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Omega 3 fatty acids, gestation and pregnancy outcomes

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Abstract

Pregnancy is associated with a reduction in maternal serum docosahexaenoic acid (DHA, 22:6 n-3) percentage and its possible depletion in the maternal store. Since the synthesis of long chain polyunsaturated fatty acids (LCPUFA) in the fetus and placenta is low, both the maternal LCPUFA status and placental function are critical for their supply to the fetus. Maternal supplementation with DHA up to 1 g/d or 2·7 g n-3 LCPUFA did not have any harmful effect. DHA supplementation in large studies slightly the enhanced length of gestation (by about 2 days), which may increase the birth weight by about 50 g at delivery. However no advice can be given on their general using to avoid preterm deliveries in low or high risk pregnancies. Several studies, but not all, reported improvements of the offspring in some neurodevelopmental tests as a result of DHA supplementation during gestation, or, at least, positive relationships between maternal or cord serum DHA percentages and cognitive skills in young children. The effect seems more evident in children with low DHA proportions, which raises the question of how to identify those mothers who might have a poor DHA status and who could benefit from such supplementation. Most studies on the effects of n-3 LCPUFA supplementation during pregnancy on maternal depression were judged to be of low-to-moderate quality, mainly due to small sample sizes and failure to adhere to Consolidated Standards of Reporting Trials guidelines. In contrast, the effects of n-3 LCPUFA supplementation on reducing allergic diseases in offspring are promising.

Key words: fatty acids: DHA: n-3 LC-PUFA: birth weight: length of gestation: neurodevelopment: systematic review

Numerous observational studies agree that fatty acid concentration in maternal plasma increases during pregnancy as a direct consequence of physiological gestational hyperlipidemia. Plasma triglyceride levels rise markedly during pregnancy whereas the increase in the other lipid fractions is more moderate[1,2]. Phospholipids (PL) are the richest source of polyunsaturated fatty acids (PUFA); during pregnancy, the increment observed for docosahexaenoic acid (DHA, 22:6 n-3) concentration was the highest for all PUFA in both maternal plasma PL[3,4] and erythrocytes[5]. The improved absolute maternal DHA status in plasma PL can not be explained simply by the modification of dietary habits, and the most accepted hypothesis is the enhanced mobilization of DHA from the maternal adipose tissue depots, although an increase in the activity of the enzymes involved in their synthesis in the mother can not be excluded[3]. The placenta also partly regulates the mobilization of fatty acids from adipose tissue through leptin secretion to the maternal and fetal circulation[6], although leptin resistance arises near the end of pregnancy.

Despite the increase in the absolute concentrations, the relative amounts of the fatty acids show a different pattern; several studies reported a continuous decline from the first trimester until delivery in the percentage of DHA in maternal plasma PL and erythrocytes[3,7], as well as in total plasma[7,8], respect to the total fatty acid content; in addition, a reduction in the overall functional essential fatty acid (EFA) status in maternal plasma PL, reflected by the ratio between essential n-3 plus n-6 and the non-essential n-7 plus n-9 unsaturated fatty[3,9], might reflect the mother's inability to mobilize adequate amounts of long-chain polyunsaturated fatty acids (LCPUFA) for optimal fetal development. These observations were consistent across populations selected from five different countries despite the variation in maternal EFA status between countries[9]. The high prenatal accumulation in the fetal brain of DHA during the third trimester of pregnancy[10,11], the selective and preferential maternal-fetal transfer of LCPUFA across the placenta[12–18] and the low desaturase activity in both placenta[19] and fetal liver[20] could explain this depletion of LCPUFA in the maternal compartment. In recent years, great attention has turned to considering whether low DHA intakes in pregnant women may achieve an optimal central nervous system development of the fetus[21].

Several studies pointed to an association between the percentage of maternal plasma DHA during gestation and the development of cognitive functions in the neonate. The previous DHA status of the mother, the bioavalilability and dose of LCPUFA used in the maternal supplements, and the

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functionality of the placenta could affect the fetal levels of LCPUFA and their effect on neurodevelopment. Maternal DHA supplementation during pregnancy significantly increased maternal DHA percentages at delivery[22–29], while cord blood DHA proportions increased in many of these studies[22,27] but not in all[8,30]. The association between maternal plasma DHA status, the dietary intake of DHA during gestation, and the development of cognitive functions in the neonate and thereafter in the child has been addressed in several human trials (Table 1). Here, we discuss such studies and the potential roles of LCPUFA supplementation during pregnancy under the perspective of preventive nutrition.

