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Supplementation of a low dose of DHA or DHA+AA does not prevent peripartum depressive symptoms in a small population based sample ☆

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ABSTRACT

Background: The decrease of maternal docosahexaenoic (DHA) status during pregnancy has been associated with postpartum depression, especially in women with a low intake of DHA. Since the DHA intake in the Netherlands is low, we investigated whether supplementation of low doses of DHA or DHA plus arachidonic acid (AA) during pregnancy and lactation could prevent depressive symptoms and sleep disturbances in this period.

Methods: Women were supplemented daily with placebo, DHA (220 mg) or DHA+AA (220 mg each) from week 16 of pregnancy till three months postpartum. Fatty acid analyses were performed in the available plasma samples at 16 and 36 weeks of pregnancy. Depressive symptoms were measured in weeks 16 and 36 of pregnancy and six weeks postpartum using EPDS and within one week postpartum using a blues questionnaire.

Results: 119 women completed the study. The average frequency of fish intake was low, 0.94 times per week, and did not differ between the groups. The supplementation groups did not differ in mean EPDS scores or changes in EPDS scores, nor in incidence or severity of postpartum blues. Red blood cell DHA, AA and DHA/AA ratio did not correlate with EPDS or blues scores. Indices of sleep quality did not differ between the groups.

Conclusion: Supplementation of 220 mg/day DHA or DHA+AA (220 mg/day each) does not prevent peripartum depressive symptoms, in a population based sample with low background DHA intake.

Trial registration: ISRCTN Register nr. ISRCTN58176213.

1. Introduction

About 50% of women experience depressive and other mood-associated symptoms during pregnancy and lactation, and approximately 9% of all mothers develop postpartum depression (Vesga-Lopez et al., 2008). Two affective syndromes are distinguished in the peri-partum, i.e. major depressive disorder, fulfilling DSM criteria for depression, with a specific category of postpartum onset (American Psychiatric Association, 1994); and postpartum blues, which is a transient affective syndrome lasting 1–2 days and occurring in about half of the women in the first week after delivery (Gitlin and Pasnau, 1989; Henshaw, 2003). Concomitant with peri-partum depressive disorders is the worsening of sleep quality in this period (Ross et al., 2005; Parry et al., 2006).

The long chain polyunsaturated fatty acids (LCP) docosahexaenoic acid (DHA, 22:6ω3) and arachidonic acid (AA, 20:4ω6) are important structural components of brain phospholipids, precursors of eicosanoids and modulators of gene expression. DHA, but also eicosapentaenoic acid (EPA, 20:5ω3) mainly derive from fatty fish, while meat and eggs are the principal dietary sources of AA. The low fish

Abbreviations: AA, Arachidonic Acid, 20:4ω6; DHA, Docosahexaenoic Acid, 22:6ω3; EPDS, Edinburgh Postpartum Depression Scale; LCP, Long Chain Polyunsaturated Fatty Acids; EPA, Eicosapentaenoic Acid, 20:5ω3; OOS, Obstetric Optimality Score; RBC, Red Blood Cells.

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consumption in most western countries likely causes low EPA and DHA status of their inhabitants (Simopoulos, 2000), and this condition has repeatedly been implicated in depression in both epidemiological and intervention studies (Parker et al., 2006; Williams et al., 2006; Sinclair et al., 2007; Owen et al., 2008).

Maternal LCP status declines during pregnancy and lactation, partly due to high fetal LCP needs (Hornstra et al., 1995). An epidemiological study showed that the highest incidence of postpartum depression occurs in countries that are characterized by the lowest fish consumption and breast milk DHA contents (Hibbeln, 2002). Some observational studies showed the predictive value of low DHA status for the occurrence of postpartum depression a few weeks later (Otto et al., 2003; De Vriese et al., 2003). Treatment of peripartum depression with LCPω3 seemed effective in a small open label trial (Freeman et al., 2006) and one randomized, placebo controlled clinical trial (RCT) (Su et al., 2008), although other studies reported negative findings (Marangell et al., 2004; Freeman et al., 2008).

The average DHA intake in the Netherlands is 84 mg/day which is very low (Hulshof et al., 2004). The consequently low DHA status is thought to induce depression, especially during challenging periods as pregnancy (Hibbeln, 2002; Otto et al., 2003). Therefore pregnancy is an excellent period to investigate whether depression can be prevented by restoring DHA status with supplementation. Only one placebo controlled trial investigated whether daily DHA supplementation (200 mg) in the postpartum period could prevent postpartum depression (Llorente et al., 2003). No influences on self-ratings, diagnostic measures of depression, or information processing were noted. One explanation of the negative outcome might be the relatively late initiation of the supplement, as compared with the gradual decline of maternal DHA status during pregnancy. With this limitation in mind, we conducted an RCT in which DHA (220 mg daily) or DHA+AA (both 220 mg) were supplemented from week 16 of pregnancy until 12 weeks postpartum. Supplementation is in line with the Dutch daily recommendation of 450 mg LCPω3 (i.e. about 170 mg DHA) (Hulshof et al., 2004). Endpoints of our study were maternal mental health, but also infant neurodevelopment. Neonatal neurodevelopment proved positive associations with neonatal AA status, since we added AA to DHA (Dijck-Brouwer et al., 2005; Bouwstra et al., 2006). The effect of AA on maternal mental health during pregnancy has not been investigated until now.

