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Increased risk of postpartum depressive symptoms is associated with slower normalization after pregnancy of the functional docosahexaenoic acid status

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Abstract

Observational studies suggest an association between a low docosahexaenoic acid (DHA, 22:6n-3) status after pregnancy and the occurrence of postpartum depression. However, a comparison of the actual biochemical plasma DHA status among women with and without postpartum depression has not been reported yet.

The contents of DHA and of its status indicator n-6 docosapentaenoic acid (n-6DPA, 22:5n-6) were measured in the plasma phospholipids of 112 women at delivery and 32 weeks postpartum. At this latter time point, the Edinburgh Postnatal Depression Scale (EPDS) questionnaire was completed to measure postpartum depression retrospectively. The EPDS cutoff score of 10 was used to define 'possibly depressed' (EPDS score $\geqslant 10$) and non-depressed women (EPDS score <10). Odds ratios (OR) were calculated using a multiple logistic regression analysis with the EPDS cutoff score as dependent and fatty acid concentrations and ratio's as explanatory variables, while controlling for different covariables. The results demonstrated that the postpartum increase of the functional DHA status, expressed as the ratio DHA/n-6DPA, was significantly lower in the 'possibly depressed' group compared to the non-depressed group (2.34 ± 5.56 versus 4.86 ± 5.41, respectively; OR $=0.88$, $P = 0.03$). Lactating women were not more predisposed than non-lactating women were to develop depressive symptoms. From this observation it seems that the availability of DHA in the postpartum period is less in women developing depressive symptoms. Although further studies are needed for confirmation, increasing the dietary DHA intake during pregnancy and postpartum, seems prudent.

Keywords: Docosahexaenoic acid; Postpartum depression; Edinburg postnatal depression scale; Fatty acids

1. Introduction

Accumulating evidence supports the hypothesis that the occurrence of depression is associated with a low n-3 long chain polyunsaturated fatty acid (LCPUFA) status [1–5]. Thus, epidemiological studies have shown that populations with high intakes of n-3 fatty acids have lower rates of depression than populations with low consumption of these fatty acids [6]. In addition, the proportions of n-3 LCPUFA in plasma and/or erythrocytes have repeatedly been reported to be significantly lower in depressed patients compared to healthy control subjects [6–10].

Up till now, only one study demonstrated a significant association between lower levels of n-3 fatty acids, especially DHA, and *postpartum* depression. In this study, Hibbeln showed that both lower DHA content in mothers' milk and lower seafood consumption were associated with higher rates of postpartum depression in 23 different countries [11]. However, studies investigating the association between biochemical fatty acid markers and the prevalence of postpartum depression are still lacking.

Previously, Holman and colleagues and Al and coworkers demonstrated that pregnancy is associated with a marked reduction in the biochemical DHA status [12,13]. After an initial increase during the first trimester

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of pregnancy, a relatively strong decrease was observed in the fraction of this fatty acid in maternal plasma phospholipids. This decrease was shown to persist after delivery, particularly in women breastfeeding their infants [14]. Although it has been hypothesized that changes in the maternal DHA status during pregnancy and after delivery may contribute to the development of depression in the postpartum period [5] and supportive evidence from an ecological study has been obtained [11], so far no studies have been reported which directly compare the postpartum changes in the maternal DHA status and the occurrence of postpartum depression. Therefore, we decided to investigate the relationship between postpartum depression and the changes in DHA concentrations in maternal plasma phospholipids after delivery and during lactation.

In case of a functional DHA shortage, the conversion of 22:4n-6 to n-6 docosapentaenoic acid (n-6DPA, 22:5n-6) increases, resulting in relatively high levels of this latter fatty acid [15]. Hence, the ratio 22:6n-3/22:5n-6, the DHA sufficiency index, has been formulated to indicate a more functional DHA status [16]. Therefore, in the present study, we not only focussed on the DHA content of plasma phospholipids, but on this more functional measure of the DHA status also.

As the postpartum decline in the DHA status is significantly stronger in lactating than in non-lactating women, we also examined whether breastfeeding is related to an increased risk of postpartum depression.

