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DOI:

[10.1016/j.pnpbp.2017.05.008](https://doi.org/10.1016/j.pnpbp.2017.05.008)

Document Version

Peer reviewed version

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Citation for published version (APA):

Chang, J. P-C., Lin, C-Y., Lin, P-Y., Shih, Y-H., Chiu, T-H., Ho, M., Yang, H-T., Huang, S-Y., Gaecki, P., & Su, K-P. (2017). Polyunsaturated fatty acids and inflammatory markers in major depressive episodes during pregnancy. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*.
<https://doi.org/10.1016/j.pnpbp.2017.05.008>

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Accepted Manuscript

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PII: S0278-5846(16)30321-9

DOI: doi: [10.1016/j.pnpbp.2017.05.008](https://doi.org/10.1016/j.pnpbp.2017.05.008)

Reference: PNP 9102

To appear in: *Progress in Neuropsychopharmacology & Biological Psychiatry*

Received date: 2 January 2017

Revised date: 25 April 2017

Accepted date: 9 May 2017

Please cite this article as: Jane Pei-Chen Chang, Chih-Ying Lin, Pan-Yen Lin, Yin-Hua Shih, Tsan-Hung Chiu, Ming Ho, Hui-Ting Yang, Shih-Yih Huang, Piotr Gałecki, Kuan-Pin Su, Polyunsaturated fatty acids and inflammatory markers in major depressive episodes during pregnancy. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Pnp(2017), doi: [10.1016/j.pnpbp.2017.05.008](https://doi.org/10.1016/j.pnpbp.2017.05.008)

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Polyunsaturated Fatty Acids and Inflammatory Markers in Major Depressive Episodes during Pregnancy

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ABSTRACT

Introduction: Prenatal depression (PND) is a common psychiatric disorder in pregnant women and leads to psychosocial dysfunction, high suicidal rate, and adverse childcare. Patients with PND have omega-3 polyunsaturated fatty acid (omega-3 or n-3 PUFAs) deficits, which might link to chronic low-grade inflammatory process and the pathophysiological mechanisms of depression. In this case-control study, we examined the levels of PUFAs and inflammatory cytokines in PND.

Method: Blood samples were obtained and analyzed from 16 healthy controls and 17 depressed cases (PND group) diagnosed with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Independent sample t-test and correlation analysis were performed with Statistical Package for the Social Sciences (SPSS) logistics correlation analysis.

Results: PND group had significantly lower levels of total n-3 ($p=0.026$), docosahexaenoic acid (DHA) ($p=0.020$) and eicosapentaenoic (EPA) ($p=0.019$) but a higher omega-6 (n-6)/n-3 PUFAs ratio ($p=0.007$) and tumor necrosis factor alpha (TNF- α) ($p=0.016$) level. Moreover, the duration of current PND episodes were also significantly correlated with DHA, EPA, n-3 PUFAs, n-6/n-3 ratio and TNF- α . In terms of PUFAs and cytokine levels, only DHA was inversely correlated with TNF- α .

Conclusion: PND is significantly associated with lower DHA, EPA, and total n-3 PUFAs levels and an increased n-6/n-3 PUFAs ratio, while the duration of PND is associated with lower levels of n-3 PUFAs, including DHA and EPA. The correlation of PUFAs levels with depression and TNF- α level grant further investigation into the inflammatory process underlying PND, mediated by PUFAs.

Keywords: Perinatal depression (PND), Polyunsaturated fatty acids (PUFAs), Major depressive disorder, Inflammation

1. INTRODUCTION

Perinatal depression (PND) is major and minor depressive episodes that occur during pregnancy or within the first year after delivery (Gavin *et al.*, 2005). PND is considered as one of the most common complications with prevalence rates ranging from 6.5%~ 12.9% (Bennett *et al.*, 2004; Gavin *et al.*, 2005; Serati *et al.*, 2016; Su *et al.*, 2007). PND is detrimental to the mothers since up to 20% postpartum deaths in women with PND are due to suicide (Lindahl *et al.*, 2005). Moreover, PND further affects the mother-child interaction and further affect the child's sense of insecurity in relationships (Marmorstein *et al.*, 2004; Stein *et al.*, 1991; Su *et al.*, 2003). The unwanted consequences secondary to risky behaviors, including suicidal behaviors, unhealthy behaviors such as alcohol abuse (Bonari *et al.*, 2004) and poor child care behaviors, have urged the need for exploring the pathophysiology and biochemical mechanisms underlying PND in anticipation of better and earlier interventions (Serati *et al.*, 2016).

