight. Two trials found that the omega-3 fatty acids supplemented group had a significantly lower weight from 6 to 18 months.[31,85] The results of the meta-analysis performed on the mean weight and length measured at 4 months, from studies that compared the use of formula supplemented with DHA+AA with control, showed that the overall effect was nonstatistically significant (weight: WMD: 0.04, CI 95%: -0.30; 0.38; length: WMD: 0.09, CI 95%: -0.62; 0.80).[28,29]

Formula intake, term infants: Eighteen good quality RCTs were identified.[35-43,86-93] The effects on the growth outcomes were nonstatistically different between study arms. Yet, some inconsistent differences were found across five trials at certain timepoints and subgroup of patients.[94-98] Meta-analysis demonstrated a nonstatistically significant overall effect of formulas containing DHA+AA compared with control formula at 4 or 12 months of age for the growth parameters (**4 months:** weight: WMD: -0.06, CI 95%: -0.45; 0.34; length: WMD: -0.33, CI 95%: -1.07; 0.40; **12 months:** weight: WMD: -0.33, CI 95%: -0.87; 0.21; length: WMD: -0.37, CI 95%: -1.26; 0.51; HC: WMD: 0.14, CI 95%: -0.83; 1.12) or DHA (**4 months:** weight: WMD: -0.12, CI 95%: -0.44; 0.20; length: WMD: -0.43, CI 95%: -1.20; 0.34; HC: WMD: 0.04, CI 95%: -0.37; 0.46. **12 months:** weight: WMD: -0.33, CI 95%: -0.87; 0.21; length: WMD: -0.71, CI 95%: -2.18; 0.76; HC: WMD: -0.04, CI 95%: -0.45; 0.38) [36,39] Only four trials adjusted the results for potential confounders, such as gender, maternal education, parental socioeconomic status and center, failing to find any change in the results.[39,41,43,88]

Child biomarkers: Five were RCTs in preterm infants,[25,28,29,76,85] and five RCTs[39,43,87,88,99] and a prospective single cohort[100] in term infants.

There is a negative correlation between weight and the plasma or RBC content of DHA, and a positive correlation between weight and the content of AA in plasma or RBC. However, not all of the studies found this association. The content of omega-6 fatty acids (AA) as a biomarker may be related to weight gain in infants. The content of DHA seems to be inversely related to weight gain, yet no significant clinical outcomes were detected.

Neurological Development Outcomes

Maternal intake during pregnancy: Helland et al. failed to find a significant difference between groups in maturity as evaluated from the EEGs, neither at day 1 of life nor at 3 months of age.[54]

Maternal breast milk: Two studies, one RCT[101] and one single prospective cohort design[102] showed that maternal breast milk may not have an influence on the neurological outcome, measured with the PDI scale of the Bayley's Index.

Formula intake, preterm infants: Six good quality RCTs were identified.[28,30,31,34,82,103] For the Bayley's PDI scale, two trials did not observe a significant difference between the supplemented and the control formula.[31,34] Meta-analysis was not possible for this outcome. Only Fewtrell et al. found that there was no difference between groups in the neurological impairment assessment at 9 and 18 months of corrected age (CA), and in the Knobloch, Passamanick, and Sherrards' Developmental Screening Inventory score.[34] There is not consistent evidence to suggest that the omega-3 fatty acids supplementation of infant formula, with or without breast milk, influences the neurological development in preterm infants.

Formula intake, term infants: Eight good quality RCTs,[36-39,42,43,104] of which seven failed to find a statistically significant difference between diet groups at different follow-ups (6 to 24 months of age) in the Bayley's PDI scale.[36-39,42,43] One trial showed a significantly better Brunet-Lézine test result in the LC PUFAs supplemented group compared with control at 4 months of age (after exclusive formula intake) but not at 24 months.[104] Meta-analysis of Bayley's PDI score showed a nonstatistically significant difference between groups using formula supplemented with DHA+AA and control (WMD: -2.80, CI 95%: -7.43; 1.82) at 12 months. [36,39,42]

Maternal biomarkers: One cross-sectional study showed that maternal DHA was negatively associated with active sleep (AS), AS:QS (quiet sleep) and sleep-wake transition, and positively associated with wakefulness (postpartum day 2).[105] The ratio of n-6:n-3 in maternal plasma was positively associated with AS, AS:QS and sleep-wake transition, and negatively associated with wakefulness (day 2), suggesting a greater CNS maturity.

