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# Immune, health and endocrine characteristics of depressed postpartum mothers

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## Summary

The purpose of the study was to examine demographic, immune, endocrine, stress and health characteristics of depressed mothers, measured between 4 and 6 weeks postpartum, and compare them to non-depressed mothers. The top decile ( $N = 25$ ) of Profile of Mood States depression scores was used to categorize mothers as depressed and these data were then compared to means of the remaining mothers ( $N = 175$ ) in a study of stress and immunity during the postpartum. Depressed mothers were younger, had smaller birth weight infants, and their babies experienced more illness symptoms at 4–6 weeks postpartum. Depressed mothers were less likely to be breastfeeding and had lower serum prolactin levels. Depressed mothers were more likely to smoke, to have daytime sleepiness, and more symptoms of infection than non-depressed mothers. Depressed mothers also had higher perceived stress, postpartum stress, and negative life event reports.

There was evidence suggesting that depressed mothers had a downregulated hypothalamic–pituitary–adrenocortical (HPA) axis, in that salivary cortisol was lower in depressed mothers. Depressed mothers also had lower serum levels of Interferon-gamma (IFN- $\gamma$ ) and a lower IFN- $\gamma$ /Interleukin-10 (IL-10) ratio in both sera and in whole blood stimulated cultures, suggesting a depressed Th1/Th2 ratio in depressed mothers. The data supports the possibility that postpartum depression may be associated with a dysregulated HPA axis and possible depressed cellular immunity.

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## 1. Introduction

Postpartum depression (PPD) is described as a depressed mood, with or without anxiety, sleep disturbances, appetite disturbances, lack of energy, feelings of guilt and/or worthlessness, and decreased concentration. PPD usually

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occurs within the first 6 months of delivery (Hendrick et al., 1998) and occurs in 10–15% of postpartum woman (O'Hara and Swain, 1996). A woman is considered predisposed to PPD if she has a history of premenstrual syndrome, episodes of depression, life events that are stressful, lack of adequate support, previous PPD, or a family history of depression (O'Hara and Swain, 1996; Wisner et al., 2002). Other causative social factors include a poor marital relationship, primiparity, multiparity, and especially multiparity with short intervals between pregnancies (Gurel and Gurel, 2000). Poverty has been found to double the incidence of PPD (Hobfoll et al., 1995; Ritter et al., 2000).

Many etiologies of PPD have been proposed but it is unlikely that any single hypothesis can explain what appears to be heterogeneous. It is probable that complex interactions between hormones, neurotransmitters, and environmental factors are involved. Current prevailing hypotheses include the following: (1) dietary deficiencies and/or metabolic disorders, (2) alterations in bipterin/neopterin levels, (3) iron-deficiency anemia, (4) thyroid dysfunction and/or thyroid autoantibodies, (5) rapid changes in hormone levels in the postpartum, (6) hormonal changes and alterations in circadian rhythms and (7) hypothalamic–pituitary–adrenocortical (HPA) axis alterations and inflammatory mechanisms. Since we had completed a fairly large study of postpartum stress and immunity that included mood, endocrine and immune measures, we focused our analyses on variables suggested by the last hypothesis.

### 1.1. Suppression of the HPA response

Studies have generally not found relationships between serum cortisol levels and PPD (Hendrick et al., 1998). However, few studies have measured free cortisol, and plasma levels reflect 90% binding to cortisol binding globulin (CBG). Cortisol is active only in the unbound state, and urinary free cortisol or salivary cortisol are better measures of the active form of cortisol. An early study did not find an association between salivary cortisol and postpartum mood (Harris et al., 1994) measured through pregnancy and until 35 days postpartum. In another study, morning salivary cortisol levels were higher on days 1–5 after birth in women experiencing postpartum blues (Ehlert et al., 1990). However, PPD is a different phenomenon than postpartum blues, which are common and self-limiting, occurring in the early days after birth.