Long-chain polyunsaturated fatty acids (LC-PUFA) serve an important role in cellular and physiological function in perinatal period, especially omega-3 PUFAs (n-3 PUFAs) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Chiu *et al.*, 2004; Demmelmaier and Koletzko, 2015; Su *et al.*, 2008; Su *et al.*, 2013). The association between PUFAs and PND has been explored in recent observational study (Shiraishi *et al.*, 2015). For examples, prenatal depressive symptoms are associated with lower plasma DHA in Japanese population (Shiraishi *et al.*, 2015). Another association study further indicates that patients with higher level of EPA and DHA have lowered risks for developing depressive symptoms (De Vriese *et al.*, 2003), while a higher omega-6 (n-6)/n-3 ratio increases the odds of having depressive symptoms (De Vriese *et al.*, 2003; Pinto *et al.*, 2016). In contrast to the supporting evidence of PUFAs in PND, Sallis *et al.* (Sallis *et al.*, 2014) only found weak associations between n-3 PUFAs and PND. Chong *et al.* also claimed that there was no significant association between n-3 PUFAs and PND, but rather an association between n-3 fatty acid and antenatal anxiety (Chong *et al.*, 2015).

The hypothesized mechanisms underlying PUFAs' antidepressant effects are their action on neuroinflammation (Song *et al.*, 2016; Su, 2009, 2012; Su, 2015). Indeed, several studies have supported the association between pro-inflammatory cytokines and depression (Dowlati *et al.*, 2010; O'Brien *et al.*, 2004; Schiepers *et al.*, 2005; Su, 2012). The meta-analysis done by Dowlati *et al.*, claimed that pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF- α) increase in depressed subjects (Dowlati *et al.*, 2010).

Raison *et al.* also revealed that levels of IL-6 and C-reactive protein (CRP) rise in peripheral circulation in depressive subjects (Raison *et al.*, 2006), while IL-1 β and TNF- α are increased in both blood and cerebrospinal fluid (CSF) (Raison *et al.*, 2006). Moreover, antidepressants were shown to increase IL-10, which has an anti-inflammatory property (Raison *et al.*, 2006). However, the associations of IL-6 and TNF- α in PND still remain inconclusive, since some studies found an increase of these pro-inflammatory cytokines in depression (Boufidou *et al.*, 2009; Christian, 2012; Christian *et al.*, 2009; Maes *et al.*, 2001), while similar findings were not obtained by other groups (Blackmore *et al.*, 2011; Skalkidou *et al.*, 2009). Hence, although both cytokines and n-3 PUFAs have been explored as potential biomarkers for PND, the findings have been controversial. In this observational study, we aimed to examine the role of n-3 PUFAs and inflammatory markers and cytokines, such as CRP, TNF- α , IL-6, and IL-10, in PND. We hypothesized that the subjects with PND will have higher levels of inflammatory markers including pro-inflammatory cytokine levels and n-6 PUFAs, and lower levels of anti-inflammatory markers including IL-10 and n-3 PUFAs.

2. METHODS

2.1 Subjects

Thirty-three pregnant women (17 PND cases and 16 healthy controls) were enrolled in this study after informed consent had been obtained. The case-control study was conducted at the Department of Obstetrics of China Medical University Hospital (CMUH) in Taichung, Taiwan, where integrative care for pregnant woman was provided by the cooperation of a psychiatric team and obstetricians. The data was collected after ethical approval from the Institutional Review Board of the CMUH.

The inclusion criteria of both PND and control group were pregnant women within in 2nd trimester (16th week) or 3rd trimester (28th week) and have ages between 18 to 45 years. Among the 33 eligible participants, all are native Taiwanese and biologically unrelated. Moreover, none of the subjects were taking any psychotropic drugs or had any other medical illness upon comprehensive evaluation of medical history, physical examination and laboratory tests. The 17 PND cases were determined by certified psychiatrists, according to the diagnosis criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, 1994). Both 17 PND cases and 16

healthy controls also provided baseline blood samples for PUFAs and cytokine analysis between weeks 16 and 28 when they received the routine obstetric follow-up.