Child biomarkers: Three RCTs[37,39,43] and a prospective cohort study[100] evaluated the association between the infant's plasma and RBC DHA content and the Bayley's psychomotor developmental index (PDI) score in healthy term infants. Two RCTs found a significant positive correlation between the

plasma DHA and the PDI score.[39,43] Two other studies (including the observational study), did not find a significant correlation between the PDI and the infant content of PUfatty acids in plasma or RBC.[37,100]

Visual Function Outcomes

Maternal intake during pregnancy: One RCT failed to find a significant effect of DHA supplementation during pregnancy on the retinal sensitivity (ERG) measured at birth in term infants.[51] One cross-sectional study failed to find a statistically significant difference in mean visual function values between the exclusively breastfed group and the infants who were also receiving formula.[106]

Maternal breast milk: Five studies found that the correlation between the DHA content in breast milk and visual function was not consistent with the clinical outcomes measured in breastfed term infants of mothers who were or were not taking supplements containing high DHA.[72,101,106-108]

Formula intake, preterm infants: Nine RCTs with a quality score approaching good internal validity were identified.[25,26,28,29,76,77,82,85,103] Of five studies that measured visual evoked potentials (VEP), two did not find a statistical difference between feeding groups at any time point (from 1 to 12 months).[82,103] Three studies found that compared with the unsupplemented group, infants fed with LC PUFAs-supplemented formula had a better or faster maturation of visual function, in terms of significantly shorter waves in the VEP.[25,28,77] Two studies found a significant difference between groups in the Teller's Acuity Card test.[85] Meta-analysis of the relevant visual outcomes comparing the studies by the type of omega-3 fatty acids used in the supplemented formula (DHA or DHA+AA) and control formula, and by the type of outcome (VEP and Teller's test of visual acuity) was done. For the VEP visual acuity outcomes, only two studies were combined.[25,28] O'Connor et al. found that the use of formulas with DHA+AA resulted in a better VEP measurements compared with control formula at 6 months of age yet not at 4 months.[25,28]

No significant effect of DHA-supplementation at 2, 4, 6, or 9 months of CA,[29,76] or DHA+AA supplementation at 2, 3, 4, or 6 months of CA was found in the visual acuity measured with the Teller's Card test.[25,28,29,85,103]

Formula intake, term infants: Thirteen RCTs, of average good quality (Jadad: 3.61/5) were identified,[36,37,39,41-43,88,89,91,93,109,110] of which five trials did not find a significant difference between groups in the VEP at any age.[36,39,41,43,89] Four trials found a significantly better VEP in the LC PUFAs-supplemented group compared with the control group at a number of time points, from 1.5 to 13 months of age.[37,87,91,93] The meta-analysis performed on this outcome, by LC PUFAs content of DHA alone (or with the addition of AA), versus control, showed that the studies that compared DHA supplemented formula with control formula did not have an overall significant effect at any age.[36,37,39] Conversely, in seven studies that compared the use of DHA+AA formula with placebo, there was no difference between groups at any age,[36,37,39,87,89,91,93] with the exception of four studies that found a significant difference at 12 months of age.[36,37,91,93]

One trial that evaluated behavioral visual acuity with the Teller's test,[110] found a significantly better acuity in the LC PUFAs formula group compared with the control group at 2 months of age, yet not at 4, 6, 9, or 12 months. The remaining four trials did not observe a significant difference between groups in this outcome, at any time point.[36,42,88] The meta-analysis performed on this outcome showed that, in studies comparing the use of DHA+AA with a control intervention, acuity was only significantly better in the DHA+AA group at 2 months of age,[36,37,110] but not at 4, 6, 9, or 12 months of age.

Maternal biomarkers: One study measured the association between the maternal content of biomarkers at 2 months postpartum and the visual acuity (Teller's Card Test) in term infants at 2 months of age that failed to find a significant correlation.[106]

Child biomarkers: Twenty-one studies assessed this association. Of five studies in the preterm group, three were RCTs,[25,76,77] and two were cross-sectional studies.[111,112] Of the 16 term infant studies, nine were RCTs,[37,43,72,87-89,91,93,101] and seven were observational studies.[100,106,107,111,113-115] There was no pattern of correlation between the infant's biomarkers in blood and the visual function outcomes across 21 studies that addressed this issue.

Cognitive Development Outcomes

Maternal intake during pregnancy: One RCT addressed this question.[54] There were no differences between groups in the novelty preference (Fagan Test of Infant Intelligence) at 6 and 9 months of age.[54]

Maternal breast milk: Two RCTs[54,101] and one prospective cohort[102] were identified. The study by Helland et al. was an RCT described above,[54] and Gibson et al. included mother of term infants who intended to breastfeed.[101] They were randomized to receive five increasing doses of DHA (algal oil) during the first 3 months postpartum. The mean Bayley's Mental Developmental Index (MDI) score did not differ between groups at 1 or 2 years of age (underpowered).[101]

Formula intake preterm infants: Six good quality (Jadad: 4.4/5) RCTs were identified.[28,30,31,34,76,103] Four of the five trials

did not find an effect on the Bayley's MDI score from 3 to 24 months of age.[28,31,34,116] Two studies found a significant difference between the omega-3 fatty acids group and the control group in the Fagan Test of Infant Intelligence.[28,76] O'Connor et al. found that there was no significant differences between groups in the Infant version of the MacArthur Communicative Development Inventories at 9 months CA and 14 months CA.[28] Meta-analysis was not possible given the heterogeneity across the studies for each of the different outcomes due to the intervention characteristics (meaning dose, source of omega-3 fatty acids, duration of intervention), cointerventions, different assessment tools, and timing of the outcomes measures.

