Docosahexaenoic Acid and Neurodevelopment

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There is a lot of interest in and buzz around improving brain potential (neurodevelopment) of our children. Various types of nutrition supplements are therefore advised/consumed to boost neurodevelopment, often without proper scientific evidence. India is one of the highest ranking countries in the world for the number of children suffering from malnutrition. The first 1000 days (conception to 2 years) are very critical for the growth and development of a child. Maternal nutrition during this time impacts the development of brain structure and function. Thus poor maternal diets (lacking in important nutrients) can result in delayed brain development and diseases in the offspring. Higher intake of a specific fat type known as long-chain omega-3 fatty acids (especially DHA) has been linked to better motor and mental development. The main dietary source of DHA is fatty fish and marine oils. Indian diets are largely DHA-deficient and the population levels of plasma DHA among Indians are reported to be very low. There are no harmful effects of consuming DHA during pregnancy or lactation. Thus we carried out a high quality rigorous randomized controlled trial (#DHANI trial*) supplementing 957 pregnant Indian women with either DHA or placebo capsules to examine how DHA impacts the brain development of the offspring. These capsules were given from <20 weeks of gestation to 6 months postpartum. The infants born to these supplemented mothers were tested using a standardized non-invasive tool called the Developmental Assessment Scale for Indian infants (DASII). This provides a developmental quotient (DQ) score taking the mental and motor development into consideration. Our published study* provides evidence that the maternal supplementation through pregnancy and lactation with DHA did not benefit their infant's neurodevelopment at one year of age. Deeper insights into maternal dietary patterns, young child feeding practices, home environment, and the interactions amongst these factors are warranted to understand what shapes early neurodevelopment. Ongoing follow-up is needed, particularly given the ubiquity of DHA-supplemented health drinks, formulas and foods for children for touted cognitive enhancements in Indian markets.

Keywords: supplementation ; docosahexaenoic acid ; neurodevelopment ; pregnancy ; lactation ; India

1. Introduction

The first 1000 days are crucial for a child's neurodevelopment [1]. The brain develops rapidly through neurogenesis, axonal and dendritic growth, synaptogenesis, synaptic pruning, myelination, and gliogenesis [2]. These events build on each other, such that even small perturbations can have long-term effects on the brain's structural and functional capacity [3]. Maternal nutrition during this time influences both pre- and postnatal growth, and development of the offspring [4][5][6].

It has been suggested that n-3 long-chain polyunsaturated fatty acids (LCPUFA) (especially docosahexaenoic acid [DHA]) levels enhance infant neurodevelopment [7][8][9][10][11]. The DHA is an important structural component of the human brain and retina. DHA accumulates in all of the brain regions and retinal photoreceptors [12]. These long-chain fatty acids regulate the fluidity of cell membranes as well as the activity of ion channels, enabling synaptic transmission and providing substrate binding to membrane receptors. The deposition of DHA in human brain phospholipids occurs primarily during the last trimester of pregnancy such as week 30 until the early postnatal periods continuing during the first two years of life [13][14][15]. Human fetuses and young infants have limited ability to synthesize n-3 LCPUFA de novo and are supplied via maternal (placental transfer, breast milk) or external (formula, dietary) sources [16][17]. Approximately 67 mg of DHA is accrued by the fetus per day [18]. Deprivation of n-3 LCPUFA, whether prenatally or after birth, has deleterious effects on learning abilities, memory, and visual grating acuity in monkeys, rats, and human infants [19][20].

DHA can be obtained from marine algae, fatty fish, and marine oils. Endogenous synthesis of DHA is limited, especially in the presence of excess n-6 LCPUFA. The Food and Agriculture Organization and World Health Organization (FAO/WHO) Expert Committee recommends a diet with a 5–10:1 ratio of n-6/n-3 LCPUFA and 300 mg/day of preformed DHA during pregnancy [21][22]. Since cereal-based diets are rich in n-6 LCPUFA but largely deficient in DHA-rich sources, population levels of plasma DHA are low in India. Studies report [23][24] that mean DHA intake was lowest (11 mg) among Indian pregnant women in the third trimester [25] compared to pregnant women from other developing countries like Bangladesh, Burkina Faso, Chile, China, India, and Mexico.

Studies conducted around the world to assess the association between intakes of DHA during pregnancy or lactation and neurodevelopmental outcomes in childhood have been inconsistent [[7][26][27][28][29][30][31][32][33][34][35]. Few studies have assessed the effect of both prenatal and postnatal intake of DHA [36][37]. There is a paucity of data on the potential benefits of maternal DHA supplementation in infants, especially in the Indian population. The present study examines the hypothesis whether 400 mg/d maternal DHA supplementation from ≤20 weeks through 6 months postpartum influences infant neurodevelopment at 12 months of age. The present study DHANI (Maternal **DHA** supplementation and offspring Neurodevelopment in India) is the first to examine the effects of maternal DHA supplementation from mid-pregnancy through six months postpartum on postnatal neurodevelopment in India.

