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DHA supplementation during the perinatal period and neurodevelopment: do some babies benefit more than others?

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Abstract

A dietary supply of docosahexaenoic acid (DHA, 22:6n-3) during the perinatal period is postulated to be important for the neurodevelopmental outcome of children. This paper reviews the results of two large scale intervention trials in which equivalent dietary doses of DHA were assessed. One trial assessed the ex utero effect of DHA supplementation for preterm infants born <33 weeks' gestation while the other trial assessed the in utero effect of DHA supplementation during the second half of pregnancy. Ex utero DHA supplementation, which aimed to achieve the level of DHA accumulation that would occur in the womb, appeared more effective in improving the neurodevelopmental outcome of preterm children rather than in utero DHA supplementation of unborn infants. Significant treatment by sex and treatment by birth weight interactions were noted indicating that boys and girls respond differently to DHA supplementation and that birth weight may also be important in predicating the DHA responsiveness.

Introduction

The n-3 long chain polyunsaturated fatty acid (LCPUFA), docosahexaenoic acid (DHA, 22:6n-3) is rapidly accumulated by the fetus during the last trimester of pregnancy. Post mortem studies indicate that the fetus will accumulate a total of approximately 70mg/day, mostly as DHA, during the last trimester of pregnancy [^{1,2}]. During this time the brain also undergoes a major growth spurt and approximately doubles in size from an estimated 125g to 375g [³]. Although the growth and composition of the brain continue to develop well into the postnatal period, the last trimester of pregnancy is the window in which the brain is growing at the greatest velocity and its composition is quickly changing [⁴]. This coupled with the rapid somatic growth and the creation of nutrient body stores that also occur in the last trimester highlight the potential importance of ensuring an adequate supply of DHA [⁵]. Two scenarios, which represent different extremes, are instructive in the requirement for DHA during the perinatal period and its effect on neurodevelopment during early childhood. The first scenario relates to very preterm infants who are denied the opportunity to accumulate DHA during most of the last trimester. Instead they are born early, with immature organs and no fat reserves. It therefore logically follows that preterm infants, particularly those born at the earliest gestations would be the infants with the greatest DHA requirements and have the most to gain from supplementation. In contrast, the second scenario relates to singleton infants who are born at term, having had the benefit of a full in utero supply of DHA. The logical assumption here is that these infants will have a lower requirement of DHA than their counterparts who are born prematurely and any benefit of DHA supplementation during the equivalent period (whilst they are in utero) will be more modest than what might be expected in preterm infants. We had an opportunity to assess the validity of these hypotheses by comparing the neurodevelopmental outcomes of young children who participated in two trials of DHA supplementation. The first trial (DHA for the Improvement of Neurodevelopmental Outcome in preterm infants, DINO) evaluated the neurodevelopmental outcomes at 18 months corrected age of preterm infants born before 33 weeks' gestation who were fed a standard dose of DHA (about 0.3% of total fatty acids) during the

neonatal period compared with a dose of DHA (about 1% of total fatty acids) designed to mimic the accumulation of DHA that would have occurred in the womb [6]; while the second trial (DHA to Optimise Mother Infant Outcome, DOMInO) evaluated neurodevelopment of largely term born children at 18 months of age who were either exposed to extra DHA through maternal supplementation during the second half of pregnancy or received the natural delivery of DHA across the placenta [7]. In essence the high DHA treatment group of the DINO trial was attempting to mimic that control group of the DOMInO trial.

Methods of the DINO and DOMInO trials

The DINO trial was designed to be inclusive of as many infants as possible born <33 weeks' gestation and included infants fed breast milk and infant formula. Infants were only excluded if they had major congenital or chromosomal abnormalities; they were from a multiple birth where not all live infants were eligible; in other trials of fatty acid supplementation; or had a mother expressing breast milk with a contraindication to taking tuna oil (bleeding disorders, anticoagulants). Lactating women were randomly allocated to take six 500 mg DHA-rich tuna oil capsules per day or six 500 mg placebo soy oil capsules. If formula was required, infants were given a preterm formula with a matching DHA composition. The dietary intervention resulted in infants randomly allocated to higher-DHA receiving a DHA concentration triple that of infants allocated to standard-DHA, AA remaining constant between the two groups [6]. The DHA concentration in the diet of neonates in the higher-DHA group was approximately 0.9% of total fatty acids while the standard DHA group received milk with about 0.3% DHA as total fatty acids. Parents, clinicians and all research personnel were blinded to participant study group. 97% (614 of 632) of all live children at 18 months corrected age were assessed using the Bayley Scales of Infant Development, Second Edition (BSID-II). The Mental Development Index (MDI) which evaluates memory, habituation, problem solving, early number concepts and language was the primary outcome.

