PUBLISHED VERSION

OCL
Oilseeds & fats Crops and Lipids

RESEARCH ARTICLE – DOSSIER   OPEN ACCESS

DOSSIER

LIPIDS AND BRAIN
LIPIDES ET CERVEAU

Understanding the effects of docosahexaenoic acid (DHA) supplementation during pregnancy on multiple outcomes from the DOMInO trial
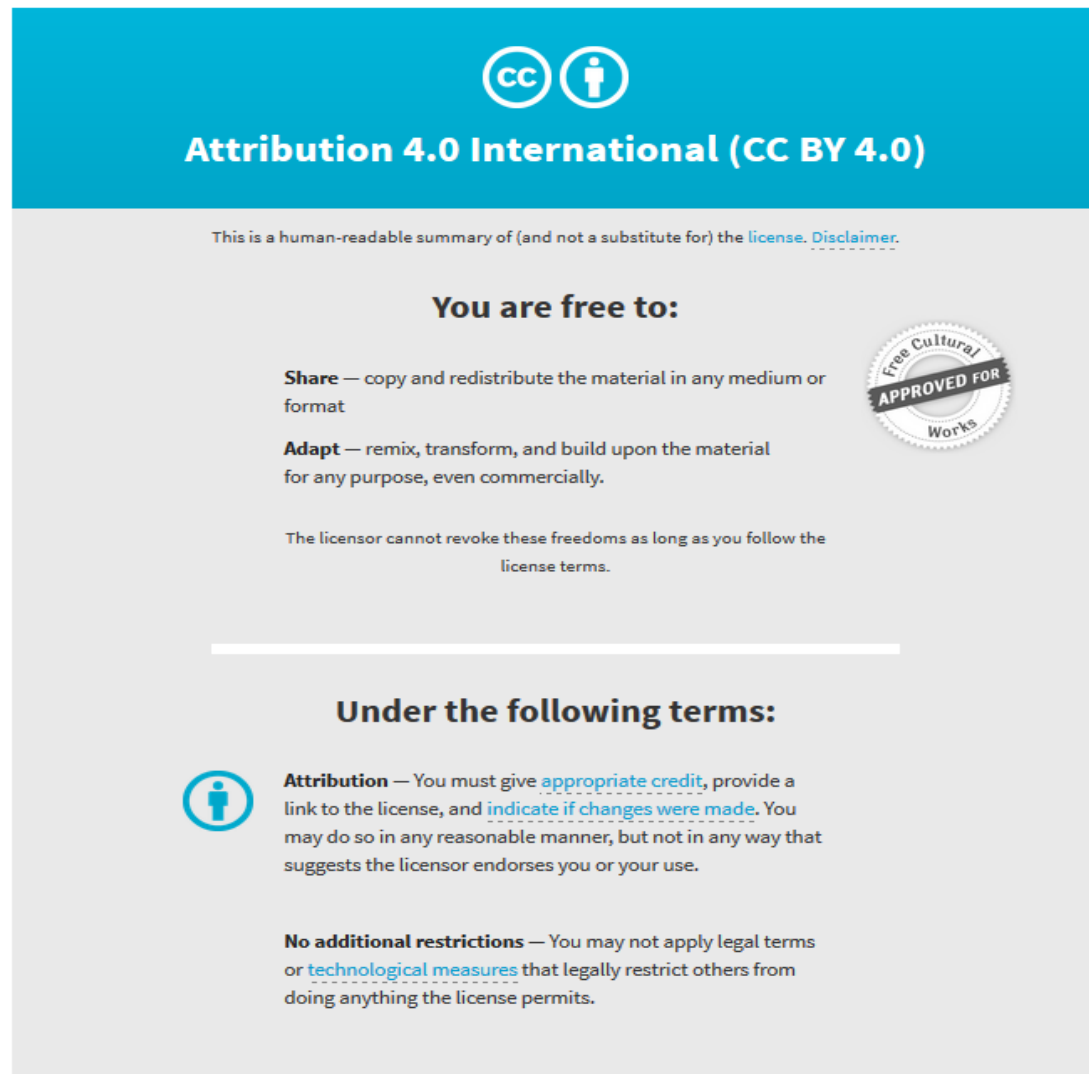
Maria Makrides[1,2,3,*]

