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RESEARCH ARTICLE

Inflammatory markers in women with postpartum depressive symptoms

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Abstract

Postpartum depression (PPD) is a devastating disorder affecting not only more than 10% of all women giving birth, but also the baby, the family, and the society. Compiling evidence suggests the involvement of the immune system in the pathophysiology of major depression; yet, the immune response in perinatal depression is not as well studied. The aim of this study was to investigate the alterations in peripheral levels of inflammatory biomarkers in 169 Swedish women with and without depressive symptoms according to the Edinburgh postnatal depression scale or the M.I.N.I neuropsychiatric interview at eight weeks postpartum. Among the 70 markers analyzed with multiplex proximity extension assay, five were significantly elevated in women with postpartum depressive symptoms in the adjusted LASSO logistic regression analysis: Tumor necrosis factor ligand superfamily member (TRANCE) (OR-per 1 *SD* increase = 1.20), Hepatocyte growth factor (HGF) (OR = 1.17) Interleukin (IL)-18 (OR = 1.06), Fibroblast growth factor 23 (FGF-23) (OR = 1.25), and C-X-C motif chemokine 1 (CXCL1) (OR 1.11). These results indicate that women with PPD have elevated levels of some inflammatory biomarkers. It is, therefore, plausible that PPD is associated with a compromised adaptability of the immune system.

KEYWORDS
cytokines, immune system, inflammation, maternal depression, pregnancy, protein markers

1 | INTRODUCTION

Postpartum depression (PPD) is a devastating disorder that affects approximately one in ten women after giving birth (O'Hara & McCabe, 2013). It has also impacts on the whole family and has been associated with developmental deficits in the offspring (Stein et al., 2014). Despite the fact that there are several known risk factors for PPD, such as history of depression, other psychiatric disorders (Wesseloo et al., 2016), and preeclampsia (Bergink et al., 2015; Hoedjes et al., 2011), there are no biological markers available.

The similarities between symptoms of depression and systematic symptoms of immune activation, the so-called "sickness behavior", as well as the increased risk of depression in immune-related diseases, have projected hypothesis on the involvement of the immune system in the pathophysiology of depression (Robinson & Klein, 2012). Increased activity of the serotonin precursor L-tryptophan metabolizing enzyme Indoleamnie-pyrrole 2,3-dioxygenase caused by cytokines (Heyes et al., 1992; Stone & Darlington, 2002) and the activated neurotoxic kynurenine metabolic pathway (Allison & Ditor, 2014) are examples that further strengthen these theories. The biological hypothesis of depression mainly focuses on neurotransmission, neuroplasticity and neurotoxicity, with multiple explanation theories (Dash, Clarke, Berk, & Jacka, 2015; Mifflin et al., 2015; Pariante & Lightman, 2008; Perlmuter et al., 2012; Spedding, 2014; Studd & Nappi, 2012; Tsuno, Besset, & Ritchie,

Significance statement

Perinatal depression is a devastating disorder and might be associated to dysfunction of immune regulation. We have identified five potential inflammatory biomarkers for postpartum depression. These results enhance our understanding of pathophysiology of the disease, while the markers may in the future be included in valuable early diagnostic tools. Preventive efforts in this field could have great impact at the individual but also societal level.

2005), and the possibility of different sub-types of depression, has been suggested (Ostergaard, Jensen, & Bech, 2011). Depression in nonpregnant/nonperinatal samples has been characterized by a low-grade inflammation, as measured by the levels of inflammatory biomarkers in the periphery (Dowlati et al., 2010; Kiecolt-Glaser & Glaser, 2002; O'Donovan et al., 2009), which is hypothesized to mirror an inflammatory process in the brain (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Licinio & Wong, 1997). However, the direction of causality between inflammation and depression are unknown (Miller & Raison, 2016).

During pregnancy, the immune system goes through a vast adaptation in order not to reject the semi-allogenic fetus and at the same time protect it against pathogens. Inflammatory responsiveness has been shown to increase toward the end of normal pregnancy (Brewster et al., 2008). Production of the cytokines Interleukin (IL)-6 and IL-8 is enhanced locally in the cervix at term pregnancy (Malmstrom et al., 2007). During cervical ripening, there is a large increase in the levels of these cytokines in the periphery (Fransson et al., 2012; Sennstrom et al., 2000). After delivery, the immune system needs to return to a nonpregnant state, while in parallel, factors that have been shown to affect the immune system and could affect mood, such as healing processes, sleep loss, variated production of oxytocin, low levels of estrogens, and loss of stress-related hormones produced by the placenta, are ongoing for months (Creti et al., 2017; Dunn, Paul, Ware, & Corwin, 2015; Kammerer, Taylor, & Glover, 2006; Kim et al., 2014; Moses-Kolko, Berga, Kalro, Sit, & Wisner, 2009; Mullington, Simpson, Meier-Ewert, & Haack, 2010; Nezi, Mastorakos, & Mouslech, 2000; Ross, Murray, & Steiner, 2005; Straub, 2007; Tsigos & Chrousos, 2002; Yuan et al., 2016).

