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Research paper

Activated neuro-oxidative and neuro-nitrosative pathways at the end of term are associated with inflammation and physio-somatic and depression symptoms, while predicting outcome characteristics in mother and baby

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ABSTRACT

Objectives: To examine oxidative & nitrosative stress (O & NS) biomarkers at the end of term in relation to perinatal affective symptoms, neuro-immune biomarkers and pregnancy-related outcome variables.
Methods: We measured plasma advanced oxidation protein products (AOPP), nitric oxide metabolites (NOx), total radical trapping antioxidant parameter (TRAP), -sulfhydryl (-SH), peroxides (LOOH) and paraoxonase (PON)1 activity in pregnant women with and without prenatal depression and non-pregnant controls.
Results: Pregnancy is accompanied by significantly increased AOPP and NOx, and lowered TRAP, -SH and LOOH. Increased O & NS and lowered LOOH and -SH levels are associated with prenatal depressive and physio-somatic symptoms (fatigue, pain, dyspepsia, gastro-intestinal symptoms). Increased AOPP and NOx are significantly associated with lowered –SH, TRAP and zinc, and with increased haptoglobin and C-reactive protein levels. Increased O & NS and lowered TRAP and PON 1 activity, at the end of term predict mother (e.g. hyperpigmentation, labor duration, caesarian section, cord length, breast milk flow) and baby (e.g. sleep and feeding problems) outcome characteristics.
Conclusions: Pregnancy is accompanied by interrelated signs of O & NS, lowered antioxidant defenses and activated neuro-immune pathways. Increased O & NS at the end of term is associated with perinatal depressive and physio-somatic symptoms and may predict obstetric and behavioral complications in mother and baby.

1. Introduction

Depression is accompanied by oxidative and nitrosative stress (O & NS) (Maes et al., 2016; Moylan et al., 2014), immune activation and a chronic mild inflammatory response (Maes et al., 2015, 1993). O & NS signs include increased peroxide levels (Liu et al., 2015), increased damage to lipids (Camkurt et al., 2016; Maes, 2008), increased nitric oxide (NO) production and nitrosative stress (Maes, 2008), increased damage to proteins, as indicated by elevated levels of advanced oxidation protein products (AOPP) (Vargas et al., 2013a), and lowered levels of antioxidants, including paraoxonase (PON)1 (Barim et al., 2009; Bortolasci et al., 2014; Maurya et al., 2016), total radical trapping potential (TRAP) (Liu et al., 2015) and -sulfhydryl (-SH) groups (Cichoń et al., 2015). Furthermore, peripheral signs of immune-inflammatory activation include upregulation of positive acute phase proteins, including haptoglobin and C-reactive protein (CRP) (Maes, 1993), and downregulation of negative acute phase reactants, including zinc (Jung et al., 2016; Styczeń et al., 2016). In depression, the

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tryptophan catabolite (TRYCAT) pathway may be activated through stimulation of indoleamine-2,3-dioxygenase (IDO) by immune and oxidative processes (Maes et al., 2011b).

Pregnancy is accompanied not only by increased immune activation (Anderson and Maes, 2013) and consequent TRYCAT pathway activation (Anderson and Maes, 2013), but also O & NS as indicated by increased lipid peroxides (Patil et al., 2006; Walsh, 1994), production of NO metabolites (NOx) (Choi et al., 2002) and AOPP levels (Fialová et al., 2003; Kalousová et al., 2002). Antioxidant defenses are lowered during pregnancy as indicated by lowered PON1 (Rojekar and Mogarekar, 2015), TRAP (Salas-Pacheco et al., 2016), -SH (De Lucca et al., 2016) and zinc (Ma et al., 2015; Nossier et al., 2015; Tabrizi and Pakdel, 2014) levels as well as other antioxidants (Salas-Pacheco et al., 2016). Increased peripheral inflammation and O & NS have been demonstrated to be associated with various obstetric complications, including preeclampsia (Kirbas et al., 2016; Ma et al., 2015; Nossier et al., 2015), glucose intolerance (Zein et al., 2016), miscarriage, fetal anomaly and growth restriction and preterm labor (Duhig et al., 2016; Mukhopadhyay et al., 2015). Moreover, these pathways may also affect neonate's outcomes, including lowered Apgar scores (Rejc et al., 2016), increased risk of asthma (Noutsios and Floros, 2014), poorer neurodevelopment outcome (especially among male babies) (Roy et al., 2015), and other specific diseases of the neonatal period, such as bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, and periventricular leukomalacia (Marseglia et al., 2014).

There is now evidence that perinatal depression and anxiety symptoms are predicted by immune activation and inflammatory responses, including lowered tryptophan availability and endogenous compounds with anti-inflammatory and antioxidant properties (Maes et al., 1992, 2000, 2001), e.g. CC16 (Maes et al., 1999), T3 popyunsaturated fatty acids (PUFAs) (De Vriese et al., 2003) and zinc, increased inflammatory cytokines and CRP levels (Anderson and Maes, 2014, 2016; Leff-Gelman et al., 2016; Roomruangwong et al., 2016a, 2016c). Recently, we published that an increased hematocrit (Hct), but not mean corpuscular volume (MCV), at the end of term may predict postnatal depressive symptoms (Roomruangwong et al., 2016b). Moreover, the severity of physio-somatic symptoms at the end of term, including fatigue, pain, dyspepsia and gastro-intestinal symptoms, is strongly associated with signs of inflammation (CRP and zinc levels) and TRYCAT pathway activation (Roomruangwong et al., 2016a).