[1] Child Nutrition Research Centre, Women's and Children's Hospital, Flinders Medical Centre and Women's and Children's Health Research Institute, 72 King William Road, North Adelaide SA 5006, Adelaide, Australia
[2] Discipline of Pediatrics, University of Adelaide, Australia
[3] South Australian Health and Medical Research Institute, Adelaide, Australia

Abstract – Docosahexaenoic acid (DHA) has been postulated to extend the period of gestation, increase birth weight, enhance neurodevelopment and reduce the risk of allergic disease. Because of its large sample size and relatively broad inclusion criteria, the DOMInO (DHA to Optimise Mother Infant Outcome) trial offers the opportunity to explore the effect of prenatal DHA supplementation of multiple outcomes. Overall, the DOMInO trial showed that prenatal DHA supplementation increases the length of gestation, reduces the risk of early preterm and low birth weight, has little or no effect on maternal postpartum depression and early childhood neurodevelopment but reduces the risk of atopic eczema and sensitisation in the first year of life. The clinical utility of prenatal DHA supplementation of reducing early birth is important and requires further investigation.

Keywords: DHA / pregnancy / child development / child allergies

Résumé – Comprendre les effets de la supplémentation en acide docosahexaénoïque (DHA) pendant la grossesse sur de multiples paramètres à partir de l'étude DOMIn0. Il a été envisagé que l'acide docosahexaénoïque (DHA) puisse prolonger la période de gestation, augmenter le poids de naissance, renforcer le développement neurologique et réduire le risque de maladie allergique. En raison de la grande taille de son échantillon et de critères d'inclusion relativement larges, l'étude DOMInO (DHA to Optimise Mother Infant Outcome) offre l'occasion d'explorer l'effet d'une supplémentation prénatale en DHA sur de multiples paramètres. Dans l'ensemble, l'étude DOMInO a montré que la supplémentation prénatale en DHA augmente la durée de la gestation, réduit le risque de prématurité précoce et de faible poids de naissance, a peu ou pas d'effet sur la dépression maternelle post-partum et sur le développement neurologique durant la petite enfance, mais réduit le risque d'eczéma atopique et de sensibilisation dans la première année de la vie. L'utilité clinique d'une supplémentation prénatale en DHA afin de réduire les naissances avant terme est importante et nécessite une enquête plus approfondie.

Mots clés : DHA / grossesse / développement de l'enfant / allergies de l'enfant

1 Introduction

The n-3 long chain polyunsaturated fatty acid (LCPUFA), docosahexaenoic acid (DHA), has multiple biochemical and physiological roles in many organ systems. This is perhaps not surprising as DHA is an integral part of all cell membranes. It also naturally follows that DHA has a number of postulated clinical effects, especially in the perinatal period which is a period characterized by anabolic change and organ growth. Some of the postulated effects of DHA in the perinatal period are to extend gestational length, enhance early childhood neuro-development and to ameliorate or prevent the development of allergic disease. While various clinical studies have evaluated the effect of DHA supplementation during pregnancy, it has been difficult to elucidate the extent of benefit for general populations as different studies have been specifically designed to assess particular outcomes. For example, many studies designed to assess the effect of DHA supplementation during pregnancy on childhood neurodevelopmental outcomes have excluded children born prematurely and do not contain data relating to the duration of pregnancy. Because of its large sample size and relatively broad inclusion criteria, the DOMInO (DHA to Optimise Mother Infant Outcome) trial offers the

* Correspondence: maria.makrides@sa.gov.au

opportunity to explore the effect of prenatal DHA supplementation of multiple outcomes. The purpose of this paper is to bring together the core outcomes of the DOMInO trial reported to date and consider the current evidence as well as the research gaps for further investigation.

