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SHORT COMMUNICATION

The association of serum C-reactive protein with the occurrence and course of postpartum depression

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Abstract

CRP has been positively correlated with depressive symptomatology but this has received less study in postpartum depression (PPD). In this secondary analysis of a trial of PPD treatment, depressive symptoms (Structured Interview Guide for the Hamilton Depression Rating Scale—Atypical Depression Symptoms (SIGH-ADS$_{29}$)) and serum CRP levels were assessed and associations between CRP and SIGH-ADS$_{29}$ scores evaluated. The associations between baseline log CRP and depression response and remission were also assessed. Of the 35 women included, neither baseline log CRP nor exit log CRP was significantly associated with SIGH-ADS$_{29}$ score. Baseline CRP was not associated with response or remission. In this sample of women with PPD, CRP was not associated with depressive symptoms nor response to treatment.

Keywords Postpartum depression · Inflammation · C-reactive protein · CRP

Introduction

Recent evidence suggests that major depressive disorder (MDD) is associated with immune dysregulation and that a pro-inflammatory milieu contributes to depressive symptomatology both in the general population (Howren et al. 2009) and during pregnancy (Maes et al. 2002). One measure of an activated inflammatory response is a rise in acute phase reactant proteins such as C-reactive protein (CRP). A positive association between elevated CRP levels and depressive symptoms in a subset of non-pregnant patients has been described (Howren et al. 2009). Moreover, in these populations, CRP was associated with a decreased likelihood of response to traditional psychotherapeutic and psychopharmacologic treatments (Lanquillon et al. 2000). The use of CRP holds promise as a marker to personalize care for patients with MDD as it may differentiate patients who respond to classes of antidepressants (Jha et al. 2017).

The need for biomarkers of disease and treatment response is even more pronounced in the perinatal setting and literature on an association between perinatal depression and inflammation is emerging (Chang et al. 2018). Given the overlap in symptomatology between postpartum physiology and postpartum MDD, biomarkers of depression could help with the accurate diagnosis of MDD. Furthermore, as only one third of women with perinatal depression achieve a sustained remission with treatment, predictors of response would be helpful for patient monitoring and management. However, during pregnancy and the postpartum period, profound alterations in the adaptive immune system occur and specific study of this patient population is needed. The objective of this study was to examine the relationship between CRP levels and depressive symptomatology in the postpartum period. A secondary goal was to determine whether CRP levels predict response to antidepressant treatment in the postpartum period.

Methods

This is a secondary analysis of a randomized trial of transdermal estradiol for the treatment of postpartum MDD. Full

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details of the study are described in detail elsewhere (Wisner et al. 2015). In brief, women with postpartum MDD were randomized to either transdermal estradiol (E2), sertraline, or placebo for 8 weeks. The Structured Interview Guide for the Hamilton Depression Rating Scale—Atypical Depression Symptoms (SIGH-ADS$_{29}$) was used to measure depressive symptoms. Primary outcomes were treatment response (reduction of SIGH-ADS$_{29}$ score by > 50%) and remission of depression (exit SIGH-ADS$_{29}$ score ≤ 8). Secondary outcomes included depressive symptomatology measured continuously using the SIGH-ADS$_{29}$.

Serum was collected at baseline and at exit (between 4 and 8 weeks post-study entry) study visits. CRP levels in these samples were measured on the Roche Cobas c311 chemistry analyzer (Roche Diagnostics, Indianapolis, IN 46250) by a latex particle enhanced immunoturbidimetric assay from Roche Diagnostics. CRP levels at both baseline and exit study visits were compared among the three treatments. Because depression scores, response to treatment, and CRP levels did not differ by treatment, these variables were analyzed for the entire study group without stratification by treatment arm. The primary study showed that the treatments did not differ with regard to either response or remission (Wisner et al. 2015).

For the primary analysis, the association between factors that could confound the association between postpartum MDD and CRP levels was measured. Those with significant associations with CRP were considered to be potential confounders. SIGH-ADS$_{29}$ scores, both at baseline and study exit, were then correlated with CRP levels using similar methodology. In addition, CRP levels were compared between women with mild and women with severe depression. A multivariable linear regression was performed for the outcome of baseline SIGH-ADS$_{29}$ score. Multivariable linear regression was conducted using baseline CRP as the predictor and depression scores at exit as the outcome while controlling for potential confounders.