The primary aim of this systematic review was to evaluate the effects of maternal n-3 LCPUFA supplementation during pregnancy on birth outcome (gestational length, birth weight, birth length) as well as on the development of visual and other neural functions in the offspring. The secondary aim was concerned the effects of n-3 LCPUFA supplementation during pregnancy on biochemical markers related with the immunological status in the mother or neonate as well as its influence on symptoms of maternal depression.

Methods

This paper represents a descriptive transversal study of the results obtained from bibliographic research by means of a systematic review. The selection of the articles was done following the defined inclusion and exclusion criteria.

Inclusion criteria: The existence of any registry system of data related to omega-3 fatty acids and pregnancy. We limited the search to Randomized Controlled Trials and Humans. The participants should be healthy pregnant women receiving any n-3 LCPUFA supplementation during pregnancy or pregnancy + lactation. The studies must have come from original articles published by peer-review journals.

Exclusion criteria: Studies on n-3 LCPUFA supplementation that started after delivery in children or mothers. Articles available only in abstract form. Papers not written in English, Spanish, French or German language.

Descriptors used

The cut-off date for papers was 1st March 2011. The study of the hierarchical structure of the Thesaurus "Medical Subject Heading Terms" (MeSH) considered appropriate the following descriptors:

"Omega-3 fatty acids"[MeSH]

"Pregnancy"[MeSH]

The most important biomedical databases where consulted (e.g. MEDLINE, The Cochrane Library, LILACS and ISI Web of Sciences).

Search equations

"Omega-3 fatty acids and Pregnancy". Limits Activated: Humans, Randomized Controlled Trial.

Table 1. Randomized controlled trials of n-3 LCPUFA supplementation in healthy pregnancies on birth outcomes

Study	Participants	Daily Dose	Duration	Primary functional outcome
DOMINO study Makrides *et al.* 2010[34]	2399	0·8g DHA + 0·1g EPA	Week 22 to delivery	Longer gestation and increased birth weight
POSGRAD study Ramakrishan *et al.* 2010[35] Stein *et al.* 2010[78]	370	400mg DHA	Week 18 to delivery	In primigravid, higher birth weight and head circumferenceGreater length of chidren at 18 months
Bergman *et al.* 2007[79] Bergman *et al.* 2008[22]	144	200mg DHA FOS Vit/Min	Week 21 -3 months post-delivery	Gestational length, birth weight or length (n.s) Reduced BMI at 21 months
Innis and Friesen 2008[21]	135	400 mg DHA	Week 16 to delivery	Gestational length, birth weight or length (n.s.)
Danish Cohort Olsen *et al.* 1992[36]	533	1·1g DHA + 1·6g EPA olive oil	Week 30 to delivery	Longer gestation and increased birth weight
Knudsen *et al.* 2006[38]	3098	0·1, 0·3, 0·7, 1·4g, 2·8g DHA + EPA	week 17-27 to delivery	Gestational length (n.s)
Nuheal study	195	0·5g DHA 400ug MTHF MTHF + DHA	Week 22 to delivery	
Krauss-Etchsmann *et al.* 2007[27]				Gestational length and birth weight (n.s)
Krauss-Etchsmann *et al.* 2008[73]				Reduced Th2 inflammatory cytokines in cord
Smuts *et al.* 2003[39]	53	135 mg DHA 18 mg DHA	Weeks 24-28 to delivery	Longer gestation and increased birth weight
Helland *et al.* 2001[37]	341	1·18g DHA + 0·8g EPA	Week 18 to 3 months post-delivery	Gestational length and birth weight (n.s) Greater gestational length in the highest cord DHA quartile

(n.s.) not significant.

The search made in the different databases provided 88 articles. 80 articles were found in PUBMED, which included all those found in ISI Web of Knowledge. From this bibliographic list of articles, 23 references were included because they fullfilled the inclusion criteria for the primary objectives of this systematic review, while the rest of the documents were only related articles. In addition, 7 articles were found in LILACS but none fell within the inclusion criteria. One Cochrane review was also identified on the effects of maternal n-3 supplementation during pregnancy.

Two different reviewers (EL and AG) evaluated the concordance and discrepancy of the bibliographical search. In Table 1 we present a summary of the following data: Study (first author and year of publication), dose of the n-3 LCPUFA supplements used, time of supplementation, and primary outcome results.

Results and Discussion

No harmful effect on in the mother or the neonate of n-3 LCPUFA supplementation during pregnancy was mentioned. The effect on maternal hypercholesterolemia and hypertriglyceridemia associated with gestation was low; the intake of 4 g/d fish oil did not alter triacylglycerols, total cholesterol, HDL or LDL-cholesterol during pregnancy in maternal serum or in cord blood compared with the effect of olive oil[31]. In addition, no changes were observed in maternal blood pressure[31,32]. The consensus recommendations of a panel of experts on behalf of the European Commission is that pregnant women should have an average dietary intake of at least 200 mg DHA/d; intakes of up to 1 g/d DHA or 2·7 g/d n-3 LCPUFA have been used in randomized clinical trials with no significant adverse effects[33].