In upcoming work, a distinct drop of several inflammatory markers from pregnancy to postpartum was noted (Bränn, Edvinsson, Punga, Sundstrom Poromaa, & Skalkidou, Manuscript). Divergent results on increasing peripheral activity of circulating cytokines from pregnancy to postpartum, have been reported (Christian & Porter, 2014); however, the differences in the direction of changes in the levels of inflammatory markers might be due to diversity in factors such as time-point of sampling. Natural killer cell cytotoxicity is suppressed during pregnancy and has been shown to remain suppressed for over 6 months in postpartum women (Groer et al., 2014). Regulatory B-cells as well as all T-regulatory cell (Treg cells) subsets, however, are significantly increased postpartum compared to the third trimester and parturition (Lima et al., 2016, 2017). Further, the postpartum period has been characterized by elevated cytokine levels and high infiltration of immune cells (Shynlova, Nedd-Roderique, Li, Dorogin, & Lye, 2013; Yoshii, Kitahara, Ueta, Matsuno, & Ezaki, 2014). Contradictory to the increased peripheral activity reported in the postpartum period, studies in rodents have indicated a decreased number of microglial cells in the brain and a suppression of the cytokine response in the maternal brain during late pregnancy and early postpartum (Haim et al., 2017; Posillico & Schwarz, 2016; Sherer, Posillico, & Schwarz, 2017).

Thus, the transition from pregnancy to postpartum is accompanied by a complex immunological adaptation, whereas the impact on mental health of this adaptation remains largely unexplored, with only a few markers studied, i.e., IL-1, IL-6, IL-8, IL-10, interferon gamma (IFN)-gamma, C-reactive protein and cortisol (Corwin et al., 2015; Groer & Morgan, 2007; Maes et al., 2000; Okun et al., 2011; Scrandis et al., 2008; Skalkidou et al., 2009) and the findings often present inconclusive results. We have previously shown that women with antenatal depression (Edvinsson et al., 2017) had lower levels of markers associated to M2-macrophages (exhibiting anti-inflammatory properties) compared with nondepressed pregnant controls.

The speculation on different subtypes of major depression may be extended to perinatal depression as well (Phillips, Sharpe, Matthey, & Charles, 2010; Putnam et al., 2017; Schiller, Meltzer-Brody, & Rubinow, 2015). The phenotypes of perinatal depression are divergent (Altemus et al., 2012; Putnam et al., 2017; Silverman et al., 2017). Some reports emphasize the significance of grouping women based on the onset of the depressive symptoms, pointing out that the timing of the symptoms could be associated with separate risk factors, pathophysiology, and even prognosis (Altemus et al., 2012). Identification of biological markers for these proposed subtypes, may facilitate development of an explanation model for their respective pathophysiology.

Due to the limited literature and the existing knowledge gaps regarding the role of the immune system in the pathophysiology of PPD, this study aimed to investigate whether the circulating levels of a panel of 92 inflammatory markers differed between women with postpartum depressive (PPD)- symptoms and nondepressed postpartum controls. In a sensitivity analysis, we separately compared participants based on the onset of depression symptoms, during pregnancy or postpartum.

2 | METHODS AND MATERIALS

2.1 | Subjects/participants

All women ≥18 years of age, not having confidential personal information, who speak Swedish and are scheduled for a routine pregnancy ultrasound at Uppsala University Hospital are invited to participate in an ongoing longitudinal project called the BASIC-study (Biology, Affect, Stress, Imaging and Cognition) (Hellgren,

Åkerud, Skalkidou, & Sundström-Poromaa, 2013; Iliadis, Comasco, et al., 2015; Iliadis, Koulouris, et al., 2015). The project is mainly based on online questionnaires that the women are asked to fill out during pregnancy at the 17th and 32nd gestational week and at six weeks postpartum. The surveys include questions about background characteristics (sociodemographic variables, psychiatric history, medical history etc.) and the Edinburgh Postnatal Depression Scale (EPDS), a screening tool for depression in the perinatal period, which is widely used in the Swedish context exhibiting a sensitivity of 72% and specificity of 88% (Cox, Holden, & Sagovsky, 1987; SBU, 2012; Wickberg & Hwang, 1996). The validated cut-offs for the use of EPDS in Sweden include a score ≥13 for depression during pregnancy (Rubertsson, Börjesson, Berglund, Josefsson, & Sydsjö, 2011) and a score ≥12 for PPD (Wickberg & Hwang, 1996). A subset of women participating in the BASIC-study, selected based on their depression scores, are invited at approximately eight weeks postpartum to take part in a sub-study at the research laboratory of the Women's Clinic at the Uppsala University Hospital (women with EDPS scores ≥14 and ≤8, at the online questionnaires at six weeks postpartum are invited as intended cases and controls, respectively). During the sub-study visit, the EPDS is filled out once more, and women also undergo the structured diagnostic M.I.N.I International Neuropsychiatric interview (MINI) (Sheehan et al., 1998). The MINI interview is widely used in both research and clinical settings although not validated in the postpartum period and it includes *inter alia* questions on depression history and anxiety. Further, venous blood samples are collected, after at least 90 min of fasting. The majority of the visits were scheduled at either at 9 a.m. or at 1 p.m. between with a range from 8 a.m. to 3 p.m.

