Supplementation of infant formula with long-chain polyunsaturated fatty acids does not influence the growth of term infants

Makrides M, Gibson R A, Udell T, Ried K

CRD summary
This review found no evidence to suggest that supplementation of infant formula with long-chain polyunsaturated fatty acids affects the growth of term infants. Although the results provided support this, the limited literature search and poor reporting of review methodology make it difficult to verify this conclusion.

Authors' objectives
To assess the effect of supplementing infant formula with long-chain polyunsaturated fatty acids (LCPUFAs) on the growth of term infants.

Searching
MEDLINE was searched from 1960 to July 2004; the search terms are listed in the review. The bibliographies of retrieved papers and proceedings of relevant conferences were also searched. No mention of language restrictions was made.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
The intervention was cow's milk-based infant formula supplemented with LCPUFAs. The LCPUFAs in the included interventions were docosahexaenoic acid and arachidonic acid from various sources, such as fish oils, egg phospholipid fractions, egg triacylglycerol fractions, and algal and fungal oils. The control group were given equivalent unsupplemented infant formula. Trials in which interventions were initiated within 14 days of birth and were given for at least 12 weeks were eligible for inclusion. The interventions in the included trials lasted for 3 to 12 months.

Participants included in the review
Trials of infants born at term (not defined) were eligible for inclusion.

Outcomes assessed in the review
Studies that reported data on infant growth were eligible for inclusion. Authors were contacted to obtain data on weight, length and head circumference. The included trials varied in the ages at which growth assessments were made, but most infants were assessed at 4 months.

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
The authors did not state that they assessed validity, but details of randomisation, blinding and attrition were included in the results. The authors did not state how these were assessed.

Data extraction
Two authors independently abstracted the data. The authors did not state how any differences between the two abstractors were resolved. Growth data from the included trials were abstracted on an intention-to-treat basis.
Investigators were contacted to obtain relevant outcome data and gender-specific data. Weighted mean differences and their 95% confidence intervals were calculated for each growth outcome.

**Methods of synthesis**

How were the studies combined?
A meta-analysis was performed, using a fixed-effect model when there was no significant heterogeneity between studies and a random-effects model in the presence of significant heterogeneity. Each trial was weighted by the standard deviation and the number of infants in that trial. Publication bias was not formally assessed.

How were differences between studies investigated?
Statistical heterogeneity was assessed but the authors did not report the method used. Subgroup analyses were performed to investigate whether the effects of LCPUFA supplementation differed by gender, type of LCPUFA or source.

**Results of the review**

Fourteen trials (1,846 participants) were included in the review.

Quality of the trials: all of the trials were described as randomised but allocation concealment was not always clear. Eleven trials were double-blind and six reported under 20% attrition at 4 months' follow-up.

Growth at 4 months (11 trials, 1,050 infants): there were no differences in weight, length or head circumference between infants fed supplemented or control formulas.

Growth at 12 months (9 trials, 922 infants): there were no differences in weight, length or head circumference between infants fed supplemented or control formulas.

Analyses of trials that compared n-3 LCPUFA supplemented formula with control formula found no difference in any of the growth outcomes at 4 or 12 months. Further subgroup analyses found no difference in growth between the two groups according to gender or LCPUFA source.

**Authors' conclusions**

LCPUFA supplementation of infant formula does not affect the growth of term infants.

**CRD commentary**

The research question in this review was clear. The inclusion criteria were stated, although no definition of 'term infants' was given. The search was limited to MEDLINE, conference proceedings and bibliographies of retrieved articles. This might have led to the omission of relevant trials, particularly as no attempt was made to locate unpublished trials, possibly leading to bias in the results. However, the reviewers tried to obtain unpublished data from published trials by contacting authors. Since there was no description of how papers were selected for the review, it is possible that there was bias in this process. Some information on quality of the included trials was presented, but the criteria and methods used for the validity assessment were not reported. This makes it difficult to comment on the reliability of the trials and, hence, the meta-analysis derived from them. The data synthesis was not described in sufficient detail. The test used to assess heterogeneity was not stated. The authors stated that they believed the clinical homogeneity of the studies was sufficient to justify meta-analysis.

The authors' conclusions are based on the presented evidence, but the possible sources of bias noted above mean that the conclusions may not be reliable.

The review was funded by industry, charitable organisations and government sources.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

**Funding**
Wyeth Nutrition; Financial Markets for Children, Australia; New Zealand Milk.

**Bibliographic details**

**PubMedID**
15883434

**Original Paper URL**
http://www.ajcn.org/cgi/content/full/81/5/1094

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Fatty Acids, Unsaturated /pharmacology; Food, Fortified; Growth /drug effects; Humans; Infant; Infant Formula /pharmacology; Infant, Newborn; Randomized Controlled Trials as Topic

**AccessionNumber**
12005003709

**Date bibliographic record published**
31/07/2006

**Date abstract record published**
31/07/2006

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.