2. Subjects and methods

2.1. Subjects

Subjects included in the present study participated in two earlier studies conducted to investigate maternal essential fatty acid status in pregnancy and postpartum. In the first study (Study 1), the postpartum LCPUFA courses were studied in lactating and non-lactating women, together with the maternal dietary fatty acid intake in this period [14]. The second study, a double blind, randomized-controlled intervention trial (Study 2), aimed at answering the question whether an increase in the nutritional ratio of alpha-linolenic acid (ALA, 18:3n-3) to linoleic acid (LA, 18:2n-6) during pregnancy would improve the maternal and neonatal essential fatty acid and LCPUFA status [17]. Both studies were approved by the Medical Ethics Committee of the University Hospital Maastricht, and written informed consent was obtained from each participant.

As described in detail before [14,17], the subjects had been recruited through midwives in the area of Southern Limburg (south of the Netherlands) and Departments of Obstetrics and Gynecology of hospitals in the same area. The eligibility for study entry was the absence of any metabolic, cardiovascular (including hypertension, diastolic blood pressure $\geqslant 90$ mmHg), renal, psychiatric or neurological disorders, no medication except multivitamins and iron supplementation, singleton pregnancy, term delivery ($\geqslant 37$ weeks of gestation), and no blood transfusion in the perinatal period. Additional inclusion criteria in Study 2 were a gestational age less than 14 weeks at entry, Caucasian origin, and fish consumption less than two times a week.

2.2. Assessment of postpartum depression

In both studies, postpartum depression was assessed retrospectively at week 32 after delivery, using the validated Dutch version of The Edinburgh Postnatal Depression Scale (EPDS) questionnaire. This questionnaire was developed for screening and monitoring of depression in women in the postpartum period [18] and has also been validated for clinical screening of depression in non-postpartum women [19]. The EPDS has been translated into Dutch by Pop and coworkers in 1992 and was found to have good psychometric properties [20]. Since then, this version has been applied in studies in the Netherlands, including a validation for assessing depression in menopausal women [21,22].

The EPDS is a 10-items self-reporting questionnaire. Each item is scored on a four-point scale (0–3) and thus total scores can vary between 0 (not at all depressed) and 30 (very depressed). Usually, cutoff scores of 10 or 13 are used to identify the possibly depressed women [18]. In the present study the cutoff score 10 was used to define women as "possibly depressed" (EPDS score $\geqslant 10$) or "non-depressed" (EPDS score < 10). Reason for this choice was based on the fact that the postpartum depressive symptoms were measured retrospectively, so the most sensitive depression indicator was needed.

2.3. Blood sample collection and fatty acids analysis

Venous blood samples were collected into EDTA containing tubes at week 36 of pregnancy, immediately after delivery, and 32 weeks postpartum. After blood collection, plasma was separated from the erythrocytes by centrifugation. Aliquots of the plasma samples were divided over storage cups and closed tightly under nitrogen. These samples were stored at -80°C until fatty acid analysis.

The fatty acids of phospholipids were isolated and analyzed as previously described [14,17]. Because this method was slightly different between the two studies, a dummy variable for 'study' (1 or 2) was included in the statistical analyses (see below).

Fatty acids were quantified with the help of an internal standard and expressed in absolute amounts (mg/l plasma) or in relative levels (% of total fatty acids, wt/wt). Here only relative levels are reported, because

the total absolute amounts of plasma phospholipid-associated fatty acids (mg/l) at delivery and their postpartum changes were not significantly different between the 'possibly depressed' and the 'non-depressed groups'. As the emphasis is on the maternal DHA status, the following fatty acids were included in the first analyses: docosahexaenoic acid (DHA, 22:6n-3), n-6 docosapentaenoic acid (n-6DPA, 22:5n-6), and the ratio DHA to n-6DPA, 22:6n-3/22:5n-6.

In additional analyses we explored associations with the following fatty acids: LA (18:2n-6), dihomo-gamma-linolenic acid (DGLA, 20:3n-6), arachidonic acid (AA, 20:4n-6), adrenic acid (AdrA, 22:4n-6), sum of the n-6 LCPUFA, ALA (18:3n-3), eicosapentaenoic acid (EPA, 20:5n-3), n-3 docosapentaenoic acid (n-3DPA, 22:5n-3), and sum of the n-3 LCPUFA.

The postpartum changes in the fatty acids or fatty acid ratio's were calculated by subtracting the value at delivery from the value observed at week 32 postpartum.

2.4. Other variables

Information on parity, educational level, breastfeeding, smoking and alcohol use was recorded in both studies. Educational level, measured on an 8-point scale, ranging from primary education to higher vocational training and university [23], was dichotomized into 'low' and 'medium/high', and parity into 'primiparous' and 'multiparous'. Finally, each woman was asked about her self-perceived general health.