The DOMInO trial included women with singleton pregnancies with no known fetal abnormalities at study entry (18-21 weeks gestation). Women were randomly allocated to take 3 x 0.5g capsules per day containing either high-DHA fish oil or a blend of three vegetable oils from mid-pregnancy until birth. In total 2399 women and their children from 5 perinatal centres around Australia were recruited to allow for two primary outcomes; postnatal depression in the women and cognitive development during early childhood [7]. The Bayley Scales of Infant and Toddler Development, Third edition (Bayley-III) was used to assess neurodevelopment at 18 months of age. The Cognitive and Language Composite Scales were considered primary outcomes for the neurodevelopmental assessment. The cognitive scale evaluates abilities such as sensorimotor development, exploration and manipulation, object relatedness, concept formation, memory, and simple problem solving, while the language scale is a composite of receptive communication (verbal comprehension, vocabulary) and expressive communication (babbling, gesturing, and utterances). Infants who were enrolled in Adelaide were randomly selected for the Bayley-III assessment. 96% (694 of 726) of children selected for neurodevelopmental assessment completed the tasks.

Results of the DINO and DOMInO trials

Success of intervention

The success of the DHA interventions in the DINO and DOMInO trials were evident from the DHA concentrations in the plasma phospholipid fatty acids of the neonatal blood at 40 weeks post-menstrual age (when the preterm infants were due to be born) and the cord blood at birth, respectively. As would be expected the DHA status of the preterm infants fed milk (breast milk of infant formula) with a standard concentration of DHA (about 0.3% total fatty acids) was low compared with DHA supplementation (about 0.9% total fatty acids, see figure 1a). Although this level of DHA supplementation in the DINO trial was designed to match the degree of in utero accumulation of DHA, the concentration of DHA in plasma phospholipids at 40 weeks post menstrual age was not quite comparable with the plasma phospholipid DHA concentration in cord blood from

term births suggesting that the target of DHA supplementation in the DINO trial was not quite achieved. However, the direct comparison of phospholipid fatty acids from neonatal peripheral blood at 40 weeks post menstrual age with cord blood at term may have limitations as the haemodynamic characteristics are likely to be quite different. For example, cord blood contains a significant proportion of fetal red cells while peripheral blood 10-12 weeks post birth, even from preterm infants who were born 28-30 weeks' gestation, will contain predominantly mature red cells. Nevertheless, these comparisons provide a useful guideline regarding the success of supplementation. Interestingly, supplementation of pregnant women with 800mg DHA per day for the second half of gestation in the DOMInO trial demonstrated about a 20% increase in the mean DHA concentration in cord plasma phospholipid fatty acids (see figure 1b). Collectively, these data provide a basis for understanding the requirement of DHA during the vulnerable perinatal period with regards to neurodevelopmental outcomes.

Neurodevelopmental outcome in early childhood

Although different version of the Bayley's Scales were used to assess neurodevelopmental outcomes in the DINO and DOMInO trials, the developmental quotient (DQ) scores are nevertheless instructive as the assessments in both versions are based on similar tasks and the scoring has been standardised to a mean of 100 with a standard deviation of 15 (range from 50 to 150). In this regard it is interesting to note that the mean DQ score on the mental/cognitive scale for preterm children in DINO was approximately 94 while the mean DQ for the term children in DOMInO was approximately 102. This difference in DQ between preterm children and their counterparts born at term is well established in the literature, particularly when considering the most vulnerable preterm children born <33 weeks' as included in DINO [8]. Supplementation with higher dose DHA in the DINO trial resulted in a non-significant increase in mean DQ compared with the standard dose of DHA, while DHA supplementation during pregnancy in the DOMInO trial resulted in no change in the mean cognitive DQ (Figure 2 a-b). However, in both cases these non-significant differences in the mean

