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The influence of supplemental docosahexaenoic and arachidonic acids during pregnancy and lactation on neurodevelopment at eighteen months

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ABSTRACT

Docosahexaenoic acid (DHA) and arachidonic acid (AA) are important for neurodevelopment. The effects of DHA (220 mg/day, $n=41$), DHA+AA (220 mg/day, $n=39$) or placebo ($n=34$) during pregnancy and lactation on neurodevelopment at 18 months, and the relations between umbilical cord DHA, AA and Mead acid and neurodevelopment were studied. An age-specific, standardized neurological assessment for the evaluation of minor neurological dysfunction (MND), and the Bayley Scales of Infant Development (BSID) were used. The intervention did not influence any of the outcomes. Umbilical venous (UV) Mead acid was negatively and n-6 fatty acids were weakly positively associated to the BSID mental developmental index. Children with simple MND had lower UV DHA compared to normally classified children. We conclude that relatively short-term maternal DHA or DHA+AA supplementation does not influence neurodevelopment at toddler age, although some parameters of brain development are related to perinatal DHA and AA status.

1. Introduction

The long chain polyunsaturated fatty acids (LCPUFA) docosahexaenoic acid (DHA, 22:6n-3) and arachidonic acid (ARA, 20:4n-6) are considered important for brain development. DHA, ARA and eicosapentaenoic acid (EPA, 20:5n-3) are structural components of membrane phospholipids, modulators of gene expression and precursors of eicosanoids (ARA, EPA), resolvins (ARA, EPA, DHA) and (neuro)protectins (DHA) [1,2]. EPA and DHA are mainly derived from fish, while meat, poultry and eggs are the principal sources of ARA. Brain DHA and ARA contents increase rapidly from the last trimester of pregnancy up to 2 years postpartum [3]. There are many studies on the influence of DHA or fish oil supplementation on early brain development, but their outcomes are inconclusive in a meta analysis [4]. Since the beneficial effects of DHA in maternal supplementation studies do not seem dose-dependent, and effects are mainly found in older infants and toddlers and not in early infancy [5,6], it is conceivable that potentially positive effects of DHA on neurodevelopmental outcome first become expressed after early infancy.

In a previous study, postnatal supplemental LCPUFA did not affect neurological outcome at 18 months [7]. In the same study we showed that lower DHA and ARA in umbilical vessels were associated with a less favorable neurological condition as assessed with the Hempel technique, although no relations were demonstrable with the Bayley Scales of Infant Development [10]. The Hempel assessment [8,9] is an age-specific and standardized neurological assessment designed for the evaluation of minor neurological dysfunction (MND). Next to classic signs of neurological function, such as muscle tone and reflexes, ample attention is paid to the quality of motor behavior. The outcome is either a clinical classification in terms of MND or major neurological dysfunction, or a neurological optimality score (NOS). The NOS at 18 months proved sensitive for detecting subtle differences in prenatal environmental or nutritional changes, such as exposure to polychlorinated biphenyls (PCBs) [9], LCPUFA [10] and feeding with formula or breast milk [9,11].

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The lower umbilical vessel DHA and ARA of children with a less optimal neurological condition at ages 3 [12] and 18 [10] months support the idea that adequate prenatal LCPUFA status is important for neurological development. We therefore explored the effects of supplemental DHA and DHA+ARA during pregnancy and lactation on the children's neurological development at the age of 3 and 18 months. At the age of 3 months, we assessed neurological development by recording general movement (GM) quality. We found that 60% of the children exhibited mildly abnormal GMs in the DHA supplementation group. The neurological condition of infants in the DHA+ARA groups was similar (DHA+ARA 34%; placebo 31% mildly abnormal GMs) [13]. Taken together, these results suggested a typical but less optimal neurological condition in early infancy [14] following maternal supplementation with DHA-only. In the current study we report the neurological outcome of this trial at 18 months, assessed using the Hempel technique and Bayley Scales of Infant Development. In addition, we studied whether prenatal LCPUFA status was related to brain development.

2. Subjects and methods

2.1. Subjects

This study was part of a double-blind placebo-controlled randomized trial in which we explored the influence of DHA with or without ARA during pregnancy and lactation on infant neurological condition [13,15], maternal mood [15] and cognition as well as milk fatty acid composition [16]. The study design has been reported in detail elsewhere [16]. In short, apparently healthy women were enrolled between the fourteenth and twentieth weeks of pregnancy, with the majority (80%) being enrolled between 15.6 and 17.4 weeks postmenstrual age (mean 16.5 weeks). A vegan diet was an exclusion criterion and (gestational) diabetes mellitus and preterm birth, i.e. birth before 37 weeks of pregnancy, were termination criteria. At enrollment, women were randomized into 3 groups using block randomization. The initial research protocol and the follow-up were approved by the Central Committee on Research Involving Human Subjects (CCMO, Den Haag, The Netherlands; protocol number P03.1071C). All women gave written informed consent. The trial is registered under ISRCTN58176213.