2.5. Statistical analyses

The DHA status resulting from the supplementation in Study 2 was assumed to be functionally equivalent to the DHA status caused by habitual feeding. Therefore, it was felt justified to combine the fatty acid data of both studies in the current analysis.

The data are presented as mean $\pm$ SD.

In order to evaluate whether differences in subjects' characteristics existed between the groups originating from the two different studies (Study 1 and Study 2) the Mann–Whitney test and the Chi-square test were applied for comparison of continuous and dichotomous variables, respectively.

Possible correlations between the population characteristics and total EPDS scores were assessed by the Spearman rank correlation test. To test whether there were differences in subject characteristics between the women diagnosed as "possibly depressed" (EPDS score $\geqslant 10$) or as "non-depressed" (EPDS score <10), the Mann–Whitney test and the Chi-square test were used.

Multiple linear regression analyses were used in order to investigate which of the fatty acids or fatty acid changes were associated with depression. In these analyses, the total EPDS score (continuous) was included as the dependent variable and the fatty acids of interest or their postpartum changes as independent variables. Maternal age at test moment, parity, educational level, breast-/bottle-feeding, smoking, and use of alcohol were included as covariables. In addition, a dummy variable was included for the two initial studies (see above). To analyze the potential fatty acid differences between "possibly depressed" and "non-depressed" women (EPDS scores dichotomized at the cutoff score $\geqslant 10$), multiple logistic regression analyses were performed.

The same statistical regression models were applied to examine the relationship between the total EPDS score and maternal feeding practice, breast- or bottle-feeding, as independent variable.

Statistical differences were considered significant at P-values <0.05 (two-sided). All analyses were performed using the statistical package SPSS 10 for Windows (release 10.0.7, SPSS Inc., Chicago, IL).

3. Results

Only women who completed the Edinburgh Postnatal Depression Scale (EPDS) questionnaire (see below) and for whom fatty acid data at both delivery and at week 32 postpartum were available were included. Ultimately, the study comprised 112 women, of which 57 were derived from Study 1 and 55 from Study 2.

3.1. Characteristics of the study populations

Table 1 shows the characteristics of the study populations, originating from the two initial studies. The average duration of pregnancy in Study 1 tended to be significantly longer, approximately 5 days, than that observed in Study 2 ($P = 0.076$). The distributions of educational level (low or medium/high) were significantly different between the two study populations ($P = 0.046$). The majority of the women (87.7%) included in Study 1 had completed a school of medium or higher educational level, whereas this was 72.2% in Study 2. However, further analyses within the respective studies showed no significant correlation between educational level and the EPDS scores. Therefore, it was decided to analyze both data sets jointly.

3.2. Edinburgh Postnatal Depression Scale (EPDS) scores

3.2.1. Relation with population characteristics

Twenty-one percent (=24 women) of the 112 women in the present study had a total EPDS score of 10 or above and were, therefore, diagnosed as "possibly depressed" in the postpartum period. No correlation was found between the EPDS score treated as a

Table 1
Characteristics of the study populations[a,b]

	Study 1 ($n = 57$)	Study 2 ($n = 55$)	All ($n = 112$)
Age (yr) *at week 32 postpartum*	30.81 ± 3.13	30.51 ± 3.46	30.66 ± 3.28
Height (cm)	168.86 ± 6.37	169.02 ± 5.68	168.94 ± 6.02
Weight (kg) *before pregnancy*	66.49 ± 10.47	71.06 ± 14.16	68.74 ± 12.58
Gestational age (wk) at delivery	40.3 ± 1.22	39.7 ± 1.46[c]	40.0 ± 1.37
Breastfeeding (yes/no)	35/22	33/22	68/44
Educational level (low/medium + high)	7/50	15/40[d]	22/90
Parity (primi-/multiparous)	28/29	22/33	50/62

[a] Data are mean ± SD.
[b] Entry in Study 1 is week 36 of pregnancy and in Study 2 before week 14 of pregnancy.
[c] Tendency for significant difference between studies 1 and 2 ($P = 0.076$, Mann–Whitney test).
[d] Significant difference between the two studies ($P = 0.046$, Chi-square test).

