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Supplementation of a low dose of DHA and 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 17 of pregnancy till three months postpartum. Fatty acid analyses were performed in the available plasma samples at 16 and 36 weeks postpartum. 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 peri-partum depressive symptoms, in a population based sample with low background DHA intake.

**Keywords:** Arachidonic Acid (AA); Docosahexaenoic Acid (DHA); Edinburgh Postpartum Depression Scale (EPDS); peri-partum depression; postpartum blues; Sleep efficiency

**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.
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 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 Sr. et al., 2003). Treatment of peri-partum 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 consequent 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 LCP_ω3 (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 mental health during pregnancy has not been investigated until now.

Subjects and methods

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 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.

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 was 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 (JL 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 x100%].

**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).

**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 $\chi^2$ 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 and 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.

**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 the supplementation groups, and did not change over time (data not shown). Supplementation of DHA and AA resulted in a significant increase of RBC DHA and AA respectively, as shown in table 1.

EPDS scores of 12 or more were found for 8 women (6.7%) in week 36 of pregnancy and 7 women (5.9%) at 6 weeks postpartum. The EPDS scores and Delta EPDS scores are shown in table 2. Kruskal-Wallis testing did not show significant between-group differences at any moment. EPDS scores did not differ significantly between week 36 of pregnancy and 6 weeks postpartum for any group. RBC DHA, AA and DHA/AA ratio did not correlate with EPDS or Delta EPDS scores.

Despite reminders, only sixty participants completed the blues questionnaire. Women who did and did-not complete a blues questionnaire did not differ in mean EPDS scores in week 36. 16 (27%) women had a blues score of 12 or more and were considered to suffer from postpartum blues. Median blues scores (25th, 75th percentile) were 8.0 (4.0; 10.0) for placebo, 6.0 (3.0; 8.50) for DHA and 8.5 (4.5; 13.5) for DHA + AA. There were no statistically significant between-group differences.

Indices of sleep quality are shown in table 3. No between-group effects were noted. The indices of sleep quality did not change significantly over time in any group. In a significant regression model (F_{3,81}=15.240; p<0.001) EPDS score from week 36 (β=0.600, p<0.001), and sleep efficiency 4 weeks postpartum (β= -0.257, p=0.007) but not supplementation group (β= -0.004, p=0.969) explained EPDS scores week 6 postpartum (R² 0.370 and Adjusted R² 0.345).
Discussion

In a group of pregnant women with a low LCP intake, daily supplementation of 220 mg DHA alone or 220 mg DHA + 220 mg AA had no effect on mean depression scores, change in depression scores, blues scores or indices of sleep quality.

The mean EPDS score postpartum found in this study is comparable with data from the Dutch population i.e. 4.03 ± 3.9 (Pop et al., 1992). Compared to the literature the incidence of EPDS score of 12 or more was lower in week 36 of pregnancy (12.5%) but comparable with the literature 6 weeks postpartum (8.9%) (Heron et al., 2004).

Prevalence of postpartum blues is lower compared to the 50% reported in previous studies (Gitlin and Pasnau, 1989; Henshaw, 2003).

Strong points of the study include: the relatively long supplementation period, already starting early in the pregnancy; additional evaluation of the effects of LCP supplementation on indices of sleep quality, since sleep is causally related to depressive symptoms; evaluation of the effects of additional AA supplementation; use of a population-based sample and supplementation of the Dutch recommended DHA intake, allowing generalization to a large segment of pregnant women; it is the first investigation of the effects of DHA supplementation on late pregnancy mood symptoms and postpartum blues. Limitations concern the relatively small sample size, caused by high drop-out, allowing the detection of large effects only, the 220 mg DHA dosage, which is relatively low when compared with dosages used for treatment of postpartum depression (EPA+ DHA 1.9 g /day) (Freeman et al., 2008). In addition, although frequently used in similar research, the EPDS is a self report questionnaire, developed as a screening tool and not as an instrument to assess effects of interventions. Furthermore sleep diaries were used, although the results from these diaries are comparable to those of the Actiwatch® (JL Kiers et al., 2007).

Apart from the previously mentioned RCT supplementing 200 mg DHA daily for the prevention of postpartum depression (Llorente et al., 2003), 4 other studies investigated the effect of DHA supplementation for the treatment or relapse prevention of postpartum depression. Three of these have major methodological shortcomings, i.e. lack of control groups, small sample sizes or additional therapy. Supplementation of 2,960 mg/day of fish oil could not prevent relapse of postpartum depression in 4 of 7 treated women (Marangell et al., 2004). In an uncontrolled dose ranging open label trial DHA supplementation (0.5 – 2.8 g/day) was found to decrease postpartum depression scores with 50% in 16 women (Freeman et al., 2006). In a second trial of the same group, women with postpartum depression (n=51) were treated with EPA plus DHA (1.9 g/
day) or placebo in combination with psychotherapy (Freeman et al., 2008). The treatment and control groups did not differ in depression scores. The lack of effect of supplementation was in part attributed to the beneficial effect of the use of psychotherapy in both groups. The last, methodologically convincing study compared supplementation of 2.2 g EPA and 1.2 g DHA (n=13) to placebo (n=11) in depressed pregnant women. Lower HAM-D scores, and higher response- and remission rates were found in the supplemented group (Su et al., 2008).

Results of the current study imply that supplementation of 220 mg DHA and DHA + AA do not prevent the occurrence peri-partum depressive symptoms. However, it might be that the effect is too subtle to detect with the current sample size. Furthermore, higher dosages might be needed. The latter is suggested by dosages up to 1.9 g and 3.4 g EPA+DHA/day used for treatment of depression (Freeman et al., 2008; Su et al., 2008). Finally, the dosage of supplemented EPA was very low. EPA is the major LCP found to be effective in the treatment of depression (Parker et al., 2006; Lin and Su, 2007), and all above mentioned studies showing an effect of DHA on depression, also supplemented EPA.

Supplementation had no effect on sleep quality. The possible effects (if any) may be masked by other causes of peri-partum sleep disturbances like frequent micturation, restless legs and nightly (breast) feeding. Neither of these is known to be sensitive to LCP status. The relation between sleep efficiency 4 weeks postpartum and depression scores 6 weeks postpartum has previously been noted for both depression and postpartum depression (Ross et al., 2005; Tsuno et al., 2005; Parry et al., 2006).

**Conclusion**

Supplementation of 220 mg DHA/day or DHA + AA (220 mg/day each) during pregnancy and lactation does not prevent the occurrence depressive symptoms in this small population based sample. Future studies should aim at a larger study population, and higher dosages of DHA, in combination with EPA.
Reference List


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Chapter 4