DQs were associated with significant reductions in the proportion of young children with delayed cognitive development with DHA supplementation regardless of whether supplementation occurred during the neonatal period for preterm infants or while in utero for those infants born largely at term (Figure 3 a-d). The reduction in the percentage of young children with delayed cognitive development at 18 months was most notable in preterm children because of the relatively high proportion of children with delayed development and the halving of the number of children with severely delayed development (DQ <70, 2SD below the standardised population mean) in the higher-DHA group (Figure 3c, RR 0.50, 95% CI 0.26 to 0.93; P=0.03). It was interesting to note that there was no effect of DHA supplementation on the high performing side of the distribution and that there was no increase in the proportion of children with advanced development in either the DINO or the DOMInO trials. Additionally, the cognitive scores of the children in the DOMInO trial (regardless of supplementation) were close to or better than what would be expected for a normal population. Collectively these data suggest that any effect of DHA supplementation during the perinatal period on early childhood neurodevelopment may be confined to children on the lower performing end of the normal distribution and that DHA supplementation during the perinatal period will not result in children with advanced cognitive scores. This also raises the possibility that there may be specific subgroups that may benefit from supplementation while others do not respond, perhaps because of their adequate DHA status.

Differential response to DHA supplementation: sex

One of the most controversial and topical issues to recently emerge is whether boys and girls have different DHA requirements and therefore respond different to DHA supplementation. Previous studies have consistently documented the slower and poorer neurodevelopmental scores of boys compared with girls in early childhood, particularly in preterm children [^{9,10}]. This together with the metabolic suggestion that females may more efficiently synthesise DHA from precursor fatty acids than males led to the hypothesis that boys may benefit from DHA supplementation more than girls.

Both the DINO and DOMInO trials were specifically designed and powdered to address whether there were differential effects of DHA supplementation on cognitive development scores according to infant sex. In DOMInO there was no interaction between dietary treatment and sex indicating no differential response between boys and girls of DHA supplementation during pregnancy [7]. Conversely in the DINO trial a significant interaction between higher-DHA treatment and sex was noted indicating that girls and boys responded differently to DHA treatment. Higher-DHA significantly improved the mean mental/cognitive development of girls (RR 4.5; 95% CI 0.5 to 8.5; P=0.03) and reduced mild (DQ score<85) and severe (DQ score<70) cognitive delay (RR 0.43, 95% CI 0.23 to 0.80; P=0.01 and RR 0.17, 95% CI 0.04 to 0.72; P=0.02 respectively), while no effect of higher-DHA was noted in boys [6].

Differential response to DHA supplementation: birth weight

The vast majority of term infants are born with birth weights >2500g having had the benefit of a normal in utero supply of DHA across the placenta, while for preterm infants their birth weights can vary from <1000g to about 2000g largely depending on their gestational age at birth. As already noted, the neurodevelopmental outcomes of normal weight term children are significantly better than their counterparts who are born preterm with lower DHA status. What has not been well studied is whether there is a specific dietary requirement for DHA for term children who are growth restricted in utero and generally do not achieve birth weights >2500g.

For preterm infants in the DINO trial, we had pre-planned analyses to assess whether there was a differential effect of higher dietary DHA in the birth weight randomisation strata (<1250g and ≥1250g). We did indeed observe an interaction effect which demonstrated that infants born weighing <1250g and fed the higher DHA diet had a 4-point improvement in mental development scores compared with control, while the mental development scores of infants born weighing ≥1250g did not differ between groups [6]. Similarly the risk of mild mental delay (DQ <85) was decreased in infants born weighing <1250g (RR 0.57, 95% CI 0.36 to 0.91; P=0.02), while there was

no difference between the groups in infants born weighing $\geq 1250\text{g}$ [6]. Collectively these data indicate that infants born weighing $< 1250\text{g}$ may have the highest DHA requirements and therefore showing responsiveness to tests assessing neurodevelopmental outcomes.

Although this paper highlights that infant sex and infant birth weight may be two characteristics of an individual that may modulate the response to DHA supplementation, further work is needed to substantiate these findings and to also explore and understand how other biological and socio-demographic variables affect the DHA requirement during the perinatal period.

Summary and Conclusions

The two studies reviewed here were focussed on assessing the effect of in utero and ex utero DHA supplementation during roughly the same time period, that of the last trimester of pregnancy. Ex utero DHA supplementation targeted at achieving the level of DHA accumulation that would occur in the womb appeared more effective in improving the neurodevelopmental outcome of preterm children rather than in utero DHA supplementation of unborn infants. This is perhaps not surprising when one considers that infants who are born healthy and at term have had the full benefit of an uninterrupted DHA supply across the placenta together with other necessary nutrients.

Furthermore this nutritional supply is subject to a number of physiological adaptations that are all aimed at maintaining nutrient delivery to the fetus often at the expense of the maternal requirement. Nevertheless our data have also highlighted that there are children who are responsive to DHA supplementation regardless of whether it was delivered in utero or ex utero and further work is needed to better define the sub-groups of children who will benefit from supplementation.

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