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Original Article

The Effect of Supplementation of Long-Chain Polyunsaturated Fatty Acids During Lactation on Neurodevelopmental Outcomes of Preterm Infant From Infancy to School Age: A Systematic Review and Meta-analysis

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ABSTRACT

BACKGROUND AND OBJECTIVE: Long-chain polyunsaturated fatty acids, especially docosahexaenoic acid, have been suggested as a nutrition factor affecting visual and neurobehavioral development of preterm infants. Several randomized controlled trials (RCTs) have investigated the effect of supplementation of long-chain polyunsaturated fatty acids on preterm infants. We conducted a systematic review and meta-analysis to examine the efficacy of long-chain polyunsaturated fatty acid supplementation of formula or breast milk on the neurodevelopment outcomes of preterm infants. **METHODS:** Two authors searched PubMed and Cochrane Library (CENTRAL) for RCTs assessing efficacy of long-chain polyunsaturated fatty acids supplementation on the neurobehavioral and development outcomes of preterm infant. Human RCTs which supplemented long-chain polyunsaturated fatty acids during lactation and assessed neurodevelopment were included. The quality of each RCT was assessed, and the results of eligible trials were included in the systematic review and meta-analysis. **RESULTS:** We included 11 RCTs with 2272 total participants. Methodologic limitations existed to some extent in most RCTs that were included. Because the age of the participants from different trails was not the same, different scales and indexes had been assessed from different RCTs. Our meta-analysis indicated a significant effect of long-chain polyunsaturated fatty acids supplementation on the neurodevelopment of preterm infants assessed by the Mental Development Index of the Bayley Scales at one to three years of age versus the control groups. **CONCLUSION:** Analysis of our consolidated data indicates that long-chain fatty acid supplementation results in a significant improvement in the neurodevelopment of preterm infants as assessed by the Mental Development Index at one to three years of age. The available evidence suggests that long-chain polyunsaturated fatty acid supplementation during lactation may accelerate the pace of neurodevelopment in preterm infants, although their final developmental outcome may be unchanged.

Keywords: preterm, neurodevelopmental outcome, long chain polyunsaturated fatty acids, RCTs, meta-analysis

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Introduction

Long-chain polyunsaturated fatty acids have been assessed as an essential nutrient for infants and adults,[1,2] and long-chain polyunsaturated fatty acid consumption has been assumed to play a role in determining differences in cognitive development between babies fed with breast milk and those consuming an infant formula. Long-chain polyunsaturated fatty acids are crucial for the integrity of cell membranes of different body tissues, especially retina and cerebral cortex. Docosahexaenoic acid (DHA) and arachidonic acid (AA) are two of the most important long-chain polyunsaturated fatty acids; they play a vital part in

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Conflict of Interest: All authors declare that they have no conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

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development during pregnancy and the lactation period. Guided by short-term beneficial development effects, there have been recommendation to use formulas with a proportion of DHA between 0.2% and 0.5% of total quality of fatty acids and amount of AA being at least as much as DHA.[3] According to Clandinin et al., postmortem studies demonstrate that, during the last trimester of pregnancy, the fetus should accumulate a total of approximately 70 mg/day, mostly as DHA. And during this time, the brain of the fetus also underwent a rapid growth spurt and respectively from an estimated 125 g to 375 g,[4,5] which suggests that preterm birth is a risk factor of DHA deficiency.

According to a review by McCann and Ames,[6] animals fed a severely restricted N-3 long-chain polyunsaturated fatty acid diet exhibited lower concentrations of DHA in the brain and worse cognitive and behavioral performance. Pregnant rhesus monkeys and their pups which received higher N-3 fatty acids exhibit better visual acuity scores at 4 to 12 weeks compared with mother and infant monkey pairs which received lower N-3 fatty acids.[7] However, related clinical studies have reported different outcomes. Several studies of preterm infants found no significant difference between long-chain polyunsaturated fatty acids intervention groups and the control groups,[7-14] whereas others suggested that there might be an association between long-chain polyunsaturated fatty acid intervention and neurological or anthropometric progress of preterm infant.[15,16]

Systematic reviews and meta-analysis have been reported.[17-19] However, not all trials were included in the earlier meta-analyses and new randomized controlled trials (RCTs) have been published since 2011.[8,10,20,21] A comprehensive and reliable systematic review and meta-analysis of RCTs according to the Cochrane Handbook is needed. This article assesses the efficacy of supplementation with breast milk or preterm formula which contained long-chain polyunsaturated fatty acid during lactation, compared with a control formula on neurodevelopment of the offspring. The question addressed was whether there is a global effect of long-chain polyunsaturated fatty acid supplementation on neurodevelopment or an indiscoverable effect confined to subgroups of preterm infants or toddlers or even preschool- or school-age children.