2. Discussion

In this well designed and executed RCT, pre- and postnatal maternal supplementation with 400 mg/d DHA did not improve the infant's development score as measured by DASII at 12 months of age. Our findings are in accordance with some other trials [38][39][40][41]. The reviews published so far in this field to understand the association between maternal DHA supplementation and infant neurodevelopment have also reported the evidence of a positive association between maternal DHA supplementation and infant neurodevelopment to be either too low or inconsistent, with a majority of the RCTs showing no positive effect [36]. Makrides et al. provided 800 mg/d and [42] showed no difference in children's cognitive scores between the intervention and control group at 18 months. Similarly, Helland et al. [41] found no effect of prenatal supplementation with cod liver oil on cognitive development among 288 three-month-old children in Norway. On the other hand, the randomized trial of Colombo et al. [43] found that lower doses of DHA supplementation of the infants (4 to 9 months of age) showed better cognitive outcomes in terms of their attention span. Studies have reported maternal DHA status in pregnancy to be positively associated with infant's brain volume at 1 month [44], improved infant's attention [45], and enhanced problem-solving skills at 12 months [46]. Rees et al. [26] showed that the infants of mothers who had a higher dietary DHA intake during the second and third trimesters of their pregnancy performed better on cognitive assessment measures (habituation and sustained visual attention) at 4.5 and 9 months of age. However, it was also observed that the infants from the medium dietary DHA group [0.64% of fatty acids from DHA (34 mg/100 kcal)] performed significantly better than the low-DHA [0.32% (17 mg/100 kcal)] and high-DHA group [0.96% (51 mg/100 kcal)], with the latter showing the worst performance [26][43]. Additionally, some studies have reported improved cognition among older children whose mothers were supplemented with 400–600 mg/d DHA prenatally, after they turned four years old [27][30][35].

The neurodevelopment in the current study was assessed with the help of the DASII test which is BSID's adaptation. Although BSID is a global standardized test for assessing cognitive functioning and has been frequently utilized in neurodevelopment effects of LCPUFA in infants [47], its sensitivity to pick up some subtle differences in infant cognitive ability has been questioned [48]. Experts suggest that differences in intellectual functioning that are sensitive to pathways influenced by n-3 fatty acids may only be detected with more sensitive measures of neurodevelopment such as neuroimaging techniques [49], neuropsychological testing [50], distinct cognitive abilities, or executive functioning [51]. The suitability of these approaches for large field-based trials in low resource settings warrants further exploration.

Few possible limitations of our single-center trial may include lack of details on home environment and detailed dietary data on the children which may have influenced the neurodevelopment in the first year of life. The measure of neurodevelopment used in the study (i.e., the DQ score) has not been validated against the functional magnetic resonance imaging (fMRI) which is currently considered the gold standard noninvasive hemodynamic-based neuroimaging technology. The fatty acid composition of the blood and breast milk collected from the enrolled women are not currently available. We also did not estimate dietary n-3 LCPUFA intakes in all the study subjects; however, the biomarker (RBC phospholipid DHA) is very responsive to intake and was measured at both enrollment and immediately after birth as an indicator of prior status and study DHA intake. Further, other fatty acids like AA and DHA:AA ratios may play a key role in neurodevelopment [52]. To the best of our knowledge, our study is the first one to examine the effects of in utero and early-life DHA exposure (through maternal supplementation from mid-pregnancy through six months postpartum) on postnatal neurodevelopment of Indian infants. Through a long supplementation phase and follow-up period, the participants of our trial reported good compliance and very low attrition. Genetic predisposition, prenatal and postnatal care and nutrition, and social and physical environment may all be critical in shaping the neurodevelopment of an infant. We collected maternal dietary data at baseline but not at later visits. Changes throughout the pregnancy with respect to not only n-3 LCPUFA but also other nutrients such as vitamin D or iron [53][54]] may affect offspring neurodevelopment.

While DHA is a key intrinsic factor constituting more than 40% of brain polyunsaturated fatty acids [55][56], external factors like care and stimulation in the home environment also play a significant role in a child's cognitive development [57][58]. Poor physical conditions of home and limited access to age-appropriate learning materials have been linked with social–

emotional problems in children. Ramakrishnan et al. [38] indicated a possible attenuating effect of DHA on the positive association between home environment and psychomotor development. DHA may be especially helpful for children living in home environments characterized by reduced caregiver interactions and opportunities for early childhood stimulation [59]. It might have been useful to have these data in the present study. Further, the mean DQ score of girl children in the placebo group was higher. This inconsistency may be due to chance. Some studies also attribute gender-related differences in neurodevelopment to sex hormones [60] and/or social context [61], but since these were not assessed in our trial, we cannot be certain of this.

In summary, supplementing mothers through pregnancy and lactation with 400 mg/d DHA (vs. placebo) did not benefit offspring neurodevelopment at one year of age in this Indian setting. Deeper insights into maternal dietary patterns, young child feeding practices, home environment, and the interactions amongst these factors are warranted to understand what shapes early neurodevelopment.

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