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The effect of alpha-linolenic acid and linoleic acid on the growth and development of formula-fed infants: a systematic review and meta-analysis of randomized controlled trials

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Review published: 2005.

CRD summary

This review assessed alpha-linolenic acid (ALA) and linoleic acid-enriched formula for term and pre-term infants. The authors concluded that ALA supplementation may improve docosahexaenoic acid (DHA), but further research is required to assess its effects on growth and development. The limited number of infants analysed and the insufficient reporting of review methodology make the robustness of the DHA results uncertain.

Authors' objectives

To assess the effects of alpha-linolenic (ALA) and linoleic acid (LA)-enriched formula on the growth and development of term and pre-term infants.

Searching

The authors searched MEDLINE, the Cochrane Controlled Trials Register, abstracts and conference proceedings. Sources were searched to May 2004 and the keywords were reported.

Study selection

Study designs of evaluations included in the review

Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review

Studies in which the ALA (18-carbon polyunsaturated fatty acid; ALA, 18:3n-3) and/or LA (18:2n-6) level of the formula was varied and other nutrients were kept at constant levels were eligible for inclusion. Studies of long-chain PUFA-containing test diets were excluded. Studies of term infants had to start the test formula within 14 days of birth and use it for at least 8 weeks; studies of pre-term infants had to be fed the test formula for at least 3 weeks. The included studies of term infants used formula enriched with ALA (3.2 to 4.8 wt%) or both ALA (5 wt%) and LA (34 wt%). All studies of pre-term infants used ALA supplementation (2.0 to 3.2 wt%).

Participants included in the review

Studies of formula-fed term and pre-term infants were eligible for inclusion.

Outcomes assessed in the review

Studies that assessed growth or development were eligible for inclusion. The primary review outcomes were weight, length, head circumference and neurological development. The most commonly assessed developmental outcomes in the included studies were visual function and global neurodevelopment. Visual function was assessed using Teller acuity cards, and visual evoked potential acuity and latency. Global neurodevelopment was assessed using Bayley Scales of Infant Development and other listed measures. The primary outcomes were assessed in term infants at 4 and 12 months, and in pre-term infants at 37 to 42 weeks and 57 weeks postmenstrual age (PMA). The review also assessed plasma and erythrocyte phospholipid docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA, 20:5n-3) and arachidonic acid (AA, 20:4n-6) levels.

How were decisions on the relevance of primary studies made?

The authors did not state how the studies were selected for the review, or how many reviewers performed the selection.

Assessment of study quality

Studies were assessed for adequacy of allocation concealment, blinding of the parents and study staff, attrition and sample size. The authors did not state who performed the validity assessment.

Data extraction

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Authors were contacted for further information about missing and unclear data, and for unpublished data about growth, development and mean fatty acid. For studies with more than two test diets, the reviewers extracted data for the diet with an LA-to-ALA balance closest to that of current commercially available formulas (about 10 to 1).

Methods of synthesis

How were the studies combined?

Where possible, the pooled weighted mean differences (WMDs) between treatments were calculated along with 95% confidence intervals (CIs). A fixed-effect model was used where there was no statistically significant heterogeneity. Studies were weighted by the standard deviation and the sample size. Otherwise, the studies were combined in a narrative.

How were differences between studies investigated?

The studies were grouped by characteristic of the infant (term or pre-term) and by type of supplementation (ALA or ALA plus LA). Statistical heterogeneity was investigated but the results were not reported.

Results of the review

Five RCTs of term infants (at least 292 randomised, 2 RCTs did not report the number randomised; n=301 analysed) and 3 RCTs of pre-term infants (157 randomised; 116 analysed) were included.

Study quality.

For term infants, 2 RCTs reported adequate allocation concealment, 2 RCTs reported blinding of the parents and study staff, and 2 RCTs reported less than 20% attrition at 3 and 4 months of age. All trials had relatively small sample sizes.

For pre-term infants, 1 RCT reported adequate allocation concealment, 2 RCTs were double-blind, 1 RCT reported less than 20% attrition at a 37-week PMA, and 2 RCTs reported greater than 20% attrition at a 57-week PMA.

Term infants (5 RCTs).

ALA supplementation (3 RCTs): ALA-supplemented formula was associated with significantly increased weight (WMD 0.62 kg, 95% CI: 0.09, 1.15; P=0.02, based on 81 infants) and length (WMD 1.78 cm, 95% CI: 0.58, 2.97, P=0.004; based on 81 infants) at 12 months, but not at 2 and 4 months. In 1 RCT, infants in the intervention group were significantly heavier at baseline than those in the control group.

Infants given ALA-supplemented formulas had higher plasma and erythrocyte phospholipid DHA than infants given control formulas (the results were reported for DHA, EPA and AA at 2, 4 and 8 months). There were no significant differences between treatments in terms of development, but data were only available for a few infants (across outcomes, n ranged from 23 to 57 infants).

ALA plus LA (2 RCTs): individual studies found no significant differences between supplementation and control for growth at 4 months, visual acuity at 3 months or long-chain PUFA status.

Pre-term infants (3 RCTs).

There was no significant difference in the growth of pre-term infants between ALA supplementation and control up to a 57-week PMA.

One RCT found a significant increase in retinal function (electroretinogram rod log k and rod log threshold) of pre-term infants given ALA supplementation at a 36-week PMA compared with control, but found no difference at a 57-week PMA.

Pre-term infants given ALA supplemented formulas had higher plasma and erythrocyte phospholipid EPA and DHA at term and at a 57-week PMA than infants given control formula.

The results of all the above analyses were reported.

Authors' conclusions

The findings of the review suggested that ALA-supplemented formulas improved DHA in infants, but that further research is required to assess the effects of ALA supplementation on the growth and development of infants.

CRD commentary

The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. The literature search was not described in full: the conference proceedings searched were not listed. Attempts were made to locate unpublished data, thus reducing the potential for publication bias. However, it was not stated whether any language restrictions were applied, so the potential for language bias could not be assessed. Validity was assessed using established criteria and the results of the assessment were reported. The numbers analysed varied across outcomes and some studies had attrition rates of over 20%, but there was no discussion of the influence of these drop-outs on the results. Meta-analyses were performed without

an assessment of statistical heterogeneity, hence the appropriateness of pooling the studies cannot be judged. The limited number of infants analysed, the small number of studies identified, and the lack of reporting of review methodology make the robustness of the DHA results uncertain. The evidence, as presented, appears to support the need for further research.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that there is a need for adequately powered, longer-term studies to assess the effects of supplementation on growth and development.

Bibliographic details

Udell T, Gibson R A, Makrides M, PUFA Study Group. The effect of alpha-linolenic acid and linoleic acid on the growth and development of formula-fed infants: a systematic review and meta-analysis of randomized controlled trials. *Lipids* 2005; 40(1): 1-11. [PubMed: 15825825]

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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.

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CRD has determined that this article meets the [DARE scientific quality criteria](#) for a systematic review.

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