2 The DOMInO trial

The DOMInO trial is a multi-center, double-blind randomized controlled trial that was originally designed to test the effect of DHA supplementation during the last half of pregnancy on reducing the symptoms of post-partum depression and enhancing early childhood development (DOMInO Trial: ACTRN12605000569606). The DOMInO trial is the largest DHA supplementation study in pregnancy reported to date, and the methods have been previously published (Makrides *et al.*, 2010). To summarize, women at 5 study sites around Australia, with singleton pregnancies less than 21 weeks gestation were invited to participate (between October 2005–January 2008). Women were excluded if they were already taking a supplement containing DHA, their fetus had a known major abnormality, they had a bleeding disorder in which fish oil was contraindicated, were taking anticoagulant therapy, had a documented history of drug or alcohol abuse, were participating in another fatty acid trial, were unable to give written or informed consent or if English was not the main language spoken at home. Enrolled women were assigned a unique study number corresponding to allocation of a treatment pack through a computer driven telephone randomization service according to an independently generated randomization schedule, stratified by center and parity. Women allocated to the DHA group were asked to consume three 500 mg capsules per day of DHA-rich fish oil providing ~800 mg/d DHA and 100 mg/d of eicosapentaenoic acid (EPA) (Incromega 500 TG, Croda Chemicals, East Yorkshire, England) and women in the control group were asked to consume three 500 mg vegetable oil (rapeseed, sunflower and palm oil) capsules (without DHA) per day, from study entry until birth. All capsules were identical in size, shape and color and donated by Efamol, Surrey, England. A total of 2399 women were randomized into the DOMInO trial. Of these, 1197 were randomly assigned to treatment with DHA and 1202 to control treatment. Outcome measures for the DOMInO trial included major pregnancy and birth outcomes, maternal symptoms of post-partum depression, as well as neurodevelopment and allergic disease in early childhood for specific subgroups of children.

3 Outcome assessments

Pregnancy outcome data were collected *via* a blinded review of women's and infant's medical records including duration of gestation, the frequency of preterm birth < 37 weeks' gestation and early preterm birth < 34 weeks gestation, gestational diabetes mellitus (GDM), preeclampsia and pregnancy induced hypertension (Makrides *et al.*, 2010; Zhou *et al.*, 2012). Other outcomes included small for gestational age for weight, length, and head circumference was defined as below the 10th percentile for birth weight, length, and head circumference, and large for gestational age for weight, length, and

head circumference was defined as below the 90th percentile for birth weight, length, and head circumference for the corresponding gestational age and sex. Perinatal death was defined as stillbirth or death within the first 28 days of life.

Postpartum Depression was assessed using the self-reported Edinburgh Postnatal Depression Scale (EPDS) questionnaire in English at six weeks and six months Postpartum (Cox *et al.*, 1987). Validation studies indicate high sensitivity (68–95%) and high specificity (78–96%) of the EPDS against a clinical psychiatric diagnosis of PPD (Cox *et al.*, 1987; Boyce *et al.*, 1993; Murray and Carothers, 1990). A score of more than 12 on the EPDS is widely used to indicate a probable depressive disorder (Hiscock and Wake, 2001; Murray, 1992).

Neurodevelopment at 18 months and 4 years: a subset of infants, consisting of 630 randomly selected term infants and 96 preterm infants, from two centres in Adelaide were selected for neurodevelopmental assessments at 18 months and 4 years of age. Assessments were performed by study psychologists who were blinded to treatment group allocation and previous results. Infants were assessed with the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) at 18 months (Bayley, 2006). Child neurodevelopment at 4 years was assessed using the General Conceptual Ability (GCA) score of the Differential Ability Scales Second Edition (DAS II) (Elliot, 2007). The Bayley-III and DAS II have age-standardized scores with a mean of 100 and SD of 15 (range 50–150). Standardized scores more than one SD below the mean (< 85) were considered delayed. For children born preterm, their corrected age was used to standardize test scores.

Allergy assessments at 1 and 3 years of age: infants whose mothers were enrolled at either of two centres in Adelaide and who had a first-degree relative with medically diagnosed allergic disease (asthma, allergic rhinitis, eczema) were eligible for the allergy follow-up. Medically diagnosed atopic (or IgE associated) disease at 1 and 3 years, defined as a positive skin prick test together with clinical symptoms of allergy (eczema, asthma, allergic rhinitis or food allergy) was assessed by blinded study doctors (Palmer *et al.*, 2013). A total of $n = 706$ women enrolled, with $n = 368$ women in the intervention group and $n = 338$ women in the control group. At 1 year of age, the food allergens tested were whole hens' egg, cows' milk, wheat, tuna and peanut, and the aeroallergens tested were ryegrass pollen, olive tree pollen, *Alternaria tenuis*, cat hair and house dust mite (*Dermatophagoides pteronyssinus*). At 3 years of age, the same allergens were tested with the addition of two foods (cashew nut and sesame seed) and one aeroallergen (house dust mite, *Dermatophagoides farinae*).