For this nested case-control study, all women who participated in the sub-study at 8 weeks postpartum during the years 2010–2014 were included (n = 178). Excluded were women who were smoking, women with twin pregnancies and women who were on cortisone medication. The women were categorized in two groups. The first, PPD-symptoms group (n = 62), included women who screened positive for depressive symptoms postpartum (EPDS ≥ 12 at 6 or 8 weeks postpartum) and/or were positive for ongoing depressive episode at the MINI interview. Additionally, this group included women who were on antidepressants at time of blood sampling, regardless of screening results (in line with a previous study from this research group (Edvinsson et al., 2017) that showed similar inflammatory profile for all depressed women regardless of medication status). Out of these 62 women, 24 were categorized as having depressive symptoms based on EPDS scores ≥12 solely, 25 women had EPDS ≥ 12 and did also report having an ongoing depression episode according to the MINI interview. Five women were categorized based on EPDS ≥ 12 while also being on antidepressants and the remaining eight had EPDS scores <12 and were categorized as having depressive symptoms based on ongoing depression episode according to the MINI interview (n = 1), positive on the MINI and also on antidepressants (n = 1) or taking antidepressants only (n = 6). The second group, nondepressed controls, included women who were negative for depressive symptoms at all the survey time points and negative for ongoing depressive episode in the MINI interviews (n = 107). Further, women with depressive symptoms during pregnancy but without depressive symptoms postpartum were excluded from the analysis since this group was too small to perform meaningful analyses (n = 9), resulting in 169 women included in the statistical analyses.

For the sensitivity analysis, the women in the PPD-symptoms group were separated based on the onset of the symptoms; (1) during pregnancy (EPDS ≥ 13 in gestational week 17 or 32 and EPDS ≥ 12 at 6 or 8 weeks postpartum and/or ongoing depression episode according to the MINI interview; or use of antidepressants during pregnancy and postpartum) (n = 40) or (2) after delivery (EPDS < 13 in gestational week 17 and 32 and EPDS ≥ 12 at 6 or 8 weeks postpartum and/or ongoing depression episode according to the MINI interview; or no use of antidepressants during pregnancy but use of antidepressants postpartum) (n = 22).

2.2 | Inflammatory biomarkers

Blood samples were collected and plasma were prepared by centrifugation for 10 min at room temperature in 1,500 R.C.F and stored in −70°C within one hr. For each plate, 90 thawed plasma samples were transferred to 96-well plates along with 6 controls (three negative controls (buffer) and three interplate controls).

The relative levels of 92 inflammation-related proteins was analyzed using the Proseek Multiplex Inflammation I panel (Olink Bioscience, Sweden) based on multiplex extension assay (PEA) (Assarsson et al., 2014; Lundberg, Eriksson, Tran, Assarsson, & Fredriksson, 2011). The proteins included in the panel, with their Uniprot identities, are listed in (Larsson et al., 2015). The multiplex PEA technology uses two paired oligonucleotide-conjugated antibodies as probe for each protein. When a pair of probes recognize and bind to a common target protein, the DNA oligonucleotides are brought in proximity and are able to hybridize, allowing enzymatic DNA polymerization to produce a new amplifiable DNA molecule (amplicon). The amplicon is subsequently detected and quantified using a microfluidic real-time PCR platform. The technology has sensitivity down to fg/mL, and currently it cannot be used to report absolute quantification but only relative protein values, allowing comparison between groups of samples.

Briefly, 1 μL of the plasma sample was mixed with 3 μL incubation mix containing 92 pairs of probes, each consisting of an antibody labeled with a unique corresponding DNA oligonucleotide. All samples were spiked with two incubation controls (green fluorescent protein and phy-coerythrin), one extension control and one detection control. The mixture was incubated at 4°C overnight. Then, 96 μL extension mix containing PEA enzymes and PCR reagents was added, and the samples were incubated for 5 min at room temperature before the plate was transferred to the thermal cycler for an initial DNA extension at 50°C for 20 min followed by 17 cycles of DNA amplification. A 96.96 Dynamic Array IFC

(Fluidigm, South San Francisco, CA, USA) was prepared and primed according to the manufacturer's instructions. In a new plate, 2.8 μL of sample mixture was mixed with 7.2 μL detection mix from which 5 μL was loaded into the right side of the primed 96.96 Dynamic Array IFC. The unique primer pairs for each protein were loaded into the left side of the 96.96 Dynamic Array IFC, and the protein expression program was run in BioMarkTM HD Fluidigm real-time PCR (Fluidigm, South San Francisco, CA, USA) according to the instructions for Proseek.

Results were presented in Normalized Protein Expression (NPX) in log2. Using Olink Wizard, obtained in GenEx software, the quantification cycle (Cq) values, generated in the real-time PCR, were normalized against extension- and interplate controls and a correction factor. Subtracting the extension control from the Cq-value of every sample corrects for technical variation and subtracting the interplate control compensate for possible variation between runs. The NPX is further calculated by normalization against the calculation correction factor. To summarize, the NPX is calculated in three steps from the Cq-values: (i) $\Delta Cq_{sample} = Cq_{sample} - Cq_{extensioncontrol}$, (ii) $\Delta\Delta Cq = \Delta Cq_{sample} - \Delta Cq_{interplatecontrol}$, (iii) NPX = Correction factor – $\Delta\Delta Cq_{sample}$. Validation data for all antibodies used in this panel and the performance of each assay are available at the manufacture's webpage of (www.olink.com).

With this calculation NPX values corresponds to a relative quantification between samples and with a high NPX value corresponding to a high protein concentration. Limit of detection (LOD) was determined for each biomarker based on the mean value of triplicate negative controls analyzed in each run. Only markers with values above LOD for more than 50% of the samples were used for further statistical analyses.

2.3 | Statistics

Seventy-one out of 92 markers had normalized protein expression for more than 50% of the participants. The results for one marker (Brain-derived neurotrophic factor, BDNF) has recently been appointed with a potential technical issue and was therefore excluded resulting in 70 markers in the statistical analyses. For markers that still had missing values, these where replaced by the LOD value divided by the square root of two (NHANES, 2013). Descriptive univariate analyses were performed using Chi-square test, Mann-Whitney U test and Independent *t*-test as appropriate.