Table 1 details the randomized controlled trials until March 2011 that evaluated the effect of n-3 LCPUFA supplementation during pregnancy on birth outcomes; in some of them a follow up of the cohort was reported. In table 2, we included the randomized controlled trials that have evaluated the effect of n-3 LCPUFA supplementation during pregnancy on the neuronal function of the offspring.

Birth Outcomes

Several studies showed that the maternal intake of n-3 LCPUFA during pregnancy resulted in a slightly longer gestation period and somewhat higher birth weight (Table 1). The sample size is critical for identifying differences in these variables, and large studies such as DOMINO[34], POSGRAD[35], or the Danish Cohort[36] found differences in birth outcomes as a result of n-3 supplementation during pregnancy (Table 1). It is important to consider that the higher birth weight reported for n-3 LCPUFA supplementation during pregnancy was probably due to the greater length of these pregnancies, since the differences in birth weight disappeared when using the gestational age as covariable[34]. Helland *et al*[37] did not find differences in the duration of gestation or birth weight in 341 subjects (148 subjects receiving cod liver with 1·18 g DHA + 0·8 g EPA vs. 137 subjects receiving corn oil); nevertheless, when they compared the quartile with the highest concentration of DHA

Table 2. Randomized controlled trials of n-3 LCPUFA supplementation during pregnancy on neurodevelopmental function of the offspring

Study	Participants	Daily dose	Duration	Primary functional outcome
DOMINO study Makrides *et al* 2010[34]	2399	0·8g DHA + 0·1g EPA	Week 22 to delivery	Language or cognitive skills at 18 months (n.s.) Postpartum maternal depression (n.s.)
Innis and Friesen 2008[21]	135	400 mg DHA	Week 16 to delivery	More girls in placebo than in the DHA group had visual acuity below average at 2 months
Judge *et al* 2007b[56]	29	0·214 g DHA	Week 24 to delivery	Problem-solving improved at 9 months. Fagan test of infant intelligence (n.s)
Judge *et al* 2007a[54]	30			Visual acuity (Teller cards) improved at age 4 months; at age 6 months (n.s)
Tofail *et al* 2006[58]	249	1·2g DHA +1·8g EPA 0·27g ALA +2·3g LA	Week 25 to delivery	Bayley MDI and PDI at age 10 months (n.s) Associations by multiple regression analyses
Colombo *et al* 2004[57]	77	135 mg DHA 35 mg DHA	Weeks 24-28 to delivery	Mental processing improved at 4 and 6 months but not at 8 months. Increase in examining and less distractibility between age 1 and 2y; attentional disengagement (n.s.).
Dunstan *et al* 2008[55]	72	2·2g DHA +1·1g EPA	Week 20 to delivery	Eye-hand coordination favored at 2·5 years.
Malcolm *et al.* 2003a[53] Malcolm *et al.* 2003b[30]	100	200 mg fish oil	Week 15 to delivery	Visual acuity (VEP, ERG) (n.s.). Correlations VEP and ERG with infant DHA
Helland *et al* 2001[37]	341	1·18g DHA + 0·8g EPA	Week 18 to 3 months post-delivery	EEG and Fagan test (n.s.) during the 1st year. Correlation of EEG on day 2 and cord DHA
Helland *et al.* 2003[50] (4-year)	84			IQ at age 4y favoured with DHA Correlation of IQ with maternal DHA intake
Helland *et al.* 2008[51] (7-year)	142			IQ (n.s.). Significant correlation at age 7 with maternal DHA during pregnancy

(n.s.) not significant; VEP, visual evoked potentials; ERG, electroretinogram; EEG, electroencephalography; MDI, mental development score; PDI, psychomotor development score.

in umbilical plasma phospholipids with the quartile with the lowest concentration of DHA, they found a longer gestational period in the group of babies with higher DHA cord concentration. In addition, Knudsen *et al.*[38] suggested that the effect of n-3 LCPUFA on the length of gestation could be a "quick-acting" effect, since they did not find any association between the intake of n-3 LCPUFA or α-linolenic acid and the timing of spontaneous delivery in their study in which a large proportion of the women stopped taking the capsules before they delivered. For smaller studies, limitations in their statistical power for such variables could explain the lack of differences for these parameters[21,22,27,39].