CRP levels were dichotomized at 3 mg/L. Sensitivity analyses utilized a cutoff of 5 mg/L. The frequencies of high CRP at each time point were similar across the study arms and so associations were analyzed for the entire study group without stratification by treatment arm. The association between high CRP at baseline and at study exit with the confounders listed above was examined. SIGH-ADS$_{29}$ scores were then compared between dichotomized CRP levels at each time point using Student's *t* test. Multivariable regressions were used to control for potential confounders.

To examine the predictive relationship of baseline CRP with response to treatment, we examined the association of baseline CRP with response (defined as reduction in SIGH-ADS$_{29}$ by at least 50%) and remission (defined as an SIGH-ADS$_{29}$ ≤ 8) of postpartum MDD. Analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL). All tests were two tailed and $p < 0.05$ was used to define statistical significance. The data were de-identified prior to analysis and consequently, this study was considered exempt from review by the Institutional Review Board of Northwestern University.

Results

Women ($N = 35$) had both baseline and exit serum specimens available for CRP analysis. The median (interquartile range) CRP values at baseline and at study exit were 3.62 mg/L (1.47–6.83) and 3.47 mg/L (1.44–7.28), respectively. After examining distributions of CRP levels at baseline and study exit, we log transformed these estimates to meet the normality assumption for all subsequent analyses.

Baseline clinical characteristics of the sample are shown in Table 1. Baseline mean log CRP levels were not significantly different when stratified by history of prior MDD, breastfeeding, delivery type, or prior abuse history (Table 2). Baseline log CRP was not significantly correlated with total nightly sleep ($r = 0.29$, $p = 0.10$), but was significantly correlated with maternal body mass index (BMI) ($r = 0.58$, $p < 0.01$). Baseline log CRP was not significantly correlated with baseline SIGH-ADS$_{29}$ score ($r = 0.10$, $p = 0.73$) and this persisted ($\beta = -0.18$, 95% CI = −8.88, 3.71), even after controlling for maternal BMI.

At study exit, log CRP levels were not significantly associated with history of prior MDD, breastfeeding, delivery type, or prior abuse history (Table 2). However, study exit log

Table 1 Baseline patient characteristics

Age (years)	27.1 ± 5.4
Prior living children	1.9 ± 0.8
Prior MDD episode	25 (71.4%)
Breast feeding	18 (51.4%)
Prior history of abuse	13 (37.1%)
Maternal BMI (kg/m^2)	33.6 ± 9.2
Total nightly sleep	357.4 ± 158.7
SIGH-ADS$_{29}$ score (baseline)	24.2 ± 5.3
SIGH-ADS$_{29}$ score (study end)	12.7 ± 7.1
Depression response	20 (57.1%)
Depression remission	10 (28.6%)
CRP (baseline) (mg/dL)	0.53 ± 0.53
CRP ≥ 3 mg/dL (baseline)	20 (65.7%)
CRP range (baseline)	0.09–2.33
CRP (study end) (mg/dL)	0.72 ± 1.30
CRP ≥ 3 mg/dL (study end)	20 (57.1%)
CRP range (study end)	0.03–7.41

Data reported as mean ± standard deviation, *n* (%), or range

MDD major depressive disorder, *BMI* body mass index, *SIGH-ADS$_{29}$* Structured Interview Guide for the Hamilton Depression Rating Scale—Atypical Depression Symptoms Version, *CRP* C-reactive protein

Table 2 Mean log CRP values at baseline and study exit, stratified by potential confounders

	Baseline log CRP			Study exit log CRP		
	No	Yes	*p* value	No	Yes	*p* value
Prior MDD episode	− 0.85 ± 0.98	− 1.03 ± 0.84	0.58	− 0.81 ± 1.46	− 1.19 ± 1.05	0.40
Breast feeding	− 1.01 ± 0.75	− 0.95 ± 0.99	0.86	− 1.00 ± 1.32	− 1.17 ± 1.10	0.69
Vaginal delivery	− 0.69 ± 0.83	− 1.18 ± 0.87	0.11	− 0.81 ± 1.28	− 1.28 ± 1.09	0.27
Prior abuse history	− 0.98 ± 0.97	− 0.97 ± 0.73	0.98	− 1.26 ± 1.14	− 0.79 ± 1.23	0.26

CRP levels were inversely correlated with total nightly sleep ($r = -0.41$, $p < 0.01$) and directly correlated with maternal BMI ($r = 0.56$, $p < 0.01$). Exit log CRP was not significantly correlated with the SIGH-ADS_{29} score ($p = 0.84$) and this persisted ($\beta = -1.76$, 95% CI = − 4.33, 0.80) after controlling for baseline CRP, total nightly sleep, and maternal BMI.

