EFFECT OF N-3 POLYUNSATURATED FATTY ACID SUPPLEMENTATION IN PREGNANCY: THE NUHEAL TRIAL

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Abstract: In this placebo controlled, randomised, double blind trial, pregnant women received from the 20th week of gestation onwards either 500 mg docosahexaenoic acid (DHA), 400 mg 5-methyl-tetra-hydro-folate (5-MTHF), or placebo, or a combination of 500 mg DHA and 400 mg 5-MTHF. The dietary supplements were well tolerated; the dropout rates did not differ significantly in the active arms of the study (10% to 19%) from that seen in the placebo group (13%). DHA supplementation resulted in significant enhancement of the contribution of DHA to maternal, placental and venous cord blood lipids.

Key words: Docosahexaenoic acid, fetal nutrition, long-chain polyunsaturated fatty acid, methyl-tetra-hydro-folate, pregnancy

1. INTRODUCTION

Docosahexaenoic acid (DHA), the principal n-3 long-chain polyunsaturated fatty (LC-PUFA) plays an important role in infantile neurodevelopment. Uauy et al. (1) have recently reviewed 14 controlled trials that included formula feeding with or without LC-PUFA and functional assessment of visual and other measures of neural development in full-term infants, and concluded that there was a significant relation between the total DHA equivalent provided and the effectiveness as defined by visual acuity measurements at 4 months of age. Moreover, the significant inverse correlation demonstrated in full-term infants between cord blood DHA contents and the decline in blood DHA contents by the age of 6 weeks (2) indicates that attempts to improve infantile DHA status might be initiated even before birth.

Supplementation of DHA to the diet of pregnant mothers represents an obvious tool in attempting to improve maternal and, consequently, fetal DHA status. However, there may be also indirect ways to enhance fetal LC-PUFA supply. The significant inverse correlation reported between total homocysteine concentrations in maternal plasma and DHA contents of erythrocyte phospholipids in the offspring (3) indicates that lowering plasma homocysteine concentrations in the mother may improve DHA status of the infant. Folate supplementation offers the possibility to reduce plasma homocysteine concentrations in the healthy organism.

2. SUBJECTS AND METHODS

On the basis of the above-mentioned considerations, we investigated the effects of DHA and 5-methyl-tetra-hydro-folate (5-MTHF) supplementation to the diet of expecting mothers living in Germany, Hungary and Spain. In this placebo controlled, randomized, double blind trial, expecting women received daily from the 20th week of gestation onwards either 500 mg DHA, or 400 mg 5-MTHF, or placebo, or the combination of 500 mg DHA and 400 mg 5-MTHF. The four supplements were milk based and contained vitamins and minerals in amounts meeting the estimated additional requirements of expecting women during the second half of pregnancy(Laboratorios Ordesa, Barcelona, Spain). The DHA supplemented was of fish oil origin and was given to the supplement in microencapsulated form. All mothers were encouraged to breast-fed. Infants who were not fully breastfed were provided infant formula either with DHA, if the mother was supplemented with DHA, or without DHA, if the mother did not receive DHA supplementation.

The mothers were investigated at the 20th and 30th weeks of gestation and at delivery: physical examination was performed, dietary data were collected by using standardized food frequency questionnaires, and venous blood samples were taken for the analysis of fatty acid and folate statuses. The infants were investigated immediately following birth and at the ages of 8 and 26 weeks: physical examination was performed, development was assessed by anthropometrical methods and nutrient intakes were evaluated. Visual evoked potential techniques and Bayley’s

Infantile Mental Developmental Index were used as major tools for the evaluation of neurodevelopment.

3. RESULTS

The dietary supplement was well tolerated by the mothers. The dropout rates were moderate and did not appear to differ considerably between the active and the placebo arms of the study (Table 1).