Formula intake term infants: Six (of eight) good quality RCTs[36-39,42,43,92] did not find a significant difference between groups (supplemented vs. control) in the Bayley's MDI score from 6 to 18 months of age.[36-39,42,43] Birch et al. observed that the DHA+AA group had a significantly higher score compared with the control group at 18 months of age.[37]

The Knobloch, Passamanik, and Sherrards Development Screening Inventory test (9 months),[117] and the Fagan Test of Infant Intelligence (6 and 9 months)[98] did not differ between groups. The IQ (Stanford-Binet), Receptive Vocabulary (PPVT-R), Expressive Vocabulary, and Visual-Motor Index scores, as well as the Problem-Solving scores, did not differ between groups in two studies.[36,92]

A meta-analysis using the Bayley's MDI score at 12 months of age showed a nonstatistical difference between groups (DHA+AA vs. control) from three trials (WMD: -0.80, CI 95%: -3.24; 1.63).[36,39,42]

Child biomarkers: Four good quality RCTs and two single prospective cohort studies[100,118] showed inconsistent results.

Discussion

Studies investigating the influence of omega-3 fatty acids on child and maternal health revealed the absence of a notable safety profile (i.e., moderate-to-severe adverse events). Pregnancy outcomes were either unaffected by omega-3 fatty acids supplementation, or the results were inconclusive. Results suggested the absence of effects with respect to the impact of supplementation on the incidence of GHT, preeclampsia or eclampsia, as well as on infants being born SGA. However, regarding evaluations of the duration of gestation, some discrepancies were observed, although most of the studies failed to detect a statistically significant effect. Biomarker data failed to clarify patterns in pregnancy outcome data.

Results concerning the impact of the intake of omega-3 fatty acids on the development of infants are primarily, although not uniformly, inconclusive. The inconsistencies in study results may be attributable to numerous factors.

In addition, making clear sense of the absolute or relative effects of individual omega-3 fatty acids, or even omega-3 fatty acids combinations, on child outcomes is complicated or precluded by the following problem. Studies typically employed interventions that involved various cointerventional or background constituents (e.g., omega-6 fatty acids), yet whose metabolic interactions with the omega-3 fatty acids were not taken into account in interpreting the results. The dynamic interplay among these fatty acid contents (e.g., competition for enzymes), and how this interplay may influence outcomes, may differ in important ways depending on whether DHA or olive oil is added to this combination of cointerventional or background constituents, particularly in the maternal population. This strategy prevented the isolation of the exact effects relating to the omega-3 fatty acids content. It is thus very difficult to reliably ascribe definite child outcome-related benefits, or the absence thereof, to specific omega-3 fatty acids. Biomarker data failed to clarify patterns in child outcome data.

Future research should likely consider investigating the impact of specific omega-6/omega-3 fatty acids intake ratios, in no small part to control for the possible metabolic interactions involving these types of fatty acids. To produce results that are applicable to the North American population, populations consuming high omega-6/omega-3 fatty acids intake ratios should likely be randomized into trials also exhibiting better control of confounding variables than was observed, especially in the present collection of studies of child outcomes.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the University of Ottawa Evidence-based Practice Center under Contract No. 290-02-0021. It is expected to be available in August 2005. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 118, *Effects of Omega-3 Fatty Acids on Child and Maternal Health*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