2.2 Assessments

2.2.1 Mini-International Neuropsychiatric Interview (MINI)

MINI is a short structured clinical interview which enables researchers to make diagnoses of psychiatric disorders according to DSM-IV or ICD-10 (Sheehan *et al.*, 1998). The administration time of the interview is approximately 15 minutes and the interview is designed for epidemiological studies and multicenter clinical trials. The information of translation, validation and instruction of Taiwanese version of MINI can be accessed on the website of Taiwanese Society of Psychiatry (http://www.sop.org.tw/dow_a.htm).

2.2.2 Edinburgh Postnatal Depression Scale (EPDS)

Pregnant women were assessed with Edinburgh Postnatal Depression Scale (EPDS) for perinatal depressive symptoms. EPDS has been the most well-known and widely used evaluation instrument for perinatal depression (Boyd *et al.*, 2005; Chong *et al.*, 2015). EPDS is a self-reported, 10-item screening questionnaire that has been tested in different cultures and countries. The sensitivity and specificity of EPDS varied among culture and different cut off points (Zubaran *et al.*, 2010). The Taiwanese version of the Edinburgh Postnatal Depression Scale (EPDS-T) were validated and showed excellent sensitivity and specificity at the cut-off point of 12/13 (Su *et al.*, 2007; Teng *et al.*, 2005). The cut-off point of 12/13 has also been recommended in the Spitzer's Research Diagnostic Criteria (Spitzer *et al.*, 1978). Therefore, patient whose EPDS scored above 12/13 were identified as having perinatal depressive symptoms in this study.

2.3 Laboratory assessment

Blood samples were obtained in the morning (9:00-1000 am) after 12-hour fasting. Venous bloods were extracted into 10 ml K2 ethylenediaminetetraacetic acid tubes (BD, Franklin Lakes, NJ, USA) and were centrifuged at $1000 \times g$ for 10 minutes (25°C) and plasma were stored at -80 °C until further analysis. Patients enrolled in this study were assessed for the inflammatory markers including CRP, IL-6, IL-10 and TNF- α . Individual fatty acid profiles were also analyzed from the obtained blood samples. CRP levels were measured by nephelometry, a latex particle-enhanced immunoassay (TBA-200FR, Tokyo, Japan), using a fully automatic biochemical analyzer (Unicel DxC 800 Synchron Clinical System; Beckman Coulter, Fullerton, CA, USA) at the Clinical Laboratory Department of CMUH. The inter- and intra-assay coefficients of variations (CVs) were <2.0% and <1.9%,

respectively. The lower detection limit of the assay was 0.01 mg/dL. Plasma cytokine levels of IL-6, IL-10 and TNF- α were quantified by Bio-Plex Suspension Array System 200 (Bio-Rad Laboratories, Hercules, CA, USA) along with a Procarta Immunoassay Kit using polystyrene beads and an appropriate diluent Plasma Standard Diluent Kit (Affymetrix-Panomics, Santa Clara, CA, USA). This analytic measure is based on the Luminex technology and a human cytokine/chemokine 6-plex panel was used to simultaneously detect the following analytes.

Fatty acid composition of erythrocyte membranes was analyzed by thin-layer chromatography and the level of individual fatty acid was measured with gas chromatography of methyl esters (Lipid Standards, FAME, Sigma Co., St. Louis, MO, USA). Fatty acid profiles were identified by comparing the retention times with those of appropriate standard fatty acid methyl esters. The detailed step-by-step procedures have been published and described elsewhere (Chiu *et al.*, 2003; Su, K. P. *et al.*, 2003; Su *et al.*, 2010). The levels of each fatty acid were expressed as a percentage of total fatty acids. Laboratory measures were conducted on coded samples by workers who were blind to the information of the subjects.

2.4 Statistical analysis

All statistical analysis was carried out with the Statistical Package for the Social Science (SPSS), version 17.0 for windows. Demographic and clinical characteristics of patients between PND and control groups were compared by t-test or Chi-Square test where appropriate. The correlation between PUFAs profile and cytokine levels was determined with Bivariate correlation using Pearson product-moment correlation coefficient as correlation coefficient (γ). The tests of significance for correlation analysis were two-tailed. Analyses were presented with 95% confidence intervals (CIs), and a p-value <0.05 was identified as statistically significant.

3. RESULTS AND STATISTICAL ANALYSES

3.1. Characteristics of participants

There was no significant difference in terms of age, gestation times, education years, psychiatric or family history of MDD, and weeks of pregnancy (Table 1). As in coherence with the DSM-IV diagnosis, PND group had significantly higher EPDS score ($p < 0.0001$) than control group.

