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Inflammatory markers in late pregnancy in association with postpartum depression—A nested case-control study

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ABSTRACT

Recent studies indicate that the immune system adaptation during pregnancy could play a significant role in the pathophysiology of perinatal depression. The aim of this study was to investigate if inflammation markers in a late pregnancy plasma sample can predict the presence of depressive symptoms at eight weeks postpartum. Blood samples from 291 pregnant women (median and IQR for days to delivery, 13 and 7–23 days respectively) comprising 63 individuals with postpartum depressive symptoms, as assessed by the Edinburgh postnatal depression scale (EPDS ≥ 12) and/or the Mini International Neuropsychiatric Interview (M.I.N.I.) and 228 controls were analyzed with an inflammation protein panel using multiplex proximity extension assay technology, comprising of 92 inflammation-associated markers. A summary inflammation variable was also calculated. Logistic regression, LASSO and Elastic net analyses were implemented. Forty markers were lower in late pregnancy among women with depressive symptoms postpartum. The difference remained statistically significant for STAM-BP (or otherwise AMSH), AXIN-1, ADA, ST1A1 and IL-10, after Bonferroni correction. The summary inflammation variable was ranked as the second best variable, following personal history of depression, in predicting depressive symptoms postpartum. The protein-level findings for STAM-BP and ST1A1 were validated in relation to methylation status of loci in the respective genes in a different population, using openly available data. This explorative approach revealed differences in late pregnancy levels of inflammation markers between women presenting with depressive symptoms postpartum and controls, previously not described in the literature. Despite the fact that the results do not support the use of a single inflammation marker in late pregnancy for assessing risk of postpartum depression, the use of STAM-BP or the novel notion of a summary inflammation variable developed in this work might be used in combination with other biological markers in the future.

1. Introduction

Pregnancy and childbirth are life changing events. Approximately 12% of all women will suffer from depressive symptoms in the perinatal period (O'Hara and McCabe, 2013). The severity of these symptoms varies from tiredness, sleep problems, feelings of inadequacy in the new parental role, loss of appetite and loss of interests in social activity to severely depressed mood, depressive delusions, self-destructive behaviour, neglecting or harming the child and suicide (Esscher et al., 2016; Miller, 2002). Maternal depression in the perinatal period affects not only the mother but also the entire family. Studies indicate that children of mothers with perinatal depression are at increased risk of emotional problems, behavioral and psychiatric diagnoses as well as poor physical health and self-regulation (Agnafors et al., 2013; Gentile, 2017; Zijlmans et al., 2015). Maternal depression is also shown to

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be a risk factor for poor maternal-infant bonding (Dubber et al., 2015). Several risk factors have been identified for antenatal and postpartum depression (PPD), including history of depression, low socioeconomic status, stressful life events, low self-esteem, lack of social support, pregnancy and postpartum complications. The suggested biological pathways in PPD include fluctuations in hormonal and steroid levels (Brummelte and Galea, 2016; Iliadis et al., 2015a; Iliadis et al., 2015b; Skalkidou et al., 2012). The latest reviews suggest that hypothalamic-pituitary-adrenal dysregulation, genetic vulnerability and inflammatory processes represent the major biological predictors (Yim et al., 2015).

The role of inflammation in the pathogenesis of depression is increasingly acknowledged. In early studies, depressive symptoms were related to increased expression of circulating inflammatory markers, such as interleukin (IL)-6 (Maes et al., 1993). Later data has contributed to the understanding of more complex pathways pathophysiologically connected to depression; particularly, pro-inflammatory cytokines, such as IL-6, were found to activate the tryptophan metabolizing enzyme indoleamine-pyrrole 2,3-dioxygenase (IDO), causing reduced production of serotonin in the synaptic clefts and at the same time increased production of neurotoxic substances through the kynurenine pathway (Heyes et al., 1992; Stone and Darlington, 2002). One of the downstream products of the kynurenine pathway is quinolinic acid, which acts as an agonist of the N-methyl–D-aspartate (NMDA) glutamate-receptor, leading to glutamate release. Increased levels of the inflammation acute phase plasma C-reactive protein (CRP) have been also associated with altered glutamate metabolism in depressed patients (Haroon et al., 2016), whereas elevated levels of glutamate in some brain regions have been found in patients with major depression (Sanacora et al., 2004). These monoaminergic and glutamate hypotheses, focusing on inflammation, are discussed in relationship to the elevated risk for depression in patients treated with cytokines and the similarities of depression symptoms and symptoms of cytokine-induced diseases (Miller et al., 2009; Raison et al., 2006).