It has been suggested that the hypercortisolism of late pregnancy might cause the development of adrenal suppression in the postpartum after the withdrawal of the extraordinarily high levels of plasma corticotrophin releasing hormone (CRH) produced by the placenta at birth (Magiakou et al., 1996; Kalantaridou et al., 2004). High levels of placental CRH during pregnancy suppress the production of hypothalamic CRH and after birth CRH production and CRH receptors in the hypothalamus may be down-regulated, resulting in decreased ACTH response and cortisol release. Women who develop postpartum blues or PPD may be more than usually suppressed. In susceptible women this decreased CRH response may continue with production of a resultant hypoadrenal state that is further exacerbated by the drop in estradiol after birth (Kammerer

et al., 2006). A suppressed HPA axis has been suggested as a factor in the etiology of postpartum affective disorders in general. Such a CRH resistance state is similar to that observed in atypical/seasonal depression, chronic fatigue and fibromyalgia syndromes, and post-Cushing's syndrome therapy as times when patients undergo hypocortisolism.

In support of this theory, a study of 17 euthymic pregnant women, starting at week 20 of gestation, found one who developed depressive symptoms postpartum, and seven who developed the blues (Altemus et al., 1995). The euthymic women had a blunted plasma ACTH response to ovine CRH (oCRH), which returned to non-pregnant, normal levels by the 12th week postpartum. However, the women with the blues or outright depression maintained a much longer blunted plasma ACTH response to oCRH, although there were no appreciable differences in cortisol levels between the euthymic and dysthymic groups. Magiakou et al. (1996) also reported that women with PPD and postpartum dysphoria had a blunted ACTH response to oCRH. They studied the plasma ACTH response to CRH in postpartum women and found that women had a marked blunting of the ACTH response at 3 and 6 weeks postpartum, which became normal by 12 weeks. The lack of ACTH response was greater in those who developed either the blues or depression. Another small study showed that women with PPD had lower serum cortisol levels compared to controls (Parry et al., 2003). Tsigos and Chrousos (2002) suggested that CRH potentiators might be used to treat PPD and atypical depression. On the other hand, in vivo experiments with healthy women do not support blunting of the cortisol response to CRH in the postpartum. Attempting to mimic pregnancy and the puerperium in healthy, medication-free, non-pregnant women, by first injecting supraphysiological doses of estradiol and progesterone, and then precipitously withdrawing these hormones, the investigators then challenged the HPA by injecting oCRH. Cortisol release in response to ovine CRH was enhanced by supraphysiological levels of gonadal steroids (mimicking the pregnancy state) and this response was actually greater in women with a history of PPD (Bloch et al., 2005). This novel approach nevertheless does not fully reproduce the endocrinology of pregnancy or the postpartum. Estradiol has been used to treat PPD and is presumed to reestablish the normal stress response to CRH (Gregoire et al., 1996).

### 1.2. Immune changes in PPD

Potentially related to the HPA axis are the immunological changes characteristics of PPD. These studies have generally been done in the very early postpartum, however, and have focused on innate immunity. (Maes et al. (2000) found in a study of 91 pregnant women that serum IL-6, IL-1RA, and leukemia inhibitory factor receptor (LIFR) were significantly higher by the end of pregnancy and in the early postpartum period. There was a positive correlation between IL-6, IL-1RA levels and depressive and anxiety symptoms, "suggesting activation of cells of the macrophage/monocytic lineage in the former" (Maes et al., 2000, p. 133). In an earlier study, Maes et al. (1995) found that increased serum IL-1-RA levels were positively correlated with major depression.