TABLE 1

3.2. Polyunsaturated fatty acids and cytokine levels

Patients with PND had significantly lower levels of total n-3 PUFAs ($p=0.026$), EPA ($p=0.019$) and DHA ($p=0.020$) than control group (See Table 2). Moreover, PND group had a higher n-6/n-3 ratio than control group ($p=0.007$). Among the inflammatory biomarkers, only TNF- α was found to be significantly higher in PND group when compared to controls ($p=0.016$). Although no significant difference was found in AA or n-6 PUFAs, but there was a trend showing patients with PND had higher levels of AA and n-6 PUFAs than control group.

TABLE 2

3.3 Correlations of clinical variables and PUFA and cytokine levels

There was no correlation between PND severity, PUFAs and cytokines levels. However, PND duration negatively correlated with total n-3 PUFAs, EPA and DHA, with r values equal to -0.415, -0.395 and -0.392 respectively ($p<0.05$, Table 3). Moreover, current PND duration positively correlated with n-6/n-3 ratio and TNF- α , with r values equal to 0.458 and .443, respectively ($p<0.01$, Table 3).

TABLE 3

DHA was negatively correlated with TNF- α ($p<0.05$, Table 4), while no correlation was found between total n-3, n-6, n-3/n-6 ratio and EPA and cytokine levels.

TABLE 4

4. DISCUSSION

4.1 PND group had lower levels of n-3 PUFAs

This is the first study measuring both PUFAs levels and inflammatory markers in women with PND. The major finding of our study is that pregnant women with PND had lower levels of EPA, DHA and total n-3 PUFAs and a higher n-6/n-3 PUFAs ratio. Our study findings support our initial hypothesis and corresponds to the meta-analysis showing lower n-3 PUFAs profiles of depressed patients in 14 case-control studies (Lin *et al.*, 2010). Moreover, our study also showed pregnant women with PND tend to have higher levels of AA and n-6 PUFAs. This is further supported by other observational studies indicating that higher levels of EPA and DHA act as protective factor from MDD while a higher n-6/n-3 ratio acts as a risk factor of MDD in pregnant women (De Vriese *et al.*, 2003; Pinto *et al.*, 2016). Moreover, higher concentrations of DHA in breast milk and greater seafood consumption (rich in DHA) have been associated with lower prevalence rates of postpartum depression (Hibbeln, 2002). It has also been suggested that n-3 PUFAs are crucial for fetal development, and the increased demand during pregnancy may increase risk of PND in the susceptible mothers (De Vriese *et al.*, 2003; Golding *et al.*, 2009; Levant *et al.*, 2008; Markhus *et al.*, 2013; Su *et al.*, 2003). In addition, DHA and EPA have shown efficacy in treating and preventing depressive disorders (Baghai *et al.*, 2011; Clayton *et al.*, 2009; Lin *et al.*, 2010; McNamara *et al.*, 2010).

4.2 PND group had higher levels of TNF- α

In terms of the inflammatory cytokines, our initial hypothesis was only partially proven, where TNF- α was observed to increase significantly in PND in this study. Physiological pregnancy has been suggested as a state of immunosuppression, to avoid maternal attack on the fetus (Kraus *et al.*, 2012), while inflammation in pregnancy has been more commonly associated with pregnancy complications such as pre-eclampsia (Ahn *et al.*, 2011), preterm birth (Osborne and Monk, 2013) and gestational diabetes (Lowe *et al.*, 2010). The increased TNF- α levels observed in PND is supported by previous research reports (Boufidou *et al.*, 2009; Christian, 2012; Christian *et al.*, 2009; Maes *et al.*, 2001), thus inflammation involving TNF- α is speculated as a potential mechanism contributing to PND. The role of inflammation has been emphasized in depression, and an excellent example of inflammation theory of depression is interferon- α induced depression, where administration of inflammatory

cytokines results in depression (Su *et al.*, 2014). On the other hand, blockade of pro-inflammatory cytokines and their signaling pathways and factors has been shown to reduce depressive symptoms in patients with MDD (Abbott *et al.*, 2015; Kohler *et al.*, 2014; Song *et al.*, 2015; Song *et al.*, 2016; Su, 2015; Su *et al.*, 2015). Hence, inflammatory cytokines, particularly TNF- α may serve as a biological indicator or even as a harbinger of PND.