For the statistical analyses, PPD-symptoms were considered the outcome, and the plasma levels of the inflammatory biomarkers postpartum were considered the exposure variables. Crude and adjusted analyses were performed using multiple logistic regressions, with one model for each inflammatory marker (i.e., only one marker was included at a time). Further, the crude and adjusted analyses were adjusted for multiple testing using the Bonferroni correction. Finally, to confirm the results our main analysis was performed, taking multiple comparisons and possible correlations between markers into account, using adjusted LASSO logistic regression (including all confounders and inflammatory markers in one model). LASSO logistic regression is a form of penalized logistic regression, where the odds ratios are purposefully "shrunk" toward 1. An odds ratio that is not 1 is considered to be significant. LASSO regression is used to perform variable selection and to constrain the effect estimates, which is useful when there are many correlated exposures. The Bonferroni correction is known to be overly conservative, which is why we chose LASSO as our main analysis tool.

For the adjusted logistic regressions, a modified version of the 10% cut-off method was applied to choose possible confounders (Mickey & Greenland, 1989). The following variables were tested as possible confounders: age at time of delivery, prepregnancy BMI, educational level (grouped into high school level or higher), employment status (grouped into parental leave/sick leave/unemployed or fulltime/part-time/student), marital status, parity, infant gender, premature birth, delivery mode (grouped into vaginal/vacuum extraction or cesarean section), IVF-treatment, pregnancy complications based on self-rated questions, breastfeeding (grouped into yes or partly or no), history of depression (previous psychological contact or medical history of depression), history of inflammatory or autoimmune diseases, days to or from delivery until blood sample collection, medication at time of blood sampling (antibiotics, asthma/allergy medication, birth control pills, NSAID, paracetamol, levothyroxine and blood pressure medication), MINI diagnosis of anxiety syndrome (Panic syndrome, Agoraphobia, Social phobia, Obsessive compulsive disorder, Alcohol or drug addiction, Posttraumatic stress disorder, Eating disorder or Generalized anxiety disorder) and lifetime history of manic or hypomanic symptoms or psychosis according to the MINI interview. The method was modified to ensure that a consistent confounder group was used for all exposures. Markers that significantly predicted (α = 5%, no correction for multiple tests) the outcome were identified using logistic regression and the change in the log-odds-ratio of the inflammatory markers when introducing the potential confounder was recorded. Only the variables that changed the inflammation marker's log-odds-ratio by more than 10% for more than 10% of the significant markers were considered possible confounders. The 10% cut-off method, revealed age, history of depression, MINI diagnosis of anxiety, antihypertensive medications, premature delivery, employment status, delivery mode, asthma/allergy medications, NSAIDs, levothyroxine and lifetime history of manic or hypomanic symptoms or psychosis according to the MINI interview as possible confounders. As breastfeeding might be considered as a mediator rather than a confounder, the adjusted analysis was made in two steps; (a) not including breastfeeding and (b) including breastfeeding in the model.

For the sensitivity analysis, significant markers in the adjusted LASSO logistic regression were used as exposures to compare (1) women with pregnancy onset of depressive symptoms to nondepressed controls, (2) women with postpartum onset of depressive symptoms to nondepressed controls and (3) women with pregnancy onset of depressive symptoms to women with postpartum onset of depressive symptoms, separately in logistic regressions.

TABLE 1 Demographic characteristic; means, standard deviations (*SD*), inter quartile range (IQR) and *n* (%), of women with Postpartum depressive (PPD)-symptoms, and Nondepressed controls

Variable	PPD-symptoms† (*n* = 62)	Nondepressed controls (*n* = 107)	*p*-value‡	Average change in OR	% of significant markers changed
Background characteristics					
Age at time of delivery, years, (Mean ± *SD*)	30.5 ± 4.9	32.1 ± 4.0	0.028*	0.102	62.5
Prepregnancy BMI, km/m2, (Median, IQR)	23.1. 4.6	23.1. 4.1	0.831	0.026	0
Education University/college, *n* (%)	50 (80.6)	91 (85.0)	0.458	0.016	0
Employment (parental leave/sick leave/ unemployed), *n* (%)	8 (12.9)	3 (2.8)	0.010*	0.066	12.5
History of depression, *n* (%)	48 (77.4)	52 (44.8)	0.000*	0.188	62.5
Inflammatory or autoimmune disease, *n* (%)	3 (4.8)	1 (0.9)	0.108	0.037	0
Married or cohabiting, *n* (%)	62 (100.0)	105 (98.1)	0.279	0.031	0
Pregnancy variables					
Parity (nulliparous), *n* (%)	35 (56.5)	54 (50.5)	0.453	0.022	0
Infant gender (boy), *n* (%)	33 (53.2)	52 (48.6)	0.562	0.01	0
IVF-treatment, *n* (%)	5 (8.1)	9 (8.4)	0.937	0.003	0
Pregnancy complications, *n* (%)	27 (43.5)	43 (40.2)	0.669	0.007	0
Delivery variables					
Premature, *n* (%)	1 (1.6)	6 (5.6)	0.209	0.058	25.0
Delivery mode (cesarean section), *n* (%)	7 (11.3)	21 (19.6)	0.160	0.066	12.5
Postpartum variables					
Days from delivery blood sample collected, (Mean ± *SD*)	67.8 ± 11.1	69.5 ± 9.7	0.362	0.022	0
Breastfeeding, *n* (%)			0.009*	0.155	62.5
Breastfeeding only	38 (61.3)	88 (82.2)			
Breastfeeding and formula	16 (25.8)	14 (13.1)			
Formula only	8 (12.9)	5 (4.7)			
Antibiotics at time of sampling, *n* (%)	2 (3.2)	1 (0.9)	0.277	0.029	0
Asthma/allergy medication at time of sampling, *n* (%)	3 (4.8)	2 (1.9)	0.272	0.032	12.5
Birth control pills at time of sampling, *n* (%)	3 (4.8)	7 (6.5)	0.651	0.009	0
Nonsteroidal anti-inflammatory drugs (NSAID) at time of sampling, *n* (%)	3 (4.8)	1 (0.9)	0.108	0.071	12.5
Paracetamol at time of sampling. *n* (%)	3 (4.8)	2 (1.9)	0.272	0.034	0
Levothyroxine at time of sampling	2 (3.2)	2 (1.9)	0.576	0.023	12.5
Blood pressure medication at time of sampling, *n* (%)	0 (0.0)	5 (4.7)	0.084	0.079	37.5
Lifetime manic/hypomanic symptoms/ psychosis according to MINI, *n* (%)	8 (12.9)	2 (1.9)	0.005*	0.054	12.5
MINI diagnosis anxiety, *n* (%)	28 (45.2)	17 (15.9)	0.000*	0.128	50.0