Maes et al. (2004) studied whether primiparae were more anxious in the early postpartum and more likely than multiparae to develop PPD. Previous work (Maes et al. (2000)) had shown that changes in serum prolyl endopeptidase (PEP) were correlated to increased anxiety and PPD. PEP may play a role in unipolar, bipolar, and major depressive disorders (Maes et al., 1994; Williams et al., 2002). PEP cleaves peptide bonds on the carboxyl side of proline in several active neuropeptides, including arginine vasopressin (AVP), thyrotropin-releasing hormone (TRH), substance P, oxytocin, bradykinin, and neurotensin (Welches et al., 1993). Maes et al. (2004) found that the neuroimmune response in primiparae was different than in multiparae both quantitatively and qualitatively. Primiparae demonstrated (1) higher anxiety levels and (2) changes in the immune response system and PEP. Their findings raise the question of length of time higher levels of PEP and lowered immune response continue in primiparous mothers (or in any mothers with anxiety and depression) since their study measured serum levels only within the first 6 days post delivery. Of relevance to the current research is Maes et al.'s (1994) finding that PEP activity was negatively correlated with post-Dexamethasone Suppression Test (DST) cortisol levels.

Few studies have simultaneously examined both endocrine and immune variables in postpartum women. Yet, there is a large body of research demonstrating relationships between stress hormones, depression and immune function. The general finding is that elevated stress hormones act via specific immune cell receptors to activate macrophages, inhibit Th1 cell activity, and activate the Th2 axis (Vedhara and Irwin, 2005). However, the postpartum is a unique state in terms of the HPA axis, and depression in the postpartum may manifest in a different manner than at other times of life. Since depression is so common in the postpartum, and other research has found relationships between depression, the HPA axis, and immunity, these were the variables of interest in this study.

## 2. Method

Data collected in a large study of stress and immunity in postpartum women (Groer et al., 2005) allowed the researchers to do a secondary analysis to examine those women who were significantly depressed, as measured by scores on the Profile of Mood States-Depression (POMS-D), at 4–6 weeks postpartum and compare them to non-depressed women. Demographic, endocrine, immune, stress, mood, and health characteristics of the depressed mothers were compared to non-depressed mothers. Variables chosen were measures of stress and dysphoric moods, endocrine variables associated with stress and mood, immune variables that reflected cellular, humoral, and innate immune function, and illness symptoms in both mothers and their infants.

The original study was approved by the university and hospital IRBs and women were recruited after giving birth in the postpartum unit of the university hospital in a southern US city. Mothers were either exclusively or near-exclusively breastfeeding or formula feeding from birth. Mothers in the study were visited in their homes once by a research nurse between 8 a.m. and 11 a.m., between the 4th and 6th

postpartum week, and all data were collected cross-sectionally at this one time period. The saliva was collected in the early morning and refrigerated until pickup by the nurse. The questionnaire packet was sent ahead of the visit and mothers were asked to complete it on the day of the visit. Participating mothers were given a gift of 50 dollars for their time.

### 2.1. Instruments

#### 2.1.1. Carr Infection Symptom Checklist

Reports of symptoms of infection experienced by the mother since the birth were inventoried by the Carr Infection Symptom Checklist (Carr SCL). The Carr SCL, originally developed by the investigators, consists of 30 common symptoms of infectious illnesses, ranked by severity on a 0–4 point Likert scale. There are respiratory, gastrointestinal, genitourinary, skin/eye, and general flu subscales and a total score can be computed as the sum of the subscales. Scores may be computed for both symptom frequency and severity. The scale was originally developed in a study of stress and infection in the menstrual cycle (Groer et al., 1993).

#### 2.1.2. Perceived Stress Scale (PSS)

The PSS (Cohen et al., 1983) is a 14-item instrument that evaluates cognitions and emotions related to perceived general stress. The items indicate the degree to which respondents find their lives unpredictable, uncontrollable, and overloading. There is a 5-point Likert scale with options ranging from “never” (0) to “very often” (4) and the scale has a range 0–56. Cronbach’s alpha for this scale in this study was .837. The Cronbach’s alpha has been reported to range from .84 to .86 in other published studies (Cohen et al., 1983).

#### 2.1.3. Inventory of Small Life Event (ISLE) (Zautra, 1996)

The Inventory of Small Life Events measures small, daily negative and positive life events in a person’s relationships with friends, spouses, and family. These are relationship events occurring within everyday life, or “naturalistic” stress. The scale lists 37 relationship events and 14 health-related events, and participants indicate how many times they have experienced each event since the baby was born. It is scored by adding the number of times each event was experienced. Cronbach’s alpha for the ISLE in this study was .806.

