Formula supplemented with docosahexaenoic acid (DHA) and arachidonic acid (ARA): a critical review of the research

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CRD summary
The review assessed whether infant formula supplemented with long chain polyunsaturated fatty acids (docosahexaenoic acid and arachidonic acid) has an effect on growth and development. The authors concluded that clinical trials have failed to show an improvement in the development of term infants. The authors did not report sufficient information about the included studies to support their conclusion.

Authors' objectives
To assess the effect of infant formula supplemented with docosahexaenoic acid (DHA) and arachidonic acid (ARA) on the growth and development of healthy term infants.

Searching
MEDLINE, CINAHL, Academic Search Elite, AltHealthWatch, Biomedical Reference Collection, Clinical Pharmacology, Health Source: Nursing/Academic Edition and the Cochrane Library were searched. The searches were limited to 'clinical trials/controlled trials' (1997 to 2003) and the English language. Search terms were reported. Additional studies were identified from the references in the included articles and by contacting the authors of each article selected.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. Observational follow-up studies that followed on from two of the included trials were also included in the review. The duration of the trials varied from 4 months to 2 years. The duration of the two follow-up studies was to 18 and 39 months of age.

Specific interventions included in the review
Studies of infant formula to which n-3 long-chain polyunsaturated fatty acids (DHA) had been added with or without n-6 long-chain polyunsaturated fatty acids (ARA) were eligible for inclusion. In some of the included studies both DHA and ARA (from sources such as fish oil, egg lipid, algal oil and fungal oil) were added in various proportions, while in others only DHA was added. The time at which the intervention was started varied from immediately up to 6 weeks, while its duration varied from 17 to 51 weeks. All the studies were described as having a control or standard formula group; some also had a breast fed reference group. The control intervention used for randomised comparison of effects in the included studies appeared to be non-supplemented formula.

Participants included in the review
Studies of healthy, term infants were eligible for inclusion. Studies of pre-term infants and low birth weight newborns were excluded. The infants in the included studies were newborns of at least 37 weeks' gestation. Some trials excluded infants with milk protein intolerance or a family history of such.

Outcomes assessed in the review
Inclusion criteria were not stated. The outcomes of interest appeared to be growth and cognitive, neurological and visual development. The outcomes reported in the included studies were anthropometrics, the amount of fatty acids in the blood, visual acuity, neurodevelopment (Bayley Scales of Infant Development II), information processing or intelligence quotient or cognitive development, language skills, temperament and morbidity.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.
Assessment of study quality
Two reviewers independently assessed the quality of the included studies using the Boyack and Lookinland Methodological Quality Index (MQI). The MQI has 25 items that assess reporting of the study design, outcomes, treatment effect and magnitude of differences in effect. Each study was assigned a percentage score, which was calculated from the number of criteria with which a study complied out of the total number of items that were applicable to that study. Inter-rater reliability was measured and any disagreements were resolved by consensus.

Data extraction
Two reviewers independently extracted the data using the MQI following pre-testing between reviewers. No details of the outcome data extracted from each study were reported.

Methods of synthesis
How were the studies combined?
There was a narrative summary of the results and a count of the number of studies that found the intervention to be beneficial and the number that found no significant effect (p<0.05).

How were differences between studies investigated?
Differences in study, patient and treatment characteristics and clinical outcomes were addressed in separate sections in the text. Study characteristics and strengths and weaknesses based on the MQI score were tabulated. The table separated studies showing no significant effect from those showing a beneficial effect.

Results of the review
The review included seven RCTs involving 1,323 participants. Two observational follow-up studies of 276 participants from two of the RCTs were also included as separate studies. The authors reported that 10 studies altogether were included because two reports of different outcomes from the same RCT were counted as two separate studies.

The MQI scores for the seven RCTs ranged from 48 to 83%. The strengths and weaknesses of each study varied.

Three RCTs and a follow-up study from one of them found a beneficial effect of supplementation on the development of cognitive, neurological and/or visual function. The other four RCTs and one follow-up study found no effect of DHA and ARA on infant development.

The review reported that standard and supplemented formulas seemed to be well tolerated but did not provide any supporting data from the included studies.

Cost information
The supplemented formula cost 15 to 30% more than the traditional formula in the USA.

Authors' conclusions
Clinical trials of formula supplementation with DHA and ARA have failed to show an improvement in mental and motor development in term infants. Visual acuity might be improved, but the effect of this in global development has not been determined.

CRD commentary
The review appeared to address a clear question although the outcomes were not defined in the inclusion criteria and the design of the included studies was poorly reported. An adequate number of sources were searched but relevant studies could have been missed by limiting the searches to the English language. The authors did not explain why they only sought studies published within a 6-year time period. They also did not report taking steps to minimise bias in the selection of studies for inclusion in the review. A systematic method was used to assess the quality of the included
studies, but the usefulness of composite scores is questionable in the absence of complete reporting.

It was unclear how the MQI was used for data extraction (as it was not designed for that purpose) and the results from each of the included studies were not shown. Counting the number of studies showing or not showing benefit to inform conclusions is potentially misleading, while counting multiple reports from the same study and follow-up phases as entirely separate studies exacerbates the problem. The interventions varied widely. There were insufficient details of the included studies to make an independent judgment on the reliability of the authors’ conclusions.

**Implications of the review for practice and research**

**Practice:** The authors stated that infant formula with endogenous DHA and ARA is not necessary for term infants.

**Research:** The authors stated that studies assessing the long-term effects of long-chain polyunsaturated fatty acid supplementation on neurodevelopment are underway.

**Bibliographic details**

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