Note. †Postpartum depressive (PPD)- symptoms; EPDS ≥ 12 or positive on ongoing depression according to Mini International Neuropsychiatric Interview (MINI) or on antidepressants

Average change in odds ratio (OR) when adding variable as confounder and percentage of significant markers changed more than ten percentages when adding the variable

*p-value < 0.05

‡p-values derived from Chi-square test, Mann-Whitney U test and Independent t-test

3 | RESULTS

Women with PPD-symptoms were slightly younger, were more likely to be on parental leave/sick leave or unemployed, reported lower rates of breastfeeding and were more likely to have anxiety, a history of depression or previous manic or hypomanic symptoms or psychosis according to the MINI interview, compared with the non-depressed controls (Table 1).

When not considering multiple testing, eight biomarkers were found to be significantly higher among women with PPD-symptoms in the crude logistic regression model, however, none of the markers were significant after considering multiple testing using Bonferroni correction. Furthermore, when again not considering multiple testing, six biomarkers were significantly higher among women with PPD-symptoms in the adjusted logistic regression model (a) where breastfeeding were not included (Tumor necrosis factor ligand superfamily member 11 (TRANCE) (OR = 2.73, 95% CI = 1.33, 5.63), Hepatocyte growth factor (HGF) (OR = 5.25, 95% CI = 1.52, 18.16), IL-18 (OR = 2.07, 95% CI = 1.13, 3.82), TRANCE 14 (TNFSF14(/LIGHT)) (OR = 2.46, 95% CI = 1.06, 5.70), Fibroblast growth factor 23 (FGF-23) (OR = 3.10, 95% CI = 1.35, 7.10) and C-X-C motif chemokine 1 (CXCL1) (OR = 2.33, 95% CI = 1.41, 3.84)) and four markers were significant in the adjusted logistic regression model (b) including breastfeeding (TRANCE (OR = 2.39, 95% CI = 1.15, 4.99), HGF (OR = 4.84, 95%CI = 1.39, 16.90), FGF-23 (OR = 2.50, 95% CI = 1.06, 5.89) and CXCL1 (OR = 2.32, 95% CI = 1.39, 3.86)). However, these results were not significant after Bonferroni correction.

Including all confounders identified in the 10% cut-off method and all inflammatory markers in a multivariate adjusted LASSO logistic regression model (which accounts for multiple comparisons in a less conservative manner than Bonferroni correction), five biomarkers were identified to be significantly higher among women with PPD-symptoms (TRANCE penalized OR = 1.20, HGF penalized OR = 1.17 IL-18 penalized OR = 1.06, FGF-23 penalized OR = 1.25 and CXCL1 penalized OR = 1.11) (Table 2).

Moreover, in the sensitivity analysis based on time of onset of depressive symptoms (pregnancy vs. postpartum), three out of the five markers in the adjusted LASSO logistic regression were significantly higher in women with depressive symptoms already during pregnancy than the nondepressed controls (TRANCE (OR = 2.09, 95% CI = 1.08, 4.05), HGF (OR = 4.39, 95% CI = 1.41, 13.66) and IL-18 (OR = 2.84, 95% CI = 1.33, 6.08)) in the crude logistic regression model. Similar results were found when studying the women with postpartum onset to nondepressed controls, although not reaching the statistical significance. No differences in inflammatory markers were found when comparing women with pregnancy onset to women with postpartum onset (Supporting information Table 1).

4 | DISCUSSION

In this study, we aimed to investigate potential differences in plasma levels of inflammatory markers postpartum between women with and without depressive symptoms. We identified higher plasma levels for five inflammatory markers, TRANCE, HGF, IL-18, FGF-23 and CXCL1, among women with PPD symptoms, compared with nondepressed controls. The markers identified in this study are linked to early stress response and depressive symptoms in other studies (Sawicki et al., 2015; Yang et al., 2010). Several markers are linked to pro-inflammatory processes while others, such as HGF, have anti-inflammatory properties and are linked to restorative mechanisms (Jamali-raoufi, Haghani, Roghani, Fahanik-Babaei, & Baluchnejadmojarad, 2017; Wright & Harding, 2015).