4.3 Duration of PND associates with lower levels of n-3 PUFAs

The duration of PND associated positively with lower levels of total n-3 PUFAs, EPA and DHA and a higher n-6/n-3 PUFAs ratio. This further implies that the progression of PND might alter the erythrocyte profiles of PUFAs and enhance inflammatory response. Pregnancy is a state consisting of both physiological and psychological stress that may trigger the release of pro-inflammatory cytokines which later lead to neurotransmitter alterations and behavioral changes (Maier and Watkins, 1998). Although glucocorticoids may help to halt the pro-inflammatory cytokine production in acute phase, the development of glucocorticoid resistance as the result of chronic stress, such as depression, may result in excess production and accumulation of pro-inflammatory cytokines in the system (Maes *et al.*, 1998; Pariante *et al.*, 1999).

N-3 PUFAs such as DHA, on the other hand, has been shown to have anti-inflammatory effects via immunomodulation and counteracting HPA axis dysfunction. For example, Song *et al.* (Song and Wang, 2011) suggested that DHA could reduce the production of certain pro-inflammatory cytokine that leads to depression. Other studies further demonstrated that n-3 PUFAs induce suppression of eicosanoids by inhibiting TNF- α , IL-6 and IL-1 β (James *et al.*, 2000; Park *et al.*, 2012). It has also been suggested that n-3 PUFAs are able to inhibit the actions of leukotriene B-4 (LTB-4), which is synthesized from n-6 derived arachidonic acid (AA). In addition, anti-inflammatory effect of DHA in depression has also been suggested to involve the monoamine neurotransmitter system and the HPA axis, where DHA is able to attenuate the hyperactivity of the HPA axis (Cowen, 2008; McNamara *et al.*, 2010). Hence, n-3 PUFAs such as DHA and EPA may be serving as potential protective factors of PND in pregnant women.

4.4 Limitations

Due to the nature of observational study, we were not able to determine the casual relationship among DHA, EPA, cytokine levels and depression. Though our sample size is small, the case and control groups in this study are relatively homogenous in terms of age, education level, psychiatric and family history of MDD, smoking habits and gestation weeks,

which generally serve as confounding factors. By minimizing the heterogeneity of confounding factors, we enhance the validity of the results. There are other limitations, such as the lack of dietary controls and records of n-3 PUFAs consumption and the wide range of recruitment time points from weeks 16 to 28. Replication of our study with a longitudinal model study will be needed to support our findings. The strength of this study is that it is the first study measuring both PUFAs levels and inflammatory markers in women with PND. Moreover, the associations of n-3 PUFAs and cytokine levels in our study correspond well with other studies.

5. CONCLUSION

PND is significantly associated with lower DHA, EPA, and total n-3 PUFAs, and increased n-6: n-3 PUFAs ratio, while longer duration of depressive episode is associated with lower n-3 PUFAs. DHA is inversely associated with pro-inflammatory cytokine such as TNF- α in PND. Future studies with larger sample size are also required to replicate our findings and to help elucidate the inflammation mechanism with regards to PUFAs in patients with PND.

ACKNOWLEDGEMENTS

The work was supported by the following grants: MOST104-2314-B-039-022-MY2, 104-2314-B-039-050-MY3, 103-2320-B-038-012-MY3, 103-2320-B-039-036, 103-2320-B-039-039-MY3, 103-2923-B-039-002-MY3, and 102-2911-I-039-501 (Joint Research Projects between Taiwan and Poland) from the Ministry of Science and Technology; NHRI-EX105-10528NI from the National Health Research Institutes; and CMU103-S-03, DMR-103-078, CMU104-S-1603 & CMU104-S44 from the China Medical University in Taiwan. We would like to thank Miss Grace Chien and Dr. Palani Mahalakshmi for assisting the qRT-PCR experiments and clinical experiments.

FUNDING

The work was supported by the following grants: MOST104-2314-B-039-022-MY2, 104-2314-B-039-050-MY3, 103-2320-B-038-012-MY3, 103-2320-B-039-036, 103-2320-B-039-039-MY3, 103-2923-B-039-002-MY3, and 102-2911-I-039-501 (Joint Research Projects between Taiwan and Poland) from the Ministry of Science and Technology; NHRI-EX105-10528NI from the National Health Research Institutes; and CMU103-S-03, DMR-103-078, CMU104-S-1603 & CMU104-S44 from the China Medical University in

Taiwan.