#### 2.1.4. Profile of Mood States (POMS)

The Profile of Mood States (McNair et al., 1992) is a 65-item measure of dysphoric or distressful moods. Mothers were asked to report on their moods over the time since the baby was born. The usual way that the POMS has generally been used is to report over the past week, but it has been used to measure moods over shorter and longer periods (McNair et al., 1992). It utilizes a 0–4 point Likert scale for items that describe ranges of moods. There are six mood subscales. In this study, the POMS-depression scale was used to divide the participants into depressed and non-depressed groups. The internal consistency ranges from .87 to .92 and test–retest reliability from .68 to .74 (McNair et al., 1992).

The POMS was deemed ideal for assessing a range of common moods experienced by postpartum women. In this study, the total mood disturbance score Cronbach's alpha was .95. For the subscales, the following were the Cronbach alphas: depression, .936; anger .925; fatigue, .89; anxiety, .888.

### 2.1.5. The Infant Symptom Checklist

The Infant SCL consists of 11 symptoms of common illnesses in young infants (colds, red eyes, thrush, diarrhea, vomiting, ear infections, fevers, skin infections, rashes, and others). The mothers report on the frequencies of the symptoms since birth. The scale was used in one previous study of infant health (Bass and Groer, 1997). The range in the current study was 0–60, with a mean frequency was  $7.2 \pm 9.7$  symptom occurrences. The common symptoms were colic (32%), rashes (24%), eye infections and colds (19% each). The rarest were fevers and ear infections (less than 2%).

### 2.1.6. Epworth Sleepiness Scale (EPS)

The Epworth Sleepiness Scale is a self-report Likert scale instrument that describes eight different situations and respondents rate how likely they are to fall asleep in each situation (Johns, 1991) on a 0–4 point Likert scale. The test has a high degree of internal consistency (Cronbach's alpha of .73–.88) and measures a single construct, daytime sleep propensity (Miletin and Hanly, 2003). Fatigue and daytime sleepiness are one of the most common and distressing aspects of the postpartum period.

## 2.2. Procedure

Participants collected a 5 min timed saliva sample in the early morning of the day of data collection. They were instructed in a 5 min timed saliva collection by the drool method and were advised not to eat, do any oral hygiene, or smoke for 1 h before saliva collection. The saliva was collected in a 30 ml conical tube, and refrigerated for pickup by the research nurse. A venipuncture was performed by the nurse and blood was collected into a serum separator tube and into sterile heparinized vacutainers. The serum and saliva tubes were placed on ice and the sample was immediately transported to the lab. The serum was spun at 3800 rpm for 25 min, aliquoted, and frozen at  $-20^{\circ}\text{C}$ . The saliva was spun at 1500 rpm for 15 min, and the supernatant was aliquoted into eppendorf tubes and stored at  $-20^{\circ}\text{C}$  until later analysis. The heparinized blood was diluted 1:5 with RPMI supplemented with glutamine and gentamycin, with no fetal calf serum added. One ml aliquots were added to wells to which  $5\ \mu\text{g/ml}$  *Escherichia coli* lipopolysaccharide (LPS) (Sigma) and  $5\ \mu\text{g/ml}$  phytohemagglutinin (PHA) (Sigma) were added. The mitogens in this ex vivo assay vigorously and non-specifically stimulate both Th1 and Th2 cytokine production from these whole blood cultures. The cultures were incubated at  $37^{\circ}\text{C}$  for 66 h, then centrifuged at 1500 for 5 min and the supernatants were aliquoted and frozen at  $-80^{\circ}\text{C}$  until analysis.