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References

1. McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. N Engl J Med 1985; 312(2):82-90.
2. Lemons JA, Bauer CR, Oh W, et al. Very low birth weight outcomes of the National Institute of Child health and human development neonatal research network, January 1995 through December 1996. NICHD Neonatal Research Network. Pediatrics 2001; 107(1):E1.
3. Vohr BR, Msall ME. Neuropsychological and functional outcomes of very low birth weight infants. Semin Perinatol 1997; 21(3):202-220.
4. Saigal S. Follow-up of very low birthweight babies to adolescence. Semin Neonatol 2000; 5(2):107-118.
5. Kramer MS, Demissie K, Yang H, et al. The contribution of mild and moderate preterm birth to infant mortality. Fetal and Infant Health Study Group of the Canadian Perinatal Surveillance System. JAMA 2000; 284(7):843-849.
6. Olsen SF, Hansen HS, Sorensen TI, et al. Intake of marine fat, rich in (n-3)-polyunsaturated fatty acids, may increase birthweight by prolonging gestation. Lancet 1986; 2(8503):367-369.
7. Olsen SF. Consumption of marine n-3 fatty acids during pregnancy as a possible determinant of birth weight. A review of the current epidemiologic evidence. [Review] [112 refs]. Epidemiol Rev 1993; 15(2):399-413.
8. Olsen SF, Hansen HS, Sorensen TI, et al. Intake of marine fat, rich in (n-3)-polyunsaturated fatty acids, may increase birthweight by prolonging gestation. Lancet 1986; 2(8503):367-369.
9. Andersen HJ, Andersen LF, Fuchs AR. Diet, pre-eclampsia, and intrauterine growth retardation. Lancet 1989; 1(8647):1146.
10. Olsen SF, Olsen J, Frische G. Does fish consumption during pregnancy increase fetal growth? A study of the size of the newborn, placental weight and gestational age in relation to fish consumption during pregnancy. Int J Epidemiol 1990; 19(4):971-977.
11. Olsen SF, Secher NJ, Tabor A, et al. Randomised clinical trials of fish oil supplementation in high risk pregnancies. Fish Oil Trials In Pregnancy (FOTIP) Team. BJOG 2000; 107(3):382-395.
12. Dyerberg J, Bang HO. Pre-eclampsia and prostaglandins. Lancet 1985; 1(8440).
13. England MJ, Atkinson PM, Sonnendecker EW. Pregnancy induced hypertension: will treatment with dietary eicosapentaenoic acid be effective? [Review] [50 refs]. Med Hypotheses 1987; 24(2):179-186.
14. Secher NJ, Olsen SF. Fish-oil and pre-eclampsia.[comment]. [Review] [25 refs]. Br J Obstet Gynaecol 1990; 97(12):1077-1079.
15. Giusto NM, Pasquare SJ, Salvador GA, et al. Lipid metabolism in vertebrate retinal rod outer segments. Prog Lipid Res 2000; 39(4):315-391.
16. Sastry PS. Lipids of nervous tissue: composition and metabolism. Prog Lipid Res 1985; 24(2):69-176.
17. Innis S, Uauy R, Heird W, et al. Mechanisms of action of LC PUFAs effects on infant growth and neurodevelopment: Perinatal biochemistry and physiology of LC PUFAs discussion. J Pediatr 2003; 143(4 Suppl).
18. Carlson SE, Rhodes PG, Ferguson MG. Docosahexaenoic acid status of preterm infants at birth and following feeding with human milk or formula. Am J Clin Nutr 1986; 44(6):798-804.
19. Anderson JW, Johnstone BM, Remley DT. Breast-feeding and cognitive development: A meta-analysis. Am J Clin Nutr 1999; 70(4).
20. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 1999; 354(9193):1896-1900.
21. Hofmann M, Bahlmann F, Pollow K, et al. Phospholipid and triglycerid composition in patients with preeclampsia compared with normal pregnancies - Deficiency of essential polyunsaturated fatty acids. Geburtshilfe Frauenheilkd 1998; 58(9).
22. Olsen SF, Secher NJ, Tabor A, et al. Randomised clinical trials of fish oil supplementation in high risk pregnancies. Fish Oil Trials In Pregnancy (FOTIP) Team. BJOG 2000; 107(3):382-395.
23. Onwude JL, Lilford RJ, Hjartardottir H, et al. A randomised double blind placebo controlled trial of fish oil in high risk pregnancy. Br J Obstet Gynaecol 1995; 102(2):95-100.
24. McClead REJr, Meng HC, Gregory SA, et al. Comparison of the clinical and biochemical effect of increased alpha-linolenic acid in a safflower oil intravenous fat emulsion. J Pediatr Gastroenterol Nutr 1985; 4(2):234-239.
25. Birch DG, Birch EE, Hoffman DR, et al. Retinal development in very-low-birth-weight infants fed diets differing in omega-3 fatty acids. Invest Ophthalmol Vis Sci 1992; 33(8):2365-2376.
26. Koletzko B, Edenhofer S, Lipowsky G, et al. Effects of a low birthweight infant formula containing human milk levels of docosahexaenoic and arachidonic acids. J Pediatr Gastroenterol Nutr 1995; 21(2):200-208.
27. Vanderhoof J, Gross S, Hegyi T, et al. Evaluation of a long-chain polyunsaturated fatty acid supplemented formula on growth, tolerance, and plasma lipids in preterm infants up to 48 weeks postconceptional age. J Pediatr Gastroenterol Nutr 1999; 29(3):318-326.
28. O'Connor DL, Hall R, Adamkin D, et al. Growth and development in preterm infants fed long-chain polyunsaturated fatty acids: a prospective, randomized controlled trial. Pediatrics 2001; 108(2):359-371.
29. Innis SM, Adamkin DH, Hall RT, et al. Docosahexaenoic acid and arachidonic acid enhance growth with no adverse effects in preterm infants fed formula. J Pediatr 2002; 140(5):547-554.
30. Clandinin MTV. Growth and development of very-low-birth-weight infants (VLBW) is enhanced by formulas supplemented with docosahexaenoic acid (DHA) and arachidonic acid (ARA). J Pediatr Gastroenterol Nutr 2002; 34(4):479.
31. Fewtrell MS, Morley R, Abbott RA, et al. Double-blind, randomized trial of long-chain polyunsaturated fatty acid supplementation in formula fed to preterm infants. Pediatrics 2002; 110(1):73-82.