Power analysis for this trial was based on the NOS [17] at the age of 2 weeks [13], which revealed that 64 children per group were needed to obtain sufficient power to detect a 2 point (=0.5SD) difference between the groups. Next to the NOS at 2 weeks, we analyzed GM quality. Due to the higher rate of mildly abnormal GMs at the age of 3 months in the DHA group, inclusion was discontinued early. From the 183 women included in the study, 58 dropped out during pregnancy due to lack of motivation to fill in questionnaires on a regular basis and take supplements daily (placebo, $n=23$; DHA, $n=20$; DHA+ARA, $n=15$). Six mother–infant pairs dropped out due to obstetric complications (placebo, $n=3$; DHA, $n=1$; DHA+ARA, $n=2$). Attrition was evenly distributed among the groups ($p=0.33$). At the age of 18 months, 5 additional children were lost to follow-up. One of the infants moved and was not examined due to logistical reasons (DHA group), and 4 of the infants were not examined due to parental lack of interest (placebo, $n=2$; DHA+ARA, $n=2$). For this current report, 114 children were evaluated. Due to the early discontinuation of inclusion, the trial might lack sufficient power to detect between-group differences in any of the parameters. However, at the time the study was designed, no data were available on the effects of maternal DHA and ARA supplementation on the used neurological outcomes at the age of 18 months and power analysis was based on the NOS at 2 weeks.

2.2. Dietary intervention

All women received a supplement of vitamins and minerals according to the Dutch recommended dietary allowances. The mixture of vitamins and minerals derived from FrieslandCampina and was produced under the same conditions as those used for infant formula. The women were instructed to take 2 capsules once daily from enrollment until 3 months after delivery. The DHA+ARA group received 220 mg DHA (Marinol D40, Lipid Nutrition B.V., Wormerveer, The Netherlands, a DHA-enriched purified fish oil) and 220 mg ARA (Wuhan Alking Bioengeneering Co. Ltd., Wuhan, China). The DHA group received 220 mg DHA and 1 capsule containing soy bean oil (Wuhan Alking Bioengeneering Co. Ltd., Wuhan, China). The placebo group received 2 capsules containing soy bean oil. The daily fatty acid intakes from the capsules for each of the 3 treatment groups are shown in Table 1. The daily dosages of DHA and ARA are within the range of typical Western intakes, i.e. adding the supplements to the diet doubled the intake of DHA and ARA. The dosages of linoleic acid and alpha-linolenic acid from the capsules are only a fraction of the daily Western intakes [18].

2.3. Developmental evaluation

Eighteen months after birth, neurodevelopmental status was assessed using 2 instruments, i.e. the neurological examination according to Hempel [8,9] and the Dutch version of the Bayley Scales of Infant Development, second edition (BSID-II-NL) [19]. The Hempel examination includes the observation of spontaneous motor behavior (grasping, sitting, crawling, standing and walking) and classical neurological tests, such as the assessment of muscle tone and reflexes. In this way, fine-motor function, gross-motor function, posture and muscle tone, reflexes and visuomotor function are evaluated. Multiple signs in one of these functions result in a dysfunctional domain (previously labeled 'cluster'; [20]), of which the isolated domain of dysfunctional reflexes has no neurological implications. The neurological examination resulted in 3 types of outcome. First, the neurological classification; children are classified as normal, as having simple MND, as having complex MND or as definitely abnormal. Definitely abnormal implies the presence of a neurological syndrome like cerebral palsy. Simple MND indicates the presence of 1 dysfunctional domain and is regarded as a typical but non-optimal form of brain function. Complex MND indicates the presence of at least 2 domains of dysfunction and is considered the clinically more relevant form of MND, as it is associated with pre- and perinatal adversities and learning and behavioral problems [20]. We also used the optimality concept to summarize neurological condition. Of 58 items of the neurological examination the optimal range

Table 1
Daily intakes of fatty acids (in mg) from the supplements.

	Placebo group	DHA group	DHA+ARA group
LA	535	274	46
ALA	60	32	7
ARA	0	15	220
EPA	0	34	36
DHA	0	220	220

LA, linoleic acid, 18:2n-6; ALA, alpha-linolenic acid, 18:3n-3; ARA, arachidonic acid, 20:4n-6; EPA, eicosapentaenoic acid, 20:5n-3; DHA, docosahexaenoic acid, 22:6n-3.