Table 1. Number of mothers participating in the randomized, double blind trial on docosahexaenoic acid (DHA) and 5-methyl-tetra-hydro-folate (5-MTHF) supplementation

	DHA	5-MTHF	Placebo	DHA+5-MTHF
No. at entry	77	80	80	75
No. at delivery	69	65	70	63
Dropout rate (%)	10	19	13	17

Fatty acid composition of plasma phospholipids and erythrocyte membrane phosphatidylcholine (PC) and phosphatydilethanolamine (PE) lipids was used for the evaluation of the effect of DHA supplementation on fatty acid status. Here we report preliminary data obtained at investigating fatty acid composition of PC and PE lipids obtained at delivery in 25-25-25-25 mother-infant pairs from each study group.

At delivery, contribution of DHA to the fatty acid composition of erythrocyte membrane PC and PE lipids was significantly higher in mothers who received DHA supplementation than in those receiving placebo or 5-MTHF alone (Table 2).

Table 2. Contribution of docosahexaenoic acid (DHA) to the fatty acids of erythrocyte phophatidylcholine (PC) and phosphatidylethanolamine (PE) lipids at delivery in mothers (n = 25 each) receiving DHA and 5-methyl-tetra-hydro-folate (5-MTHF) supplementation. Data are % wt/wt, medians (ranges from the 1st to the 3rd quartile); a = P < 0.05, b, c, d, = P < 0.01

	DHA	5-MTHF	Placebo	DHA+5-MTHF
PC	3.01 (2.50)^{b}	2.94 (2.19)^{a}	2.04 (1.05)^{b,c}	3.43 (1.87)^{a,c}
PE	8.81 (3.08)^{a,b}	6.37 (2.56)^{a,c}	5.74 (2.28)^{b,d}	9.32 (2.70)^{c,d}

DHA values were also significantly higher in erythrocyte PC and PE lipids in venous cord blood in infants whose mothers received DHA supplementation as compared to those who received placebo or 5-MTHF alone. There were no significant differences between the 5-MTHF and the placebo groups (Table 2 and 3). Fatty acid composition of placental lipids showed differences similar to those seen in cord blood PC and PE lipids.

Supplementation of 5-MTHF resulted in significantly higher plasma folate and significantly lower plasma homocysteine concentrations in the mothers, whereas similar insignificant tendencies were seen in the infants. Visual evoked potential investigations showed significant difference in one subset of the test: the p1 latency measured at 1-degree angel was higher in the DHA+5-MTHF than in the placebo groups.

Table 3. Contribution of DHA to the fatty acids of erythrocyte PC and PE lipids at delivery in infants (n = 25 each) of mothers receiving DHA and 5-MTHF supplementation. For units, signs and abbreviations see Table 2

	DHA	5-MTHF	Placebo	DHA+5-MTHF
PC	3.62 (2.16)^{b}	2.64 (2.04)^{a,b}	3.00 (2.14)	3.42 (1.95)^{a}
PE	7.43 (3.26)	6.43 (2.03)^{b}	6.99 (2.61)^{c}	8.13 (3.32)^{b,c}

4. CONCLUSIONS

In the present study, supplementation of DHA in a dose of 400 mg/day from the 20th week of gestation onwards resulted in significant enhancement of the contribution of DHA to the fatty acid composition of maternal, placental and cord blood lipids. Recently Malcolm et al (4) supplemented expecting mothers with DHA in a dose of 200 mg/day and saw significant enhancement of DHA contents in maternal but not in cord blood lipids. Hence, our present results suggest that 400 mg/day might be an effective dosage of DHA supplementation during pregnancy. Neither in the present study, nor in the study of Malcolm et al (4) did visual evoked potentials investigated during the first months of life reveal robust effects of DHA supplementation. However, an association of DHA status with some parameters of the maturation of the visual pathway was seen both in the present study and in the study of Malcolm et al (4).

We conclude that supplementation of the diet of pregnant mothers with DHA offers an effective tool to improve the DHA status of the offspring, and suggest that the effects of supplementation on neurodevelopment should be carefully monitored in long-term follow-up studies.

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