When analyzed categorically, 23 (66%) women at baseline had a high (≥ 3 mg/L) CRP and 12 (34%) had a CRP ≥ 5 mg/L. A high baseline CRP was significantly associated with maternal BMI (27.6 ± 5.4 vs 36.8 ± 9.3, $p < 0.01$), but was not associated with the other variables examined. In addition, a high baseline CRP was not associated with a difference in baseline SIGH-ADS_{29} score ($p = 0.43$). After controlling for maternal BMI, a high baseline CRP remained non-significantly associated with baseline SIGH-ADS_{29} score ($\beta = -2.70$, 95% CI = − 7.12, 1.71). These findings remained consistent when a high CRP was defined as ≥ 5 mg/L.

At study exit, 18 (51%) women had a CRP ≥ 3 mg/L and 13 (39%) had a CRP ≥ 5 mg/L. A high exit CRP was associated with a higher maternal BMI (27.7 ± 6.1 vs 34.9 ± 9.3, $p = 0.04$), but was not significantly associated with any of the other examined variables, including the exit SIGH-ADS_{29} score (13.1 ± 8.2 vs 12.4 ± 6.3, $p = 0.78$). The lack of association with SIGH-ADS_{29} score ($\beta = -1.42$, 95% CI = − 8.42, 5.58) persisted after controlling for maternal BMI. These findings remained consistent when a high CRP was defined as ≥ 5 mg/L.

There were no differences in median CRP between women with mild vs severe depression at baseline ($p = 0.58$) or at study exit ($p = 0.64$). In our sample, 16 (46%) women experienced a response and 10 (29%) experienced a remission of their postpartum MDD. Baseline log CRP was not significantly associated with either response (− 0.98 ± 0.90 vs − 0.98 ± 0.88, $p = 0.99$) or remission (− 1.04 ± 0.94 vs − 0.80 ± 0.68, $p = 0.47$).

Discussion

We did not confirm our hypothesis that CRP would be associated with depressive symptomatology in the postpartum period. One reason for the discordance between our results and those from patients with MDD outside of the context of parturition is the unique physiology. Childbirth is associated with a profound elevation in pro-inflammatory markers including CRP, with median levels immediately postpartum of 2.5 mg/L and 4 weeks postpartum of 0.3 mg/L (Christian and Porter 2014). These baseline elevations could preclude identification of the more subtle increases (in the range of 0.02 mg/L) that have been associated with depressive symptoms (Krogh et al. 2014). Another reason for the absence of an observed relationship is that we were not able to account for the use of anti-inflammatory agents. As nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly employed to alleviate postpartum discomfort, the response to treatment observed in the study sample could have been bolstered by the adjuvant use of anti-inflammatory agents. Finally, there are emerging data regarding genetic variants, particularly those in polyunsaturated fatty acid metabolism, that may predispose to inflammatory depression (Chang et al. 2017). Accounting for the role of these polymorphisms in postpartum depression should be an area of future research.

One consistent finding in these analyses is the correlation between maternal BMI and CRP which mirrors observations in the general population (Visser et al. 1999) and in pregnancy (Pendeloski et al. 2017). Given the rising prevalence of obesity in the USA, any clinical implications of this associated rise in CRP have enormous public health impact. The association between obesity and inflammation has been found to be stronger in women, suggesting potentially heightened importance in perinatal populations (Choi et al. 2013).

Our study had a limited time of follow-up. While depressive symptomatology may have improved, a reduction in levels of chronic inflammatory markers, such as CRP, could lag behind changes in depressive scores. While one prior study demonstrated a decline in CRP levels within 4 weeks of treatment initiation (O'Brien et al. 2006), other data failed to demonstrate a decrease within 4 weeks after depression treatment (Chang et al. 2012).

While CRP did not serve as a biomarker of depression or a predictor of response to treatment in this sample, the prevalence of elevated CRP levels in our sample of women with postpartum depression lends support to the pro-inflammatory theory of postpartum MDD. Future work should characterize the remainder of the immunologic milieu, aside from CRP, in this patient population, as an understanding of the molecular

underpinnings of postpartum depression is a key to optimizing treatment choices for this vulnerable population.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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