4 Outcome data from the DOMInO trial

Pregnancy outcomes: there were fewer very preterm births (< 34 weeks' gestation) in the DHA group compared with the control group (1.09% *vs.* 2.25%; adjusted RR, 0.49; 95% CI, 0.25–0.94; $P = 0.03$) and this was associated with fewer infants requiring admission to neonatal intensive care in the DHA group (1.75% *vs.* 3.08%, RR 0.57; 95% CI 0.34–0.97; $P = 0.04$) (Makrides *et al.*, 2010). However, DHA supplementation resulted in more postterm births requiring obstetric intervention (inductions or cesarean deliveries) compared

with the control group (17.59% *vs.* 13.72%; adjusted RR, 1.28; 95% CI, 1.06–1.54; *P* = 0.01) (Makrides *et al.*, 2010). This overall shift in the length of gestation resulted in a higher mean birth weight (68 g, 95% CI, 23–114 g; *P* = 0.003) and fewer infants of low birth weight (3.41% *vs.* 5.27%; adjusted RR, 0.65; 95% CI, 0.44–0.96; *P* = 0.03) in the DHA group compared with the control group. Mean birth weight *z* scores (corrected for gestational age and sex) did not differ between groups, strongly indicating that group differences in birth size were largely a function of gestational age at birth (Makrides *et al.*, 2010). No statistically significant differences in the RR of small for gestational age or large for gestational age for weight, length, or head circumference were found between the groups. Five infants had brain injury at birth and 5 had neonatal convulsion in the control group compared with none in the DHA rich fish-oil group (*P* = 0.03). There were 12 perinatal deaths among infants of control mothers and 3 among infants of the fish-oil – supplemented mothers (*P* = 0.03). No differences were observed between the groups in other pregnancy or perinatal complications, including the incidence of GDM, PE, pregnancy induced hypertension, and neonatal hypoglycaemia, resuscitation at birth or other neonatal complications (Zhou *et al.*, 2012). The tantalising data suggesting that supplementation with 800 mg of DHA per day can reduce the risk of early preterm birth by about 50% is consistent with the Cochrane systematic review that was completed before the inclusion of the DOMInO trial and included trials that largely supplemented pregnant women with marine oil dominant in EPA rather than DHA. While n-3 LCPUFA supplementation during pregnancy appears to increase the length of gestation, the clinical utility of our findings and their incorporation into clinical practice guidelines requires further work.

Postpartum Depression: the percentage of women with depressive symptoms (EPDS score > 12) during the first 6 months postpartum did not differ between the DHA and control groups (9.67% *vs.* 11.19%; adjusted RR, 0.85; 95% CI, 0.70–1.02; *P* = 0.09) (Makrides *et al.*, 2010). Depressive symptoms were more common among women with a previous or current diagnosis of depression at trial entry, but did not differ between groups. The percentage of women with a new medical diagnosis for depression during the trial or a diagnosis requiring treatment also did not differ between groups (Makrides *et al.*, 2010). Overall, our data do not support DHA supplementation during pregnancy as a strategy to prevent post-partum depression.

Neurodevelopment of children at 18 months and 4 years: at 18 months of age, mean cognitive composite scores (adjusted mean difference, 0.01; 95% CI, −1.36 to 1.37; *P* = 0.99) and mean language composite scores (adjusted mean difference, −1.42; 95% CI, −3.07 to 0.22; *P* = 0.09) of children in the DHA group did not differ from children in the control group, although fewer children from the DHA group had cognitive scores indicating delayed cognitive development compared with controls (Makrides *et al.*, 2010). At 4 years of age, 703 were eligible for follow-up and 646 (91.9%; *n* = 313 in DHA group and *n* = 333 in control group) were included in the analysis. Mean GCA scores of children born to women in the DHA group did not differ from children from women in the control group (adjusted mean difference 0.29, 95% CI −1.35 to

1.93, *P* = 0.73) and there was no difference in the proportion of children with impaired (GCA < 85) or advanced (*GCA* > 115) performance between the groups (Makrides *et al.*, 2014). These data support the most recent systematic review assessing the effect of DHA interventions during pregnancy on the neurodevelopmental outcomes of children (Gould *et al.*, 2013) and indicates that in largely well-nourished populations DHA supplementation has negligible benefit on longer term developmental outcomes. This is perhaps not surprising as the vast majority of children would have experienced the full benefit of in utero DHA transfer until term birth.