32. Koletzko B, Sauerwald U, Keicher U, et al. Fatty acid profiles, antioxidant status, and growth of preterm infants fed diets without or with long-chain polyunsaturated fatty acids: A randomized clinical trial. Eur J Nutr 2003; 42(5).

33. Gobel Y, Koletzko B, Bohles HJ, et al. Parenteral fat emulsions based on olive and soybean oils: a randomized clinical trial in preterm infants. J Pediatr Gastroenterol Nutr 2003; 37(2):161-167.

34. Fewtrell MS, Abbott RA, Kennedy K, et al. Randomized, double-blind trial of long-chain polyunsaturated fatty acid supplementation with fish oil and borage oil in preterm infants. J Pediatr 2004; 144(4):471-479.

35. Decsi T, Koletzko B. Growth, fatty acid composition of plasma lipid classes, and plasma retinol and alpha-tocopherol concentrations in full-term infants fed formula enriched with omega-6 and omega-3 long-chain polyunsaturated fatty acids. Acta Paediatr 1995; 84(7):725-732.

36. Auestad N, Montalto MB, Hall RT, et al. Visual acuity, erythrocyte fatty acid composition, and growth in term infants fed formulas with long chain polyunsaturated fatty acids for one year. Ross Pediatric Lipid Study. Pediatr Res 1997; 41(1):1-10.

37. Birch EE, Hoffman DR, Uauy R, et al. Visual acuity and the essentiality of docosahexaenoic acid and arachidonic acid in the diet of term infants. Pediatr Res 1998; 44(2):201-209.

38. Lucas A, Stafford M, Morley R, et al. Efficacy and safety of long-chain polyunsaturated fatty acid supplementation of infant-formula milk: a randomised trial.[comment]. Lancet 1999; 354(9194):1948-1954.

39. Makrides M, Neumann MA, Simmer K, et al. Dietary long-chain polyunsaturated fatty acids do not influence growth of term infants: A randomized clinical trial. Pediatrics 1999; 104(3 Pt 1):468-475.

40. Morris G, Moorcraft J, Mountjoy A, et al. A novel infant formula milk with added long-chain polyunsaturated fatty acids from single-cell sources: a study of growth, satisfaction and health. Eur J Clin Nutr 2000; 54(12):883-886.

41. Makrides M, Neumann MA, Jeffrey B, et al. A randomized trial of different ratios of linoleic to alpha-linolenic acid in the diet of term infants: effects on visual function and growth.[comment]. Am J Clin Nutr 2000; 71(1):120-129.

42. Auestad N, Halter R, Hall RT, 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):372-381.

43. Jensen CL, Prager TC, Fraley JK, et al. Effect of dietary linoleic/alpha-linolenic acid ratio on growth and visual function of term infants.[comment]. J Pediatr 1997; 131(2):200-209.

44. Olsen SF, Sorensen JD, Secher NJ, et al. Randomised controlled trial of effect of fish-oil supplementation on pregnancy duration.[comment]. Lancet 1992; 339(8800):1003-1007.

45. Helland IB, Saugstad OD, Smith L, et al. Similar effects on infants of n-3 and n-6 fatty acids supplementation to pregnant and lactating women. Pediatrics 2001; 108(5):E82.

46. Dunstan JA, Mori TA, Barden A, et al. Effects of n-3 polyunsaturated fatty acid supplementation in pregnancy on maternal and fetal erythrocyte fatty composition. Eur J Clin Nutr 2004; 58(3):429-437.

47. Smuts CM, Borod E, Peeples JM, et al. High-DHA eggs: feasibility as a means to enhance circulating DHA in mother and infant. Lipids 2003; 38(4):407-414.

48. de Groot RH, Hornstra G, van Houwelingen AC, et al. Effect of alpha-linolenic acid supplementation during pregnancy on maternal and neonatal polyunsaturated fatty acid status and pregnancy outcome. Am J Clin Nutr 2004; 79(2):251-260.

49. Onwude JL, Lilford RJ, Hjartardottir H, et al. A randomised double blind placebo controlled trial of fish oil in high risk pregnancy. Br J Obstet Gynaecol 1995; 102(2):95-100.

50. Smuts CM, Huang M, Mundy D, et al. A randomized trial of docosahexaenoic acid supplementation during the third trimester of pregnancy. Obstet Gynecol 2003; 101(3):469-479.

51. Malcolm CA, Hamilton R, McCulloch DL, et al. Scotopic electroretinogram in term infants born of mothers supplemented with docosahexaenoic acid during pregnancy. Invest Ophthalmol Vis Sci 2003; 44(8):3685-3691.

52. Olsen SF, Sorensen JD, Secher NJ, et al. Randomised controlled trial of effect of fish-oil supplementation on pregnancy duration.[comment]. Lancet 1992; 339(8800):1003-1007.

53. Dunstan JA, Mori TA, Barden A, et al. Effects of n-3 polyunsaturated fatty acid supplementation in pregnancy on maternal and fetal erythrocyte fatty composition. Eur J Clin Nutr 2004; 58(3):429-437.

