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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.

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., 2003b). 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; Demmelmair and Koletzko, 2015; Su et al., 2008, 2013). The association between

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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, 2015a,b). 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-1β 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 and 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 min 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 × *g* for 10 min (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 et al., 2003a, 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.