Table 2
Plasma DHA status and the partial correlation coefficients of the relation with total EPDS scores[a]

Fatty acids	At delivery			Postpartum change		
	Mean ± SD	r[b]	P-value	Mean ± SD	r[b]	P-value
22:6n-3	3.91 ± 0.94	−0.06	0.563	−0.69 ± 0.94	0.04	0.694
22:5n-6	0.47 ± 0.19	−0.01	0.927	−0.21 ± 0.16	0.04	0.681
22:6n-3/22:5n-6	9.83 ± 5.73	−0.01	0.913	4.32 ± 5.51	−0.08	0.430

[a] Mean EPDS scores = 6.5 ± 5.1.
[b] With correction for dummy variable, parity, educational level, maternal age at test moment, breast-/bottle-feeding, smoking and alcohol use.

continuous variable and any of the population characteristics (maternal age at moment of testing, educational level, parity, smoking or alcohol use).

Of the 24 "possibly depressed" women, 75% ($n = 18$) rated their general health status in the months after delivery as 'not healthy'. For the women in the "non-depressed" group this was only 6% ($n = 5$). This difference is significant ($P = 0.005$). The other above-mentioned population characteristics were not significantly different between the two groups.

3.2.2. Relationship between total EPDS scores and DHA status

The average EPDS score for the total study population was 6.5 ± 5.1.

In Table 2 the mean plasma levels of DHA, n-6DPA, and their ratio are shown for the total group of women. No significant relationship was observed between DHA, n-6DPA, or the ratio DHA to n-6DPA (22:6n-3/22:5n-6) and the total EPDS scores.

3.2.3. Difference in DHA status between "non-depressed" and "possibly depressed" women

The fatty acid compositions of plasma phospholipids at delivery and the postpartum changes are shown in Table 3 for women in the "non-depressed" group (EPDS scores <10) and for those in the "possibly depressed" group (EPDS scores $\geqslant 10$), respectively. Statistically significant relationships between depression and fatty acid status were not observed with DHA or n-6DPA, neither for the levels at delivery, nor for their postpartum changes. However, the improvement of the DHA status during the postpartum period, as reflected by the increase of the 22:6n-3/22:5n-6 ratio during this period, was higher in the non-depressed than in the depressed women (OR = 0.90 (β(SE) = −0.10 (0.05), $P = 0.040$). This indicates that the women with a slower improvement in this ratio had a 10% higher risk for the development of postpartum depression. This significant finding remained after concomitant adjustments for dummy variable (Study 1 or 2), parity, educational level, maternal age at test moment, breastfeeding, smoking and alcohol use (OR = 0.88 (β(SE) = −0.13 (0.06), $P = 0.030$).

3.2.4. Relationship with breastfeeding

No statistically significant relationship was observed between the maternal feeding practice, breast- or bottle-feeding, and the continuous EPDS scores ($r = -0.04$, $P = 0.669$, linear regression). Similarly, no statistically significant outcome was found for the EPDS scores dichotomized at the cutoff score of $\geqslant 10$ (OR = 2.10; $P = 0.160$, logistic regression).

3.2.5. Additional exploratory analyses

The other n-6 and n-3 LCPUFA considered and the sum of these LCPUFA showed no relationship with either the continuous or the dichotomized EPDS scores (Table 4).

Table 3
Plasma DHA status at delivery and postpartum increase in women with EPDS scores <10 (non-depressed) or ⩾10 (possibly depressed)[a]

Fatty acids (% wt/wt)	At delivery		Postpartum change	
	<10 ($n = 88$)	⩾10 ($n = 24$)	<10 ($n = 88$)	⩾10 ($n = 24$)
22:5n-6	0.48±0.19	0.44±0.19	−0.22±0.16	−0.18±0.15
22:6n-3	3.93±0.97	3.82±0.82	−0.68±0.98	−0.74±0.78
22:6n-3/22:5n-6	9.52±5.35	10.97±6.97	4.86±5.41	2.34±5.56[b]

Data are mean±SD.
[a] Mean EPDS scores: cutoff <10 = 4.5±2.4 and cutoff ⩾10 = 14.2±4.9.
[b] Significant outcome (logistic regression analysis, df = 1): β(SE) = −0.13 (0.06), $P = 0.030$, with correction for dummy variable, parity, educational level, maternal age at test moment, breast-/bottle-feeding, smoking and alcohol consumption.