54. Helland IB, Saugstad OD, Smith L, et al. Similar effects on infants of n-3 and n-6 fatty acids supplementation to pregnant and lactating women. Pediatrics 2001; 108(5):E82.

55. Smuts CM, Huang M, Mundy D, et al. A randomized trial of docosahexaenoic acid supplementation during the third trimester of pregnancy. Obstet Gynecol 2003; 101(3):469-479.

56. Malcolm CA, Hamilton R, McCulloch DL, et al. Scotopic electroretinogram in term infants born of mothers supplemented with docosahexaenoic acid during pregnancy. Invest Ophthalmol Vis Sci 2003; 44(8):3685-3691.

57. Smuts CM, Borod E, Peeples JM, et al. High-DHA eggs: feasibility as a means to enhance circulating DHA in mother and infant. Lipids 2003; 38(4):407-414.

58. de Groot RH, Hornstra G, van Houwelingen AC, et al. Effect of alpha-linolenic acid supplementation during pregnancy on maternal and neonatal polyunsaturated fatty acid status and pregnancy outcome. Am J Clin Nutr 2004; 79(2):251-260.

59. Bulstra-Ramakers MT, Huisjes HJ, Visser GH. The effects of 3g eicosapentaenoic acid daily on recurrence of intrauterine growth retardation and pregnancy induced hypertension. Br J Obstet Gynaecol 1995; 102(2):123-126.

60. Elias SL, Innis SM. Infant plasma trans, n-6, and n-3 fatty acids and conjugated linoleic acids are related to maternal plasma fatty acids, length of gestation, and birth weight and length.[comment]. Am J Clin Nutr 2001; 73(4):807-814.

61. Rump P, Mensink RP, Kester AD, et al. Essential fatty acid composition of plasma phospholipids and birth weight: a study in term neonates.[comment]. Am J Clin Nutr 2001; 73(4):797-806.

62. Reece MS, McGregor JA, Allen KG, et al. Maternal and perinatal long-chain fatty acids: possible roles in preterm birth.[comment]. Am J Obstet Gynecol 1997; 176(4):907-914.

63. Laivuori H, Hovatta O, Viinikka L, et al. Dietary supplementation with primrose oil or fish oil does not change urinary excretion of

prostacyclin and thromboxane metabolites in pre-eclamptic women. Prostaglandins Leukot Essent Fatty Acids 1993; 49(3):691-694.