Allergy: our data showed that there was no significant difference in the overall percentage of children with IgE mediated allergic disease in the first 3 years of life between the DHA and control groups (64/368 (17.3%) *vs.* 76/338 (22.6%); adjusted relative risk 0.78; 95% CI 0.58–1.06; *P* = 0.11) (Palmer *et al.*, 2013). At 1 year of age, the percentage of infants diagnosed as having atopic eczema was lower in the DHA group (26/368 (7%) *vs.* 39/338 (12%); unadjusted relative risk 0.61, 0.38 to 0.98, *P* = 0.04; adjusted relative risk 0.64, 0.40 to 1.02, *P* = 0.06) and fewer infants were sensitised to egg in the DHA group (34/368 (9%) *vs.* 52/338 (15%); unadjusted relative risk 0.61, 0.40 to 0.91, *P* = 0.02; adjusted relative risk 0.62, 0.41 to 0.93, *P* = 0.02) (Palmer *et al.*, 2012). However, these findings did not persist at 3 years of age. It may be that the effects were diluted as the children grow by other environmental factors or that any effect of n-3 LCPUFA, like DHA, in the prenatal period are smaller than originally anticipated. The non-significant risk reductions of up to 22% may still be of public health significance however, as the burden and cost of allergic disease on affected families are high, and fish oil intervention is safe and relatively cheap.

In conclusion, our DOMInO study with a relatively typical and large sample of pregnant women has demonstrated that DHA supplementation during the last half of pregnancy significantly increases the duration of gestation and that this results in a reduction in the number infants who are born very preterm and low birth weight. The importance of this finding is of potential global importance because of the high morbidity associated with early preterm birth. It is interesting to note that the direct longer term effects of prenatal supplementation were either not evident (such as the reduction in postpartum depression or enhanced neurodevelopment in the children) or relatively short term (such as the reduction in atopic eczema at 1 but not 3 years of age). It may be that the effect on these longer term outcomes is small and therefore not easily detectable and not clinically significant or that longer periods of supplementation may be needed.

References

Bayley N. 2006. Bayley Scales of infant and toddler development, 3rd ed. TX: Pearson Education, Inc.

Boyce P, Stubbs J, Todd A. 1993. The Edinburgh Postnatal Depression Scale: validation for an Australian sample. *Aust. N.Z. J. Psychiatry* 27: 472–476.

Cox JL, Holden JM, Sagovsky R. 1987. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale *Br. J. Psychiatry* 150: 782–786.

Elliott CD. 2007. Differential ability scales® second edition. PsychCorp, Pearson.

Gould JF, Smithers LG, Makrides M. 2013. The effect of maternal omega-3 LCPUFA supplemention during pregnancy on early childhood cognitive and visual development: a systematic review and meta-analysis of randoomized controlled trials. *Am. J. Clin. Nutr.* 97: 531–544.

Hiscock H, Wake M. 2001. Infant sleep problems and postnatal depression: A community-based study. *Pediatrics* 107: 1317–1322.

Makrides M, Gibson RA, McPhee AJ, Yelland L, Quinlivan J, Ryan P. 2010. Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: a randomized controlled trial. *J. Am. Med. Assoc.* 304: 1675–1683.

Makrides M, Gould JF, Gawlik NR, *et al.* 2014. Four-year follow-up of children born to women in a randomized trial of prenatal DHA supplementation. *J. Am. Med. Assoc.* 311: 1802–1804.

Murray L. 1992. The impact of postnatal depression on infant development. *J. Child. Psychol. Psyc.* 33: 543–561.

Murray L, Carothers AD. 1990. The validation of the Edinburgh Postnatal Depression Scale on a community sample. *Br. J. Psychiatry* 157: 288–290.

Palmer DJ, Sullivan T, Gold MS, *et al.* 2012. Effect of n-3 long chain polyunsaturated fatty acid supplementation in pregnancy on infants' allergies in first year of life: randomised controlled trial. *B.M.J.* 344: e184.

Palmer DJ, Sullivan T, Gold MS, *et al.* 2013. Randomized controlled trial of fish oil supplementation in pregnancy on childhood allergies. *Allergy* 68: 1370–1376.

Zhou SJ, Yelland L, McPhee AJ, Quinlivan J, Gibson RA, Makrides M. 2012. Fish-oil supplementation in pregnancy does not reduce the risk of gestational diabetes or preeclampsia. *Am. J. Clin. Nutr.* 95: 1378–1384.