It has now been established that the peripheral immune response is signalling to the brain, despite previous notions of the brain as separated from local immune reactions (Galea et al., 2007). Despite the fact that cytokines usually do not pass the blood-brain barrier, they have been shown to signal to the central nervous system through humoral and neuronal routes, e.g. via activation of the vagus nerve (McCusker and Kelley, 2013). Cytokine receptors are found on neurons both peripherally and locally (Licinio and Wong, 1997), whereas the brain parenchymal macrophages, microglial cells, can produce pro-inflammatory cytokines as well as prostaglandins. The engagement of different immune-to-brain communication pathways, has been shown to initiate the production of pro-inflammatory cytokines by microglial cells (Dantzer et al., 2008).

During pregnancy, the female body needs to maintain a balance between protection against pathogens and tolerance against the semi-allogeneic fetus; this requires an adaptive change in the immune system function. This adaptation is to date not fully understood. Previous theories described an upregulation of the innate immune system and a downregulation of the adaptive immune system (Luppi, 2003), a shift from the T-helper cell type 1 (Th1) to the T-helper cell type 2 (Th2) system (Raghupathy, 1997). More recent research supports a more complex balance between the two systems and emphasizes the importance of regulatory functions (La Rocca et al., 2014; Mjosberg et al., 2010).

It is now believed that the immune system regulation during normal pregnancy follows three different phases. In analogy with open wounds pathophysiology, the first phase represents a pro-inflammatory state (Mor et al., 2011). During this phase, chemokines, cytokines and growth factors are produced in the endometrium and secreted into the cavity which are thought to have an important role in the implantation and placentation processes, altering the adhesion potential and providing chemoattraction to the blastocyst (Hannan et al., 2011). The second phase, coinciding with the rapid fetal growth period, is characterized by an anti-inflammatory state that has been associated with increase in well-being for many women (Mor et al., 2011). The placenta plays an important part in the adaptation of the maternal immune system that also includes a shift from cell-mediated immune response to humoral-mediated responses in the first two trimesters (Kumpel and Manoussaka, 2012). The third phase occurs prior to delivery, when immune cells migrate into the myometrium creating a pro-inflammatory state (Brewster et al., 2008). Increase of pro-inflammatory cytokines has been observed at the end of pregnancy, both in the cervical tissue during cervix ripening (Dubicke et al., 2010; Malmstrom et al., 2007; Sennstrom et al., 2000) as well as in the peripheral blood (Fransson et al., 2011). Many diseases of pregnancy, such as preeclampsia, gestational diabetes and preterm birth are thought to be associated with inflammation (Vannuccini et al., 2016).

Postpartum period adaptation includes stabilization of bodily systems to the non-pregnant state, but also the psychological and physiological adaptation needed to care for the baby. The inflammatory response that accelerates during labor (Sennstrom et al., 2000), continues into the postpartum period where healing and involution take place, possibly mediated through both pro- and anti-inflammatory mediators (Nilsen-Hamilton et al., 2003). The postpartum immune system has also been reported to shift to a Th1 repertoire (Elenkov et al., 2001), that has been associated with increased susceptibility for infection during the immune reconstitution in the postpartum period (Singh and Perfect, 2007). The peripartum period represents one of the few biological paradigms of dynamic states in adult life. It encompasses tremendous changes in hormonal levels, inflammatory parameters, stress tolerance and the nervous system (Kim et al., 2016). This whole period, from both somatic and psychological aspects, can be considered as a stressor per se. Stress during pregnancy has been linked to preterm birth and other adverse pregnancy outcomes possibly through interactions with the immune system (Christian, 2012; Coussons-Read et al., 2012a). Likewise, alterations in the stress-immune systems crosstalk during the pregnancy and peripartum could predispose to PPD (Corwin and Pajer, 2008).

The combination of the high prevalence of depression and the dramatic immune system changes in the perinatal period indicates a role of the inflammatory response in the development of depression. However, this is still a relatively unexplored area. Among the inflammatory markers, IL-6 is one of the most well-studied ones in the field of perinatal depression research. In the review by Osbourne and Monk (Osborne and Monk, 2013), some of the studies confirm an association of IL-6 levels with antenatal or postpartum depression, while others do not (Skalkidou et al., 2009). Other associated markers described in the literature are IL-1beta, Leukemia inhibitory factor receptor (LIF-R), Tumor necrosis factor-a (TNF-a), Interferon-gamma (IFN-gamma), or ratios of some of these. Although previous research supports a positive association between markers of inflammation and depression in the general population, the associations in pregnant groups have not always been reproduced (Osborne and Monk, 2013). Comparisons cannot easily be made, as individual studies assess the inflammation markers in different body fluids using different techniques and at different time points (Boufidou et al., 2009; Christian et al., 2009; Osborne and Monk, 2013). There are also indications of disparities between groups of women, for example higher general levels of IL-6 during pregnancy in African American women (Blackmore et al., 2014; Cassidy-Bushrow et al., 2012). Moreover, alterations in the stress-immune systems crosstalk could have different impact in