Cytokines in serum and ex vivo culture supernatant, and hormones and EBV VCA capsid antigen IgG titers from serum or saliva were analyzed by commercial ELISA kits. Cytokines (IFN- $\gamma$ , IL-10, IL-6) were measured using kits from eBioscience (San Diego). Analyses were done in batches

within 3 months of collection. For prolactin, samples were analyzed by ELISA (Hope labs, Belmont, CA). Cortisol was measured by ELISA (DRG, Germany). The plates were read at the appropriate wavelengths on a scantron plate reader and the data were further analyzed using the Prism GraphPad program. The inter and intra coefficients of variation for all assays were 10% or less. The data were examined for normality and Log 10 transformations were performed on positively skewed variables (all cytokines and prolactin).

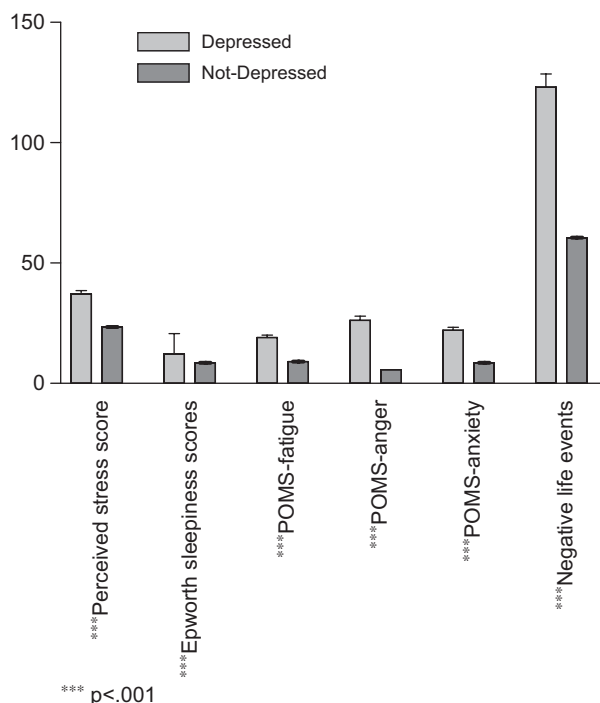
## 3. Results

There were 199 mothers, 101 exclusive or nearly exclusive breastfeeders and 98 formula feeders, who completed the study. The mean time of measurement was 5.3 weeks postpartum. Depressed mothers were categorized as those with scores in the highest decile on the POMS-D scale ( $N = 25$ ). Their POMS-D mean score was 32.1 (range 21–47). The mothers with scores below the lowest limit of the top decile ( $N = 169$ ) had a mean POMS-D scores of 5.7 (range 0–20). The top decile was chosen as a group representing depressed mothers as a score of 21 or higher on the POMS-D is consistent with significant depression and is highly correlated with other depression scales (Griffith et al., 2005). The depressed mothers were younger (mean age = 23 years) compared to non-depressed (mean age = 26 years) ( $p < .05$ ), had lower income ( $p < .06$ ), and were more likely to smoke cigarettes ( $p < .001$ ) (Table 1). Other demographic factors (marital status, parity) and birth characteristics (vaginal vs. caesarean, labor length) were not different. There was a significantly lower infant birth weight reported by the depressed mothers (7.48 vs. 6.67 lbs) ( $p < .002$ ). The percentage of mothers breastfeeding differed in the two groups as well, with 8 of the 25 depressed mothers breastfeeding (32%), compared to 55% of non-depressed mothers breastfeeding.