64. D'Almeida A, Carter JP, Anatol A, et al. Effects of a combination of evening primrose oil (gamma linolenic acid) and fish oil (eicosapentaenoic + docahexaenoic acid) versus magnesium, and versus placebo in preventing pre-eclampsia. Women Health 1992; 19(2-3):117-131.
65. Al MD, van Houwelingen AC, Badart-Smook A, et al. The essential fatty acid status of mother and child in pregnancy-induced hypertension: a prospective longitudinal study. Am J Obstet Gynecol 1995; 172(5):1605-1614.
66. Craig-Schmidt MC, Carlson SE, Crocker L, et al. Plasma total phospholipid arachidonic acid and eicosapentaenoic acid in normal and hypertensive pregnancy. World Rev Nutr Diet 1994; 76:126-129.
67. Shouk TA, Omar MN, Fayed ST. Essential fatty acids profile and lipid peroxides in severe pre-eclampsia. Ann Clin Biochem 1999; 36(Pt 1):62-65.
68. Wang YP, Kay HH, Killam AP. Decreased levels of polyunsaturated fatty acids in preeclampsia.[comment]. Am J Obstet Gynecol 1991; 164(3):812-818.
69. Vilbergsson G, Samsioe G, Wennergren M, et al. Essential fatty acids in pregnancies complicated by intrauterine growth retardation. Int J Gynaecol Obstet 1991; 36(4):277-286.
70. Matorras R, Perteagudo L, Nieto A, et al. Intrauterine growth retardation and plasma fatty acids in the mother and the fetus. Eur J Obstet Gynecol Reprod Biol 1994; 57(3):189-193.
71. Cetin I, Giovannini N, Alvino G, et al. Intrauterine growth restriction is associated with changes in polyunsaturated fatty acid fetal-maternal relationships. Pediatr Res 2002; 52(5):750-755.
72. Jensen CL, Prager TC, Zou Y, et al. Effects of maternal docosahexaenoic acid supplementation on visual function and growth of breast-fed term infants. Lipids 1999; 34(Suppl):S225.
73. Rocquelin G, Tapsoba S, Kiffer J, et al. Human milk fatty acids and growth of infants in Brazzaville (The Congo) and Ouagadougou (Burkina Faso). Public Health Nutr 2003; 6(3):241-248.
74. Xiang M, Alfven G, Blennow M, et al. Long-chain polyunsaturated fatty acids in human milk and brain growth during early infancy. Acta Paediatr 2000; 89(2):142-147.
75. Carlson SE, Rhodes PG, Rao VS, et al. Effect of fish oil supplementation on the n-3 fatty acid content of red blood cell membranes in preterm infants. Pediatr Res 1987; 21(5):507-510.
76. Carlson SE, Cooke RJ, Werkman SH, et al. First year growth of preterm infants fed standard compared to marine oil n-3 supplemented formula. Lipids 1992; 27(11):901-907.
77. Faldella G, Govoni M, Alessandroni R, et al. Visual evoked potentials and dietary long chain polyunsaturated fatty acids in preterm infants. Arch Dis Child Fetal Neonatal Ed 1996; 75(2):F108-F112.
78. Lapillonne A, Picaud JC, Chirouze V, et al. Supplementation of preterm formulas (PTF) with a low EPA fish oil: Effect on polyunsaturated fatty acids(PUfatty acidsS) status and growth. J Pediatr Gastroenterol Nutr 1997; 24(4).
79. Woltil HA, van Beusekom CM, Okken-Beukens M, et al. Development of low-birthweight infants at 19 months of age correlates with early intake and status of long-chain polyunsaturated fatty acids. Prostaglandins Leukot Essent Fatty Acids 1999; 61(4):235-241.
80. Martinez FE, Santos MMd, Sieber VM, et al. Growth and nitrogen balance in preterm infants fed formula with long chain polyunsaturated fatty acids. Nutr Res 1999; 19(10):1497-1505.
81. Ghebremeskel K, Burns L, Costeloe K, et al. Plasma vitamin A and E in preterm babies fed on breast milk or formula milk with or without long-chain polyunsaturated fatty acids. Int J Vitam Nutr Res 1999; 69(2):83-91.
82. Bougle D, Denise P, Vimard F, et al. Early neurological and neuropsychological development of the preterm infant and polyunsaturated fatty acids supply. Clin Neurophysiol 1999; 110(8):1363-1370.
83. Boue C, Combe N, Billeaud C, et al. Nutritional implications of trans fatty acids during perinatal period, in French pregnant women. Lipids, fats and oils: opportunities and responsibilities in the New Century 2001; 8(1):68-72.
84. Groh-Wargo S, Moore JJ, Catalano P, et al. Docosahexaenoic acid (DHA) and arachidonic acid (AA) supplementation does not change body composition in preterm (PT) infants. Pediatr Res 2002; 51(4):380A.
85. Carlson SE, Werkman SH, Tolley EA. Effect of long-chain n-3 fatty acid supplementation on visual acuity and growth of preterm infants with and without bronchopulmonary dysplasia. Am J Clin Nutr 1996; 63(5):687-697.
86. Ponder DL, Innis SM, Benson JD, et al. Docosahexaenoic acid status of term infants fed breast milk or infant formula containing soy oil or corn oil. Pediatr Res 1992; 32(6):683-688.
87. Makrides M, Neumann M, Simmer K, et al. Are long-chain polyunsaturated fatty acids essential nutrients in infancy?[comment]. Lancet 1995; 345(8963):1463-1468.
88. Innis SM, Akrabawi SS, Diersen-Schade DA, et al. Visual acuity and blood lipids in term infants fed human milk or formulae.[erratum appears in Lipids 1997 Apr;32(4):457]. Lipids 1997; 32(1):63-72.
89. Jorgensen MH, Holmer G, Lund P, et al. Effect of formula supplemented with docosahexaenoic acid and gamma- linolenic acid on fatty acid status and visual acuity in term infants. J Pediatr Gastroenterol Nutr 1998; 26(4):412-421.
90. Lapillonne A. Erythrocyte fatty acid composition in term infants fed human milk or a formula enriched with a low eicosapentanoic acid fish oil for 4 months. Eur J Pediatr 2000; 159(1-2):49-53.
91. Birch EE, Hoffman DR, Castaneda YS, et al. A randomized controlled trial of long-chain polyunsaturated fatty acid supplementation of formula in term infants after weaning at 6 wk of age. Am J Clin Nutr 2002; 75(3):570-580.
92. Willatts P, Forsyth JS, DiModugno MK, et al. Effect of long-chain polyunsaturated fatty acids in infant formula on problem solving at 10 months of age. Lancet British edition 1998; 352(9129):688-691.
93. Hoffman DR, Birch EE, Castaneda YS, et al. Visual function in breast-fed term infants weaned to formula with or without long-chain polyunsaturates at 4 to 6 months: a randomized clinical trial. J Pediatr 2003; 142(6):669-677.
94. Jensen CL, Prager TC, Fraley JK, et al. Effect of dietary linoleic/alpha-linolenic acid ratio on growth and visual function of term infants.[comment]. J Pediatr 1997; 131(2):200-209.

95. Makrides M, Neumann MA, Jeffrey B, et al. A randomized trial of different ratios of linoleic to alpha-linolenic acid in the diet of term infants: effects on visual function and growth.[comment]. Am J Clin Nutr 2000; 71(1):120-129.

96. Lapillonne A. Erythrocyte fatty acid composition in term infants fed human milk or a formula enriched with a low eicosapentanoic acid fish oil for 4 months. Eur J Pediatr 2000; 159(1-2):49-53.