The results on higher birth weight and length of gestation were also confirmed in different meta-analyses about the effects of n-3 LCPUFA supplementation during pregnancy[40–42]. Szajewska *et al*[41] reported that n-3 LCPUFA supplementation during pregnancy (1278 infants from 6 randomized controlled trials) enhanced the duration of the pregnancy by an average of 1·6 days, and head circumference was also 0·26 cm greater in the supplemented group. In the Cochrane review[40], covering 6 trials involving 2783 women, marine oil supplementation during pregnancy resulted in a mean gestation that was 2·6 days longer for these subjects than for women allocated to placebo or no treatment, and the birth weight was slightly higher (weight mean difference 47 g, 95 % CI 1-93 g; 3 trials, 2440 women). Recently, Salvig & Lamont[42] also reported higher birth weight (71 g) in women who received n-3 fatty acids during pregnancy compared with a placebo (3 RCT involving 1187 women), and a longer gestational period (4·5 days). However, its effect on the rate of preterm birth is controversial; only Salvig *et al.*[42] reported a significant reduction of preterm births (<37 weeks) while the reduction of early preterm birth (<34 weeks) was found to be significant in two of these meta-analyses[40,42]. However, the rate of low birth weight (<2500 g) was not statistically different in any of the 3 meta-analyses[40–42].

Although the effect of n-3 LCPUFA supplementation in high risk pregnancies is not mainly addressed in this systematic review, the results in this respect are controversial. In a European Multicenter Trial[43] involving women with a preterm delivery history, those randomly assigned to receive an n-3 LCPUFA supplement (0·9 g DHA + 1·3 g EPA) had significantly lower rate of recurrent preterm delivery before 37 weeks (mean difference 0·54 %, 95 % CI 0·30-0·98) and before 34 weeks. Moreover, in a prospective cohort study in Denmark with 8729 pregnant women, the low consumption of fish was a strong risk factor for preterm delivery and low birth weight[44]. However, recently, Harper *et al*[45] did not report changes in gestational length, birth weight or length in pregnant women receiving 17-α-hydroxyprogesterone caproate plus 800 mg/d DHA + 1·2 g EPA to prevent recurrent preterm birth. In addition, the daily intake of either 3 g EPA or placebo did not prevent the recurrence of intrauterine growth retardation or pregnancy induced hypertension in 63 subjects with high risk pregnancies. The results of the meta-analyses showed no clear difference in the relative risk of birth before 37 completed weeks in high risk pregnancies[40,46]. Thus, using n-3 LCPUFA supplements to reduce the risk of preterm birth, low birth weight or small-for-gestational age is still controversial, although a slight effect remains a possibility.

Effects on visual and cognitive functions

To date, no meta-analyses on the effect of the maternal intake of n-3 fatty acids during pregnancy on the visual or cognitive functions of the offspring have been published. Two Cochrane reviews are available on the effects of infant formulas supplemented with n-3 LCPUFA after birth in term and preterm babies but this is beyond our scope[47,48].

The available results of the present systematic review suggest some association between early DHA status and cognitive function in infancy and early childhood (Table 2). Helland *et al.*[37] reported that 1·18 g of DHA supplementation during pregnancy did not change electroencephalogram tests on the second day of life or the results of the Fagan test of intelligence at 27 and 39 weeks of age; however, neonates with mature electroencephalography scores had a higher concentration of DHA in umbilical plasma phospholipids. The Fagan test of infant cognitive function is predictive for IQ at an older age, and is comparable to the Bayley test[49]. Since it is more difficult to detect small differences in neurodevelopment early in life with these tests than later on when children are older, these authors are engaged in following up this cohort of children. In fact, at 4 years of age, these authors reported improved results in the Kaufmann ABC test of cognitive development in children from mothers receiving DHA supplements[50], and significant correlations for IQ in the sequential processing at 7 years of age with maternal DHA proportions[51].

Rudimentary forms of various attentional functions are present at birth, but each of the functions exhibits different and apparently dissociable periods of postnatal change during the first years of life.[52]. Malcolm *et al.* demonstrated an association between DHA status of term infants and retinal sensitivity within the first week of life[53], as well as visual evoked potential (VEPs) at 1 year old (50 weeks), and 66 weeks post-conceptional age[30], although no differences between supplemented and placebo groups were reported. Other studies also reported improved visual acuity (Teller cards) at 4 months but not at 6 months[54], and even improved eye-hand co-ordination at the age of 2·5 years[55]. In this line, Judge *et al.* pointed to a benefit for problem-solving skills but not for recognition memory at 9 months of age[56]. Problem solving requires that an infant both remember that a toy is hidden and be able to pay sufficient attention to execute a series of steps to achieve a goal. This result complemented the report of improved mental processing at 4 years[50]. Some authors did not find improvements of neurodevelopmental tests as a result of HA supplementation *versus* placebo during gestation[57,58], but regression analyses showed maternal DHA percentages positively related to measurements of central nervous system development in these studies. In the DOMINO study, no effect of DHA treatment during pregnancy on early childhood cognitive or language scores was reported; fewer children in the DHA treated group had delayed cognitive development compared with the control group, and girls exposed to higher-dose DHA in utero had lower