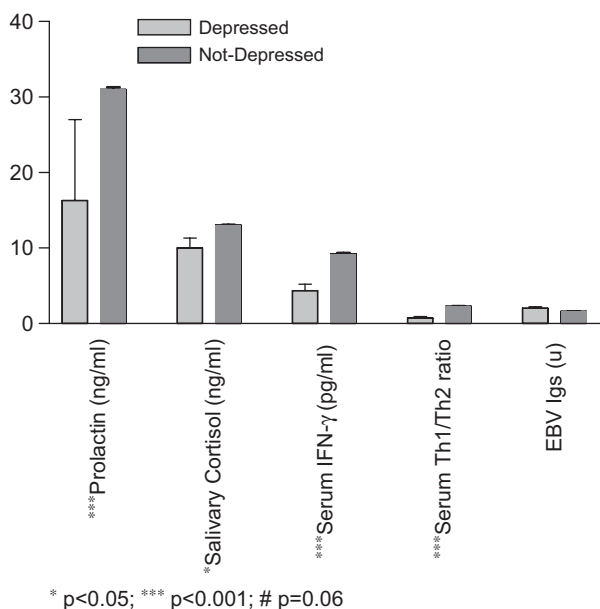
Depressed mothers reported more perceived stress, dysphoric moods and negative life events (see Fig. 1). They also had much higher reports of health-related events (sprains, dental pain, allergies, etc.). They had much higher scores on the other dysphoric moods scales on the POMS. They reported higher daytime sleepiness and more health-related events since the baby was born. The depressed mothers had much higher scores on the Carr SCL and they

**Table 1** Demographic and illness differences between depressed and non-depressed postpartum women.

	Depressed	Non-depressed	<i>t</i>	<i>p</i>
Age	23.6 $\pm$ .98	25.9 $\pm$ .46	2.17	.04
Birth weight	6.67 $\pm$ .35	7.48 $\pm$ .08	2.27	.03
Carr SCL score (# symptoms)	14.8 $\pm$ 2.3	6.9 $\pm$ .55	4.69	.000
Infant SCL score (# symptoms)	2.33 $\pm$ .37	1.61 $\pm$ .11	2.23	.03
Cigarettes smoked (#/d)	5.2 $\pm$ 1.4	1.5 $\pm$ .3	3/66	.000



**Figure 1** Stress and mood differences between depressed and non-depressed postpartum mothers.



**Figure 2** Biological differences between depressed and non-depressed mothers.

also reported more frequent symptoms of infection in their infants on the Infant SCL.

Biological differences are shown in Fig. 2. Depressed mothers had significantly lower salivary cortisol levels ( $p < .05$ ), although serum cortisol concentrations were not significantly different between the two groups. Serum and salivary cortisol levels were not correlated ( $r = .05$ ,  $p < .57$ ). Depressed mothers also had lower serum IFN- $\gamma$  ( $p < .001$ ) and

ex vivo IFN- $\gamma$  production ( $p < .08$ ), leading to lower ratios of IFN- $\gamma$ /IL-10 in both the serum ( $p < .04$ ) and whole blood culture supernatants ( $p < .009$ ). The serum IL-6 levels were three times higher in the depressed mothers, but this value was not significantly different because of the high measurement variability of this cytokine. Prolactin levels in serum from depressed mothers were lower than from the non-depressed mothers ( $p < .004$ ). Even when breastfeeding status was controlled in partial correlations using the full data set, serum prolactin and POMS-D scores remained inversely correlated ( $r = -.20$ ,  $p < .009$ ,  $df = 174$ ). EBV VCA antibody titers were marginally higher in depressed mothers ( $p < .06$ ).

#### 4. Discussion

The mothers with the highest scores on the POMS-D were demographically like mothers in other studies. The incidence of depression in this sample was approximately 10%, when using the POMS-D as the measure of depression but these mothers were measured only at one time point, so the true incidence across the postpartum year is unknown. While the POMS is highly reliable and highly correlated with other depression scales in many populations, it is not one of the gold standards for measuring depression in the postpartum, so this is a limitation.

Depressed mothers in this study gave birth to smaller infants, and infants of prenatally depressed mothers are at risk for undernutrition and growth deprivation (Rahman et al., 2004). Preexisting depression was an exclusion criterion for the present study, but it is possible that some of the depressed mothers had suffered prenatal depression and had not been diagnosed. The observation that depressed mothers reported occurrence of more illness symptoms in their infants at the time of measurement suggests that these infants were vulnerable. Older children of depressed mothers have elevated baseline cortisol levels, suggesting a reactive HPA axis (Ashman et al., 2002), but physical illness has not been studied. Depressed mothers are less likely to provide routine and preventative child care (Leiferman, 2002), which may account for this finding.