There is, however, a paucity of data on the involvement of O & NS processes in perinatal depression. There is one paper hypothesizing that increased oxidative stress in perinatal depression could contribute to cardiovascular pathology in women with pre-eclampsia (Nicholson et al., 2016). Nevertheless, elevated O & NS in pregnancy may have detrimental effects by increasing the risk towards perinatal depression and physio-somatic symptoms. Indeed, increased O & NS processes are associated not only with the onset of depression (Maes et al., 2011a), but also physio-somatic symptoms (Maes et al., 2006; Morris and Maes, 2013). In addition, O & NS processes could play a role in pathophysiological underpinnings of perinatal depression, including immune activation, inflammation and lowered T3 PUFA levels (Moylan et al., 2014). The erythron, including erythrocyte morphology, is in part modulated by increased oxidative stress and reduced levels of antioxidants (Lurie and Mamet, 2000; Peng and Pan, 2017; Tiwari et al., 2012; Waggiallah and Alzohairy, 2011).

This study aimed to examine whether O & NS biomarkers, namely AOPP, LOOH, NOx, -SH groups, TRAP, and PON1 activities in pregnant women could be associated with depressive, physio-somatic and anxiety symptoms, inflammatory biomarkers, namely CRP, haptoglobin and zinc, TRYCAT pathway activation, erythron variables, including Hct, and mother and baby outcome variables. The *a priori* hypotheses are that a) pregnancy is accompanied by signs of O & NS including lowered antioxidant defenses, b) the latter are associated with perinatal affective symptoms and immune activation, and c) increased O & NS predicts selected obstetric and behavioral complications for mother and baby.

2. Participants and methods

2.1. Participants

We recruited 24 non-pregnant women and 49 pregnant women who attended the Antenatal Clinic of the King Chulalongkorn Memorial Hospital, Bangkok, Thailand. Participants were included when they were 18 years of age or older and being able to read and write Thai language. We only included pregnant women who did plan to give birth and attend postnatal follow up consultations at the Department of Gynecology, King Chulalongkorn Memorial Hospital. We excluded pregnant women with positive VDRL or HIV serology, and medical or obstetric condition(s) that impede ability to fill in the questionnaires and women with any DSM-IV-TR axis I disorders, other than mood disorders (bipolar disorder and major depression), e.g. autism, schizophrenia, cognitive disorders and substance abuse. We excluded pregnant and non-pregnant women with medical disorders, such as (auto) immune disorders, diabetes, hypertension, chronic obstructive pulmonary disease, heart failure. Exclusionary criteria for normal controls were a lifetime or current diagnosis of any axis 1 disorders. The study was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. Written informed consent was obtained from all participants.

2.2. Measures

All pregnant and non-pregnant women were assessed by a senior psychiatrist using a structured interview, which included the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 2000; Lotrakul et al., 1996), the Beck Depression Inventory (BDI) (Beck et al., 1988; Horasut et al., 1997), the Edinburgh Postnatal Depression Scale (EPDS), Thai validated translation (Pitanupong et al., 2007; Vacharaporn et al., 2003), Spielberger's State-Trait Anxiety Inventory (STAI), state version in a Thai validated translation (Spielberger and Vagg, 1984) and the Mini International Neuropsychiatric Interview (M.I.N.I) - Thai version – to assess the diagnosis of “a life time history of mood disorders” (namely major depression, bipolar disorder or dysthymia) and “a life time history of depression” (namely major depression or dysthymia) (Sheehan et al., 1998). A senior psychiatrist and a senior gynecologist evaluated pregnant women at 2 time points, namely end of term (T1) and 4–6 weeks after delivery (T2). Pregnant women with a T1 EPDS score $\geq$ 11 were considered to have a positive screening for antenatal depression (Pitanupong et al., 2007; Vacharaporn et al., 2003). The senior research psychiatrist also assessed criteria for premenstrual syndrome (PMS), i.e. a recurrent pattern of mood (sadness, depression, anxiety, irritability, tension and lowered concentration) and physio-somatic (tender breasts, fatigue, body aches, bloating) symptoms, which appear in the luteal phase and resolve with menstruation. At T1, the senior psychiatrist assessed hyperpigmentation and physio-somatic symptoms, including fatigue, back pain, muscle pain, dyspepsia and obstipation. In addition, at T1 we assessed body weight (in kilograms, kg) with a digital weighing scale and height (in meter, m) with a manual height measure instrument and computed body mass index (BMI) as body weight (kg) / height $(m)^2$. At T2, the senior psychiatrist assessed mother and baby characteristics including baby sucking problems and inadequate breast milk flow in the first week after delivery, number of baby awakenings and total time of baby awakenings during the night the first 4 weeks after delivery. Medical and obstetric data, including caesarian section, duration of labor and placenta weight were obtained from medical records.

At 8.00 a.m. fasting (10 h) blood was collected in non-pregnant and pregnant (at T1) women for the measurement of serum O & NS and antioxidant biomarkers, including lipid peroxides, AOPP, NOx, TRAP, -SH groups, PON1 activities. Hydroperoxide (LOOH) was determined according to an adaptation of the technique described by Gonzales-Flecha et al. (Gonzalez Flecha et al., 1991) and Panis et al. (Panis et al.,