The inflammatory markers found in the main LASSO logistic regression were also significant in the regression analyses that were not corrected for multiple testing. This adds credibility to our results, as two different statistical methods identified the same inflammation markers as being associated with depressive symptoms. While these inflammation markers did not remain significant after applying the Bonferroni correction, this is not unexpected due to the well-known conservative nature of the Bonferroni correction.

Elevated levels of pro-inflammatory markers have been reported in other studies investigating the role of the immune system in patients with major depression (Dowlati et al., 2010; Howren, Lamkin, & Suls, 2009; Kiecolt-Glaser & Glaser, 2002; Kohler et al., 2017; Liu, Ho, & Mak, 2012; O'Donovan et al., 2009). TRANCE is best known for its' role in osteoclast differentiation and levels of TRANCE has been seen to increase during pregnancy (Azim et al., 2015). TRANCE is, however, not extensively studied in the context of depressive symptoms. However, one recent study demonstrated that ketamine treatment reduced peripheral levels of TRANCE in patients with major depression (Kadriu et al., 2017). Further, there are indications in the literature that HGF has neuroprotective functions (Jamali-raoufi, Haghani, Roghani, Fahanik-Babaei, & Baluchnejadmojarad, 2017; Wright & Harding, 2015). Lower HGF levels have been described in individuals with more severe clinically diagnosed depression (Russo, 2010), and an experimental study in rats suggests that inhibition of HGF might trigger depressive-like behavior (Wakatsuki et al., 2007). However, HGF have been reported elevated in older adults with subclinical symptoms of depression (Arnold et al., 2012). Moreover, elevated levels of IL-18 have been reported in response to delivery in women with depressive symptoms during pregnancy (Fransson et al., 2012). Increased IL-18 has also been associated with poststroke depression (Yang et al., 2010), while IL-18 levels have been reported to be lower in depressed patients with chronic disease (Bossu et al., 2015; Fan, Luo, Ou, & He, 2017). Furthermore, growth factors play a significant role in the maintenance of the central nervous system (Ford-Perriss, Abud, & Murphy, 2001) and dysregulation of several fibroblast growth factor system transcripts (including FGF-23) has been reported in frontal cortical regions of brains from human subjects with major depressive disorder (Evans et al., 2004). Lithium, used in treatment of major depression, has been reported to upregulate FGF-23 formation (Fakhri et al., 2014). FGF-23 is an important psychological down-regulator of the calcium up-regulating hormone 1,25-dihydroxyvitamin D (Saito & Fukumoto, 2009) and deficiencies of calcium have been associated to depression (Hullett, Potkin, Levy, & Ciasca, 1988; Kabir, Martinez-Rivera, & Rajadhyaksha, 2017; Sourial-Bassillious, Rydelius, Aperia, & Aizman, 2009). Lastly, upregulation of CXCL1 in the periphery as well as in the CNS, has been previously described in response to various stressors (Sawicki et al., 2015).

To summarize the existing literature, the markers HGF, IL-18 and FGF-23 have separately been reported lower in severe forms of depression, while high levels of IL-18 and CXCL1 have been associated

TABLE 2 Mean Normalized Protein eXpression (NPX) value and standard deviation (*SD*) of inflammatory markers for women with postpartum depressive (PPD)-symptoms and the nondepressed controls and *p*-values from logistic regression models and adjusted LASSO logistic regression

Inflammatory marker	PPD-symptoms[†] (*n* = 62), mean NPX (±*SD*)	Nondepressed Controls[‡] (*n* = 107), mean NPX (±*SD*)	p-value crude	*p*-value adjusted[§]	*p*-value adjusted[¶]	estimate LASSO
TRANCE	3.48 (0.25)	3.25 (0.35)	0.012*	0.006*	0.020*	1.20*
HGF	5.56 (0.18)	5.42 (0.09)	0.018*	0.009*	0.013*	1.17*
MCP–1	9.14 (0.17)	9.01 (0.09)	0.019*	0.128	0.148	1.00
IL18	6.81 (0.34)	6.60 (0.25)	0.019*	0.045*	0.081	1.06*
TNFSF14	0.70 (0.53)	0.50 (0.13)	0.027*	0.036*	0.071	1.00
TRAIL	7.54 (0.06)	7.45 (0.06)	0.029*	0.106	0.224	1.00
FGF23	1.68 (0.21)	1.52 (0.20)	0.037*	0.008*	0.036*	1.25*
CXCL1	7.83 (0.77)	7.56 (0.70)	0.050*	0.001*	0.001*	1.11*
CXCL10	8.34 (1.39)	8.04 (0.57)	0.051	0.030*	0.038*	1.00
MCP4	1.85 (0.32)	1.70 (0.17)	0.054	0.014*	0.037*	1.00
IL–7	1.80 (0.41)	1.64 (0.23)	0.062	0.007*	0.032*	1.00
VEGFA	9.77 (0.11)	9.67 (0.11)	0.070	0.076	0.114	1.00
IL–6	1.61 (0.57)	1.40 (0.49)	0.076	0.120	0.205	1.00
FGF21	2.82 (1.57)	2.47 (1.55)	0.085	0.211	0.155	1.00
IL–8	4.86 (0.43)	4.68 (0.36)	0.091	0.247	0.202	1.00
TGFA	0.12 (0.22)	0.02 (0.04)	0.091	0.060	0.037*	1.00
OSM	2.11 (0.95)	1.89 (0.54)	0.093	0.092	0.085	1.00
CXCL11	6.59 (1.02)	6.36 (0.58)	0.100	0.014*	0.034*	1.00
ENRAGE	0.88 (0.61)	0.72 (0.23)	0.105	0.020*	0.037*	1.00
SCF	7.31 (0.11)	7.23 (0.09)	0.106	0.257	0.347	1.00
CXCL6	6.50 (0.74)	6.31 (0.46)	0.124	0.086	0.159	1.00
NT3	1.84 (0.40)	1.70 (0.33)	0.133	0.226	0.347	1.00
MMP10	5.53 (1.05)	5.34 (0.42)	0.159	0.275	0.443	1.00
CD–5	3.23 (0.20)	3.15 (0.07)	0.159	0.366	0.326	1.00
DNER	6.23 (0.07)	6.18 (0.04)	0.161	0.199	0.095	1.00
TNFB	2.81 (0.26)	2.71 (0.15)	0.161	0.672	0.857	1.00
LAPTGF beta1	5.36 (0.18)	5.28 (0.13)	0.192	0.068	0.207	1.00
ADA	4.44 (0.55)	4.33 (0.11)	0.224	0.126	0.165	1.00
IL–18R1	5.56 (0.24)	5.48 (0.16)	0.240	0.293	0.612	1.00
MPC3	0.54 (0.27)	0.65 (0.35)	0.247	0.196	0.118	1.00
FGF19	7.20 (0.88)	7.03 (0.87)	0.257	0.418	0.483	1.00
CCL228	1.47 (0.27)	1.56 (0.25)	0.273	0.633	0.575	1.00
OPG	9.24 (0.15)	9.29 (0.09)	0.334	0.165	0.283	1.00
CST5	4.88 (0.25)	4.95 (0.20)	0.336	0.163	0.160	1.00