97. Morris G, Moorcraft J, Mountjoy A, et al. A novel infant formula milk with added long-chain polyunsaturated fatty acids from single-cell sources: a study of growth, satisfaction and health. Eur J Clin Nutr 2000; 54(12):883-886.

98. Auestad N, Halter R, Hall RT, 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):372-381.

99. Guesnet P. Blood lipid concentrations of docosahexaenoic and arachidonic acids at birth determine their relative postnatal changes in term infants fed breast milk or formula.[comment]. Am J Clin Nutr 1999; 70(2):292-298.

100. Innis SM, Gilley J, Werker J. Are human milk long-chain polyunsaturated fatty acids related to visual and neural development in breast-fed term infants? J Pediatr 2001; 139(4):532-538.

101. Gibson RA, Neumann MA, Makrides M. Effect of increasing breast milk docosahexaenoic acid on plasma and erythrocyte phospholipid fatty acids and neural indices of exclusively breast fed infants. Eur J Clin Nutr 1997; 51(9):578-584.

102. Agostoni C, Marangoni F, Giovannini M, et al. Prolonged breast-feeding (six months or more) and milk fat content at six months are associated with higher developmental scores at one year of age within a breast-fed population. Adv Exp Med Biol 2001; 501:137-141.

103. Wezel-Meijler G, van der Knaap MS, Huisman J, et al. Dietary supplementation of long-chain polyunsaturated fatty acids in preterm infants: effects on cerebral maturation. Acta Paediatr 2002; 91(9):942-950.

104. Agostoni C, Trojan S, Bellu R, et al. Neurodevelopmental quotient of healthy term infants at 4 months and feeding practice: the role of long-chain polyunsaturated fatty acids. Pediatr Res 1995; 38(2):262-266.

105. Cheruku SR, Montgomery-Downs HE, Farkas SL, et al. Higher maternal plasma docosahexaenoic acid during pregnancy is associated with more mature neonatal sleep-state patterning. Am J Clin Nutr 2002; 76(3):608-613.

106. Krasevec JM, Jones PJ, Cabrera-Hernandez A, et al. Maternal and infant essential fatty acid status in Havana, Cuba. Am J Clin Nutr 2002; 76(4):834-844.

107. Jorgensen MH, Hernell O, Hughes EL, et al. Is there a relation between docosahexaenoic acid concentration in mothers' milk and visual development in term infants? J Pediatr Gastroenterol Nutr 2001; 32(3):293-296.

108. Williams C, Birch EE, Emmett PM, et al. Stereoacuity at age 3.5 y in children born full-term is associated with prenatal and postnatal dietary factors: a report from a population-based cohort study. Am J Clin Nutr 2001; 73(2):316-322.

109. Baker PN. Possible dietary measures in the prevention of pre-eclampsia and eclampsia. [Review] [73 refs]. Baillieres Clin Obstet Gynaecol 1995; 9(3):497-507.

110. Carlson SE, Ford AJ, Werkman SH, et al. Visual acuity and fatty acid status of term infants fed human milk and formulas with and without docosahexaenoate and arachidonate from egg yolk lecithin. Pediatr Res 1996; 39(5):882-888.

111. Birch E, Birch D, Hoffman D, et al. Breast-feeding and optimal visual development. J Pediatr Ophthalmol Strabismus 1993; 30(1):33-38.

112. Leaf A, Gosbell A, McKenzie L, et al. Long chain polyunsaturated fatty acids and visual function in preterm infants. Early Hum Dev 1996; 45(1-2):35-53.

113. Makrides M, Simmer K, Goggin M, et al. Erythrocyte docosahexaenoic acid correlates with the visual response of healthy, term infants. Pediatr Res 1993; 33(4 Pt 1):425-427.

114. Innis SM, Nelson CM, Rioux MF, et al. Development of visual acuity in relation to plasma and erythrocyte omega-6 and omega-3 fatty acids in healthy term gestation infants. Am J Clin Nutr 1994; 60(3):347-352.

115. Jorgensen MH, Hernell O, Lund P, et al. Visual acuity and erythrocyte docosahexaenoic acid status in breast-fed and formula-fed term infants during the first four months of life. Lipids 1996; 31(1):99-105.

116. Su HM, Huang MC, Saad NM, et al. Fetal baboons convert 18:3n-3 to 22:6n-3 in vivo. A stable isotope tracer study. J Lipid Res 2001; 42(4):581-586.

117. Lucas A, Stafford M, Morley R, et al. Efficacy and safety of long-chain polyunsaturated fatty acid supplementation of infant-formula milk: a randomised trial.[comment]. Lancet 1999; 354(9194):1948-1954.

118. Ghys A, Bakker E, Hornstra G, et al. Red blood cell and plasma phospholipid arachidonic and docosahexaenoic acid levels at birth and cognitive development at 4 years of age. Early Hum Dev 2002; 69(1-2):83-90.

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