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Table 1 Demographic data of the perinatal depression (PND) group and control group

	DEP (N=17)	CONTROL (N=16)	p
Demographic characteristics			
Age (years), mean (SD)	31.2 (4.3)	30.6 (5.5)	0.699
Education years, , mean (SD)	16.6(1.5)	16.8(1.0)	0.725
Cigarette smoking, N (%)	0 (0)	0 (0)	----
Gestation Week, mean (SD)	23.2 (4.9)	23.2(2.8)	0.994
Clinical characteristics			
Family history of psychiatric disorders, N (%)	1 (3)	0(0)	0.325
EPDS, mean (SD)	14.6(3.6)	5.3(3.8)	<0.0001
PND Weeks, mean (SD)	7.7(2.4)	0(0)	----
History of Psychiatric Disorders, N (%)	3(9)	2 (6)	0.680

Note: CONTROL, non-depression group; DEP, depression group; EPDS, Edinburgh Postnatal Depression Scale; N, number; PND Weeks, duration of current perinatal depression in weeks; SD, standard deviation.

Table 2 Polyunsaturated fatty acid profiles and cytokine levels

	DEP (N=17)	CONTROL (N=16)	p
EPA (%)	2.6 (0.7)	3.1 (0.4)	0.019
DHA (%)	3.7 (0.7)	4.2 (0.5)	0.020
AA (%)	8.9 (1.3)	8.2 (0.6)	0.070
Total N-3 (%)	8.6 (1.1)	9.4 (0.8)	0.026
Total N-6 (%)	16.0 (1.9)	15.0 (1.4)	0.090
N-6/N-3	1.91 (0.38)	1.61 (0.16)	0.007
IL-10 (pg/ml)	1.5 (1.5)	2.0 (1.3)	0.389
IL-6 (pg/ml)	7.8 (3.2)	6.5 (1.8)	0.146
TNF-alpha (pg/ml)	1.1 (0.48)	0.7 (0.4)	0.016
CRP (mg/L)	0.8 (0.2)	0.8 (0.1)	0.182

Note: AA, arachidonic acid; CONTROL, non-depression group; CRP, high-sensitivity C-reactive protein; DEP, depression group; DHA, docosahexaenoic Acid; EPA, eicosapentaenoic acid; IL, interleukin; N, number; N-3, omega-3; N-6, omega-6; SD, standard deviation; TNF, tumor necrosis factor.

Table 3 Correlations of depression duration, severity, PUFAs, and cytokines

	EPA	DHA	N-3	N-6/N-3	CRP	IL-6	IL-10	TNF- α
	<i>R</i>	<i>R</i>	<i>R</i>	<i>R</i>	<i>R</i>	<i>R</i>	<i>R</i>	<i>R</i>
PND	-.395*	-.392*	-.415*	.458**	.304	.264	-.105	.443**
Weeks								
EPDS	-.121	-.233	-.157	.280	.142	.123	-.248	.273

Note: DHA, docosahexaenoic Acid; EPA, eicosapentaenoic acid; EPDS, Edinburgh Postnatal Depression Scale; N-3, omega-3; N-6, omega-6; N-6/N-3, omega-6: omega-3 ratio; PND Weeks, duration of current perinatal depression in weeks; *R*, Pearson coefficient; TNF, tumor necrosis factor.

* indicates statistical significance of $p < 0.05$; ** indicates statistical significance of $p < 0.01$

Table 4 Correlation of polyunsaturated fatty acids and inflammatory cytokine levels

	TNF alpha	IL-10	IL-6	CRP
	<i>R</i>	<i>R</i>	<i>R</i>	<i>R</i>
EPA	-.137	-.081	-.130	-.038
DHA	-.397*	.055	-.209	-.257
N-3	-.169	.003	.021	-.003
N-6	.083	.148	-.034	-.103
N-6/N-3	.243	.036	.003	-.018

Note: CRP, C- reactive protein; DHA, docosahexaenoic Acid; EPA, eicosapentaenoic acid; IL, interleukin; N-3, omega-3; N-6, omega-6; N-6/N-3, omega-6 to omega-3 ratio; *R*, Pearson coefficient; TNF, tumor necrosis factor.

* indicates statistical significance of $p < 0.05$

HIGHLIGHTS

- Blood samples of Prenatal depression (PND) cases were analysed for immune biomarkers
- Blood samples of PND cases were analysed for n-3 fatty acids (PUFAs).
- PND is significantly associated with lower DHA, EPA and total n-3 PUFAs
- PND is significantly associated with increased n-6/n-3 PUFAs ratio and TNF- α level.
- Duration of PND is associated with lower n-3 PUFAs levels and higher TNF- α level.