(Continues)

TABLE 2 (Continued)

Inflammatory marker	PPD-symptoms[†] (*n* = 62), mean NPX (±*SD*)	Nondepressed Controls[‡] (*n* = 107), mean NPX (±*SD*)	p-value crude	*p*-value adjusted[§]	*p*-value adjusted[¶]	estimate LASSO
CDCP1	1.48 (0.15)	1.42 (0.17)	0.337	0.155	0.219	1.00
CCL19	8.52 (0.49)	8.41 (0.55)	0.348	0.926	0.912	1.00
CD6	3.07 (0.37)	3.00 (0.18)	0.390	0.527	0.481	1.00
CXCL9	5.54 (0.64)	5.64 (0.69)	0.422	0.798	0.891	1.00
AXIN1	2.06 (1.84)	2.21 (1.50)	0.441	0.605	0.449	1.00
CSF−1	6.92 (0.06)	6.89 (0.05)	0.467	0.454	0.545	1.00
Flt33L	8.09 (0.17)	8.05 (0.16)	0.470	0.560	0.491	1.00
CASP8	0.22 (0.63)	0.15 (0.17)	0.477	0.347	0.469	1.00
BetaNGF	0.35 (0.08)	0.37 (0.05)	0.520	0.951	0.835	1.00
FGF5	0.45 (0.08)	0.50 (0.23)	0.525	0.945	0.949	1.00
IL−12B	3.63 (0.31)	3.58 (0.30)	0.553	0.540	0.618	1.00
4EBP1	4.56 (1.10)	4.48 (0.62)	0.568	0.587	0.701	1.00
IL−10	2.11 (0.22)	2.17 (0.45)	0.578	0.518	0.504	1.00
CD40	7.96 (0.23)	7.92 (0.19)	0.610	0.883	0.950	1.00
CX3CL1	4.87 (0.16)	4.84 (0.12)	0.617	0.899	0.776	1.00
SLAMF1	1.33 (0.48)	1.29 (0.20)	0.636	0.670	0.831	1.00
CXCL5	9.87 (1.70)	9.78 (1.57)	0.684	0.064	0.077	1.00
CCL20	5.52 (0.78)	5.46 (0.70)	0.703	0.779	0.818	1.00
MIP−1alpha	1.36 (0.16)	1.39 (0.15)	0.706	0.404	0.291	1.00
LIFR	1.80 (0.10)	1.78 (0.07)	0.710	0.818	0.591	1.00
IL−17C	0.85 (0.30)	0.82 (0.45)	0.764	0.775	0.748	1.00
CCL4	4.11 (0.23)	4.13 (0.29)	0.786	0.821	0.939	1.00
TWEAK	8.40 (0.13)	8.39 (0.06)	0.786	0.698	0.476	1.00
CD244	5.19 (0.12)	5.17 (0.15)	0.789	0.236	0.304	1.00
CCL225	5.21 (0.40)	5.18 (0.30)	0.816	0.877	0.878	1.00
MMP1	0.94 (0.72)	0.91 (0.72)	0.828	0.241	0.371	1.00
MCP2	7.75 (0.60)	7.78 (0.60)	0.839	0.905	0.909	1.00
CCL23	9.06 (0.22)	9.05 (0.17)	0.848	0.556	0.778	1.00
TNFRSF9	5.37 (0.15)	5.36 (0.10)	0.860	0.958	0.960	1.00
SIRT2	2.87 (1.90)	2.85 (1.15)	0.884	0.905	0.861	1.00
STAMPB	2.95 (1.28)	2.97 (0.72)	0.884	0.934	0.877	1.00
uPA	9.71 (0.06)	9.71 (0.06)	0.944	0.483	0.552	1.00
IL−15RA	−0.10 (0.14)	−0.11 (0.12)	0.967	0.726	0.623	1.00
hGDNF	1.22 (0.16)	1.22 (0.17)	0.982	0.802	0.722	1.00