Like many other studies of PPD, perceived stress, anxiety, and life events were higher in the depressed mothers. These mothers also reported much higher daytime sleepiness, and more than twice the level of fatigue as the non-depressed mothers. Along with these reports were more frequent symptoms of infection occurring since the birth of the baby. Since all of these data were self-report, it may be that depressed mothers generally over-reported negatively on all the scales. Further studies are needed to systematically and objectively measure these variables.

The lower salivary cortisol in depressed mothers suggests that free, unbound, biologically active cortisol is reduced in PPD. While the serum cortisol levels, which reflect both bound and free cortisol, were not different in the two groups, this study did not measure CBG, which is high during pregnancy and may still be exerting binding of serum cortisol. The ratio of free to bound serum cortisol would be important to include in further studies. We and others have shown that the serum hypercortisolism of later pregnancy continues into the postpartum for several weeks

(Abou-Saleh et al., 1998; Groer et al., 2005). The HPA stress response seems to be blunted during late pregnancy (Kammerer et al., 2002) and in the postpartum (Groer, 2005), in the majority of women, and the presence of lower free salivary cortisol, as in these depressed mothers, may reflect a disruption in the normal postpartum physiology. The lack of dexamethasone suppression characteristic of pregnancy lasts through the third week of pregnancy (Owens et al., 1987). The hypercortisolism of pregnancy, with extension into the postpartum, may produce decreased feedback sensitivity to cortisol at the hypothalamus and pituitary. The body may normally self-adjust during the postpartum after the extraordinary HPA hyperactivity of pregnancy, but in the case of PPD, there may be over-adjustment of feedback sensitivity, leading to hypocortisolism. The occurrence of depression in women across the perinatal period may be influenced by genetic factors that operate at different times. Depression during pregnancy appears to be melancholic and associated with hypercortisolemia, while PPD may be more atypical, triggered by abrupt withdrawal of CRH and cortisol that occurs at birth and characterized by hypocortisolemia (Kammerer et al., 2006). Hypocortisolemia may be associated with immune and stress-related diseases. The Lewis rat has less corticosterone than the syngeneic Fischer rat and is much more susceptible to inflammatory and autoimmune disturbances (Sternberg, 1997). In humans, stress-related disorders such as chronic fatigue syndrome, chronic pelvic pain, fibromyalgia, irritable bowel syndrome, low back pain, post traumatic stress disorder and atypical depression are all associated with decreased levels of free cortisol (Fries et al., 2005). In line with this, depressed mothers in the study were very fatigued and sleepy, and had many more health-related complaints than the non-depressed mothers.

The effects of pregnancy-related hormonal and immune changes are down-regulation of Th1 immunity during pregnancy with a rebound of Th1 immune function during the postpartum (Elenkov et al., 2001). This rebound may not occur in PPD. Depressed mothers evidenced some impairment in cellular immunity, compared to non-depressed mothers, along with their higher reports of symptoms of infection. The Th1/Th2 ratio was lower both in serum samples and in whole blood ex vivo culture supernatants, suggesting suppression of cellular immunity in depressed mothers. Combined with a higher EBV viral capsid antigen antibody titer, which suggests escape of latent Herpes viruses from cellular immune control, and the higher neopterin levels, these differences may help to explain the higher frequency and severity of symptoms of infections reported by depressed mothers compared to the non-depressed mothers. The majority of these symptoms were respiratory in nature, and likely of viral origin.

There were many limitations to the study. It was cross sectional and the data were collected for another study so that the instrument selected for characterizing depression was not the gold standard for PPD. The number of depressed mothers was small compared to non-depressed mothers, thus limiting power in the study. Nevertheless, this research does support other studies that suggest a role of dysregulation in the HPA recovery in PPD, and adds further to the understandings of the relationships between the endocrinology and immunology of the postpartum.

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