2. Subjects and methods

2.1. Subjects and study design

This study is part of an RCT with apparently healthy pregnant women. The primary end point was infant neurodevelopment and the secondary was maternal mental health. Inclusion criteria were first or second, singleton pregnancies. Excluded were women with a vegetarian or vegan diet or diabetes mellitus and preterm delivery (<37 weeks). Women were randomized to three groups using block randomization. All participants received a supplement of vitamins and minerals according to Dutch recommended dietary allowances and were assigned to take either soy bean oil (placebo), DHA (220 mg) or DHA+AA (220 mg each) daily from enrollment (14–20 weeks of pregnancy, mean 16.5 weeks) till three months after delivery. The research protocol was approved by the Central Committee on Research Involving Human Subjects (CCMO, Den Haag, The Netherlands; protocol number P03.1071C) and registered under ISRCTN58176213. All women gave written informed consent.

2.2. Questionnaires

For all women an Obstetric Optimality Score (OOS) was completed (Touwen et al., 1980). Depression was assessed with a Dutch version of the Edinburgh Postpartum Depression Scale (EPDS), (Cox et al., 1987; Pop et al., 1992) in week 16 and 36 of pregnancy and 6 weeks postpartum. Women were considered depressed if the EPDS score was 12 or more (Matthey et al., 2006). Postpartum blues was assessed with a Dutch version of the blues questionnaire, women with a score of 12 or more were considered to suffer from postpartum blues (Kennerley and Gath, 1989).

A food frequency questionnaire was completed during pregnancy (week 16 and 36) and the 12th postpartum week, in which women could indicate the frequency, amount and sort of fish eaten during the past week.

The quantity and quality of sleep were assessed using sleep diaries that were filled out during three consecutive days in week 36 of pregnancy and 4 weeks postpartum. The sleep diary used in this experiment has been described before and is validated by comparing its outcome with the Actiwatch®, showing high correlations between the results of both methods (Kiers et al., 2007). The diary consisted of a visual scale in which women could indicate whether they were awake or sleeping during the whole day. Mean sleep efficiency (%) was calculated for three days [total time of real (effective) sleep / the total time attempted sleep × 100%].

2.3. Fatty acid analyses

Red blood cells were collected from EDTA-anticoagulated blood at enrollment (week 16) and in week 36 of pregnancy. Red blood cell washing and fatty acid analyses were performed as previously described (Muskiet et al., 1983).

2.4. Statistics

Statistical analyses were performed using SPSS 14.0. The significance level was set at $p<0.05$. Social and obstetrical characteristics for continuous data were compared using an ANOVA test with supplementation group (placebo, DHA or DHA+AA) as between subject variable. Categorical data were analyzed with a χ^2 test.

The fatty acids, EPDS scores, blues scores and data on sleep efficiency were all skewed, also after transformations. Therefore all data were non-parametrically tested and expressed as median with 25th–75th percentile, and for fatty acids minimum and maximum levels. Effects of supplementation on depression and sleep parameters were calculated with: 1) a Kruskal–Wallis test with EPDS scores, blues scores or sleep indices in week 36 of pregnancy or postpartum as dependent variables and supplementation group (placebo, DHA or DHA+AA) as independent variable; 2) a Friedman's ANOVA comparing the EPDS score or sleep indices in week 36 of pregnancy with scores postpartum, for each treatment group; 3) the Delta depression scores (EPDS score in week 36 or 6 weeks postpartum — score in week 16) were analyzed as described in ad 2; 4) a Spearman correlation between depression scores or sleep indices in week 36 and week 36 red blood cell (RBC) DHA, AA or DHA/AA.

The relation between sleep quality, supplementation and depression scores postpartum was calculated using a linear regression analyses with supplementation groups, EPDS score in week 36 of pregnancy and sleep efficiency 4 weeks postpartum as independent variables and EDPS scores 6 weeks postpartum as dependent variable.

3. Results

We included 182 women in the trial. Fifty seven women dropped out due to lack of motivation and 6 because of pregnancy complications. All drop outs occurred before week 36 of pregnancy. The finally investigated 119 women in the three groups (placebo, $n=36$; DHA, $n=42$; and DHA+AA, $n=41$) did not differ in their social and obstetrical characteristics (data not shown). The average fish intake during the study period was 0.94 times per week, the intake of fatty fish was 0.45 times per week. The fish intake did not differ between