Inflammatory marker	PPD-symptoms† (*n* = 62), mean NPX (±*SD*)	Nondepressed Controls‡ (*n* = 107), mean NPX (±*SD*)	p-value crude	*p*-value adjusted§	*p*-value adjusted¶	estimate LASSO
IL-10RB	4.96 (0.18)	4.96 (0.09)	0.986	0.804	0.824	1.00
CCL11	6.87 (0.17)	6.86 (0.28)	0.988	0.748	0.679	1.00

Notes. †Postpartum depressive (PPD)- symptoms; EPDS ≥ 12 or positive on ongoing depression according to Mini International Neuropsychiatric Interview (MINI) or on antidepressants

§Adjusted for Age, History of depression, MINI diagnosis anxiety, Blood pressure medication, Premature, Employment, Delivery mode, Asthma/allergy medication, NSAID, Levothyroxine, MINI diagnosis history of manic or hypomanic symptoms/psychosis ‡Nondepressed Controls; EPDS < 12 and negative on ongoing depression according to Mini International Neuropsychiatric Interview (MINI) and not on antidepressants

¶Further adjusted even for Breastfeeding.

* *p*-value < 0.05

to stress responses. The analysis in the present study controlled for the effects of previous depressive episodes, anxiety and lifetime history of manic or hypomanic symptoms—all risk factors for more severe forms of depression (Hawton, Casanas, Haw, & Saunders, 2013). Further, the delivery process triggers the hypothalamic–pituitary–adrenal axis, resulting in high levels of cortisol peaking the first 24 hr after the delivery (Chrousos, Torpy, & Gold, 1998), which simulates a stress-induced immune response. Therefore, we hypothesize that the expression of these markers may differ in patients with a longer history of disease and that our results might be comparable to those seen in a stress response, which might be maladaptive in women with mild to moderate depressive symptoms. Accordingly, stress, as well as depressive symptoms during pregnancy, have been associated with exaggerated inflammatory responses to immune challenges (Christian, Franco, Iams, Sheridan, & Glaser, 2010).

We have previously reported that the plasma levels of several markers associated to anti-inflammatory M2-macrophages are lower in pregnant women with antenatal depressive symptoms compared with controls (Edvinsson et al., 2017). The majority of the markers found elevated in the present study are, however, considered pro-inflammatory. This leads us to speculate that while women depressed during pregnancy show decreased activation of the anti-inflammatory response, mainly driven by M2-macrophages (Brown, von Chamier, Allam, & Reyes, 2014), women with PPD might have decreased capacity in downregulating the pro-inflammatory response after the M1 macrophage phase triggered around delivery (Romero et al., 2006). It is thus plausible that women with depressive symptoms exhibit either an impaired cortisol reactivity or a less effective decrease of inflammation in response to glucocorticoids after the delivery (Gillespie & Nemeroff, 2005; Shelton, Schminkey, & Groer, 2015). Some inflammatory markers that have previously often been related to depression, such as IL-6, IL-8 and, IL-10 and IL-1, were not among the markers that differed statistically significantly between the groups in this study, although IL-6 and IL-8 reached borderline significance, with $p < 0.10$ in the crude model. Furthermore, TNF, IFN-γ, IL-1 and IL-13 that have previously been linked to perinatal depression could not be compared, as they were among the markers below the LOD.

In a sensitivity analysis, we found no evidence that the observed associations between inflammatory markers and PPD-symptoms are different depending on the onset of depressive symptoms, as no differences were found when comparing the women with pregnancy onset and postpartum onset. These results indicate that there might not be major differences in immune function between the depressive groups, despite different time of onset.

The simultaneous assessment of a large number of inflammatory biomarkers, the sensitive PEA method used for analyzing the markers and the combination of a widely used screening tool specific for perinatal depression, EPDS, complemented by the MINI interview are among the strengths of this study. However, the results might not be truly representative for the background population. The BASIC-cohort includes women that are older, have higher education level, and fewer pregnancy complications than the general population.

Furthermore, women with the most severe forms of PPD are probably not included in this sub-study, which required that the women actively participated in a laboratory visit. Some information in the BASIC-study is self-reported, such as pregnancy complications, which might potentially introduce a recall bias. Unfortunately, some of the relevant markers reported in the literature, such as TNF, IFN-γ and IL-13 (Blackmore et al., 2011; Christian, Franco, Glaser, & Iams, 2009; Fransson et al., 2012; Groer & Morgan, 2007), had to be excluded from our analyses due to levels under LOD for most participants.

In conclusion, this study revealed five new candidate biomarkers for PPD, including TRANCE, HGF, IL-18, FGF-23 and CXCL1, and found no significant support for differences in inflammatory parameters among subgroups according to PPD onset, before or after delivery. The markers found to differ among depressed and nondepressed individuals in this study are not distinct enough to be used as diagnostic tools, but future research should evaluate their inclusion in more complex algorithms, combining biological markers and other known risk factors.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Writing - Original Draft*, E.B. and E.F. *Formal Analysis*, E.B., E.F. and R.W. *Conceptualization*, F.C.P., I.S-P. and A.S., *Writing - Review & Editing Preparation*, E.B., E.F., J.C., Å.E. F.C.P., I.S-P. and A.S *Methodology*, M.K-M., *Supervision*, A.S.

DATA ACCESSIBILITY

The data generated and analyzed during the current study are available from the corresponding author on reasonable request.

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