language scores than girls from the control group[34], pointing to an interaction with the sex of the children. It has been suggested that the effects of n-3 fatty acids on neurodevelopment might meet a saturation point, above which no further effect of LCPUFA n-3 could be detected[21].

Observational longitudinal studies have also supported a relationship between DHA status and infant development; in Inuits from Arctic Quebec, cord DHA levels were associated with greater visual, cognitive and motor development during the first year of life[59], as well as shorter latencies of VEP in school-age children[60]. Further support for the importance of DHA availability in early life comes from the positive associations between maternal fish consumption during pregnancy and cognitive performance of the offspring, observed in large birth cohorts such as ALSPAC[61], VIVA[62] and the Danish National Birth Cohort[63]. However, these results should be interpreted with caution, considering the limitations of observational studies which often cannot fully adjust for all confounding variables.

A novel approach has been proposed to check whether a poor DHA status sufficient to delay infant development occurs among pregnant women. In this sense, an increased risk of low visual acuity scores among infants at 2 months of age born to mothers following their usual diet was reported compared with infants of women considered at low risk of inadequate DHA due to DHA supplementation[21]. Some pregnant women seem to be DHA-deficient and further studies should addressed to ascertain the dietary n-3 LCPUFA requirements during pregnancy, identificatying the asymptote in functions above which no further benefits occurs.

Effects on maternal depression and infant immunity

The effect of DHA supplementation during pregnancy on maternal depression has been addressed in very few studies, most of them with a small sample size, possibly non-specific and without placebo comparison. No clear benefit was observed in these studies. Four of these studies did not find significant effect of DHA supplementation taken for 6 or 8 weeks during pregnancy in subjects with diagnosed major depression in studies involving a small number of participants[64–67]. Only Su *et al.*[68] with 36 depressed subjects receiving 1·2 g DHA + 2·2 g EPA found reduced depression scores, although no placebo group was included in this study.

In healthy pregnant women, no effect on postpartum maternal depression was found in a study with a small number of subjects[69], or in a large study (DOMINO study) involving more than 2000 participants[34]. Recently, Jans *et al.*[70] performed a meta-analysis including 7 randomized controlled trials, in which a total of 309 women taken n-3 fatty acid supplementation were compared with 303 women following a placebo treatment, and no significant effect was found on post-treatment maternal depression (95 % CI - 0·18, 0·13; P=0·76). The quality of research in this area needs to be improved.

Concerning the effect of n-3 LCPUFA supplementation in healthy pregnancies and on the immunological function, positive effects were reported concerning a reduction in food allergy risk and Ig E associated eczema in infants during the first year of life[71], and reduced proinflammatory cytokines and Th2 promoting prostaglandin E2 in the mother[72]. These results were also supported by Krauss-Etschmann *et al.*[73], who observed reduced Th2 inflammatory cytokines in cord blood during the NUHEAL study. From the Danish cohort, a lower rate of allergic asthma was observed in 16 year old children born to mothers receiving supplementation with fish oil compared with olive oil[74]. For infants with a family history of allergic disease, maternal n-3 LCPUFA supplementation during pregnancy also decreased the risk of food allergy and Ig E eczema during the first year of life[71,75] and improved the cord blood cytokine pattern[76,77].

In conclusion, n-3 LCPUFA supplementation during pregnancy has a moderate effect on higher length of gestation and birth weight, but not enough for general recommendation in order to avoid preterm deliveries. Most of the papers found significant differences in some visual or cognitive tests in the offspring or, at least, positive associations between DHA status in the neonate and pregnant mother and neurodevelopmental outcomes. LCPUFA supplementation, in addition to an already adequate omnivorous diet, may not yield any measurable benefit, but very low LC-PUFA intakes could result in loss of function that could even be of major importance in prematurely born babies. The effect of n-3 LCPUFA supplementation during pregnancy on depressive symptoms has been evaluated in studies with too many limitations to achieve a final conclusion, although no effect was observed in these preliminary studies. In contrast, its effects on reducing allergic biomarkers in children seem very promising.

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