Materials and Methods

Search strategy

Two reviewers (Q.W. and C.Y.) used the search terms: (1) docosahexenoic acid[Mesh] OR omega 3 OR long chain polyunsaturated fatty acid OR LCPUFA OR DHA OR fish oil AND “Infant, Extremely Premature”[Mesh] OR “Premature Birth”[Mesh] OR “Infant, Premature”[Mesh] OR random* OR “Randomized Controlled Trial”[Publication Type] OR (“Randomized Controlled Trial” [Publication Type] OR “Controlled Clinical Trial” [Publication Type]) in PubMed and (2) docosahexenoic acid [Mesh] OR omega 3 OR long chain polyunsaturated fatty acid OR LCPUFA OR DHA OR fish oil AND preterm OR premature AND Randomized Controlled Trials as Topic[Mesh] in Cochrane Library. The time limitation of the search in PubMed was 1965 to 2015. References from relevant articles and related systematic reviews were also searched for additional studies. Authors of some articles were contacted for missing information when necessary. There was no limitation on the basis of language of publication.

Selection of studies

Studies were eligible for inclusion in this review if they were RCTs that assessed the effect of oral long-chain polyunsaturated fatty acid supplementation during lactation on neurodevelopment of preterm infants. Trials were considered if supplementation began within 1 month after birth. Only studies with neurodevelopment (e.g., Mental Development Index [MDI] or Psychomotor Development Index [PDI]) outcomes were chosen. Two authors (Q.W. and C.Y.) independently assessed the titles, abstract, and the full text of the article for study eligibility, which was decided by a third author (Q.C.) if different opinion existed.

Date extraction and synthesis

Data from all included studies were extracted by two reviewers (Q.W. and C.Y.) independently and separately. Some details or unpublished outcome was requested by e-mail to the authors. All reviewers independently assessed the quality of each trail according to Modified Jadad Scale ($\geq$5 indicated high quality).

Extracted data included author and reference, publication year, participant number, gestational age and birth weigh, start and duration of supplementation, and outcome measures of neurobehavioral, Modified Jadad Score ($\geq$5 indicated high quality). Neurodevelopment outcomes were analyzed separately by infants (less than one year old), toddlers (1 to 3 years old), preschool-age (3 to 5 years old) and school-age (5 to 12 years old) children. Within each age group, different assessments of neurodevelopment were included as subgroups because differences existed in scoring and procedures.

Outcome measurement

Neurodevelopmental outcome was the primary end point. However, RCTs included in this systematic review and meta-analysis contain participants from different ages and the neurodevelopment function outcomes through three months to ten years of age, so different scales or measurement had been used from different ages.

1) The MDI and PDI of the Bayley Scales of Infant Development were the primary outcomes during lactation from seven RCTs[11,13-16,22,23]; one RCT reported only MDI.[9] Motor, language, and cognitive abilities were considered as a secondary outcome for further evaluation.
2) Two of the RCTs[23,24] included considered the MacArthur Communicative Development Inventories, a standardized parent-report instrument included Vocabulary Comprehension Scores and Vocabulary Production Scores as the primary outcome of language and vocabulary development. However, one of these two RCTs reported the outcome at 26 months of age,[24] and the other reported the outcome in 9 and 14 month olds.[23] Considering this variability, we did not consider combining the outcomes from different periods reasonable.
3) The Wechsler Abbreviated Scale of Intelligence (WASI) had been assessed by two RCTs included[8,10] which detected neurobehavioral development of preterm infants during preschool or school ages. The WASI consists of four subtests: vocabulary, similarities, block design, and matrix reasoning, providing a brief and reliable estimate of child’s intellectual functioning. The primary outcome was general intellectual ability assessed by the Full Scale intelligence quotient (IQ); Verbal IQ and Performance IQ were considered as the secondary outcome.

In addition, the Strengths and Difficulties Questionnaire and the Short Temperament Scale for Children scale indicated abnormal behavior and temperament between three and five years corrected age had been reported in one RCT.[24]