Table 4
Plasma phospholipid fatty acid composition at delivery and postpartum changes in women with EPDS scores <10 (non-depressed) and ⩾10 (possibly depressed)

Fatty acids (% wt/wt)	At delivery			Postpartum change		
	All ($n = 112$)	<10 ($n = 88$)	⩾10 ($n = 24$)	All ($n = 112$)	<10 ($n = 88$)	⩾10 ($n = 24$)
18:2n-6	21.48±2.62	21.33±2.66	22.01±2.43	0.69±2.50	0.79±2.64	0.30±1.88
20:3n-6	3.44±0.70	3.44±0.68	3.46±0.80	−0.25±0.75	−0.24±0.76	−0.29±0.74
20:4n-6	8.57±1.50	8.56±1.45	8.61±1.68	1.19±1.37	1.19±1.38	1.21±1.36
22:4n-6	0.37±0.09	0.37±0.09	0.36±0.08	−0.04±0.08	−0.04±0.08	−0.02±0.07
n-6 LCPUFA	12.84±1.96	12.84±1.91	12.86±2.18	0.71±1.69	0.70±1.71	0.73±1.65
18:3n-3	0.24±0.12	0.25±0.12	0.24±0.12	−0.06±0.13	−0.06±0.13	−0.06±0.11
20:5n-3	0.35±0.18	0.35±0.19	0.33±0.15	0.31±0.39	0.31±0.40	0.30±0.35
22:5n-3	0.56±0.15	0.56±0.16	0.54±0.12	0.21±0.25	0.20±0.26	0.25±0.22
n-3 LCPUFA	4.87±1.14	4.91±1.19	4.73±0.96	−0.16±1.12	−0.16±1.20	−0.18±0.82

Data are mean±SD.

4. Discussion

The prevalence of postpartum depression varies between 10% and 15% [24]. According to the Diagnostic and Statistical Manual of mental disorders IV, this condition arises within 4 weeks after delivery [25] and may still persist at 12 months after parturition [26]. In the Netherlands, Pop et al. have shown that about 20% of women who have recently given birth are affected by postpartum depression [27]. In our present study, 21% of the women scored 10 or above on the validated Dutch version of the Edinburgh Postnatal Depression Scale (EPDS), indicating that these women had been possibly depressed. The majority of these women, 75%, reported a poor self-perception of their general health status.

The reductions of the n-3 fatty acids during pregnancy were hypothesized as a risk factor for postpartum depression [5]. Recently Hibbeln has published evidence from a cross-national analysis supporting this hypothesis [11]. Our results demonstrate that the slower postpartum normalization of the functional DHA status, which is expressed as the 22:6n-3/22:5n-6 ratio and becomes reduced during pregnancy, is related to the higher occurrence of depressive symptoms. The DHA status at delivery per se, did not correlate with the depressive symptoms. Thus, a rapid recovery of the postpartum availability of DHA seems to lower the risk of postpartum depression, whereas a relatively slow postpartum increase seems to confer a 10% higher risk for the development of this condition.

Previously, we have shown that lactating women have a delayed normalization of the postpartum DHA status [14]. Therefore, breastfeeding could increase the maternal vulnerability for postpartum depression. Hence, we also investigated whether postpartum depression is more prevalent among lactating mothers. Although the odds ratio (OR = 2.10) of the multiple logistic regression analysis suggested that lactating women were possibly more predisposed, the association between maternal feeding practice and the depressive symptoms did not reach statistical significance. Lactating mothers seem not to be at higher risk than mothers bottle-feeding their infant are. This is consistent with the finding recently reported by Josefsson et al. that lactating women were not more depressed than the non-lactating women [28]. Thus, our present findings suggest that irrespective of their feeding practice, women showing depressive

symptoms after parturition apparently have a slower normalization of their DHA status.

Our finding points to a retarded improvement of the postpartum DHA status as a possible cause for postpartum depression. However, the reduction in the DHA status that starts after the second trimester of pregnancy [13] might already be a trigger for such a mood disorder. This hypothesis is supported by the results of a recent study, showing that depressive symptoms were already present in the second trimester of pregnancy and reached a peak at week 32 [29].

5. Conclusion

Although postpartum depression was measured retrospectively, our observations indicate that a slower postpartum improvement in DHA status is possibly associated with a higher risk to develop depressive symptoms. Further prospective observational studies with larger sample sizes are required to confirm our findings, but ultimately intervention studies are required to proof the causality of this association. In the mean time, it seems prudent that women who have recently given birth increase their DHA intake.

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