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Relationships Among Prenatal Depression, Plasma Cortisol, and Inflammatory Cytokines

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Abstract

A secondary pilot study was carried out as part of a larger parent study of thyroid function in pregnancy and postpartum. All women in the parent study ($N = 631$) had blood samples, demographic data, and measures of perceived stress and dysphoric moods collected between 16 and 26 weeks' gestation. The current study was completed with a subset of 105 pregnant women to examine the relationships among perceived stress, depression, plasma cortisol and cytokines during the second trimester of pregnancy. Stress was measured using Cohen's Perceived Stress Scale and dysphoric moods using the Profile of Mood States depression/dejection scale. Cytokines were measured by a 12-plex analysis on a Luminex-200 and cortisol was measured by ELISA on stored plasma samples. Stress and depression scores were highly correlated, and depressive symptoms were inversely correlated with 3 of the 12 cytokines: interleukin (IL)-1 β , tumor necrosis factor (TNF)- α , and IL-7. Cortisol was inversely correlated with pro-inflammatory cytokines (IL-1 β , and TNF- α) and anti-inflammatory cytokines (IL-4, IL-5, IL-10, IL-13). These data support the new conceptualizations of normal pregnancy as an inflammatory state that is carefully regulated, as both excessive and inadequate inflammation are potentially hazardous to the health of the pregnancy and fetus.

Keywords

cortisol; cytokines; depression; pregnancy; stress

Recently the paradigm for the role of the immune system in pregnancy has changed. Former understandings centered on a fairly simplistic model of immune tolerance and T helper (Th)2 upregulation to prevent fetal allograft rejection (Mor, Cardenas, Abrahams, & Guller,

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2011). It is now clear that there is a great deal of interaction between placental trophoblastic cells and the maternal innate and adaptive immune systems in an evolving local and systemic immunomodulation throughout pregnancy.

Contrary to previous beliefs, the immune system at the implantation site is extraordinarily active, and in the first and early second trimester there is a local inflammatory milieu as tissues are invaded, destroyed and remodeled. During the second trimester there is decreased inflammation. Finally at third trimester, the uterus once again becomes a site of renewed inflammation in preparation for birth. These alterations modulate chronic disease activity, uterine activity and the host's response to microorganisms (Mor & Cardenas, 2010).

In particular, the innate immune system is intensely involved in the maintenance of pregnancy (Chaouat, Dubanchet, & Ledée, 2007). Pregnancy evokes an innate immune response that resembles sepsis (Sacks, Studena, Sargent, & Redman, 1998), and some have likened pregnancy to an "open wound" (Mor & Cardenas, 2010, p. 427). In addition, an inflammatory environment is needed for implantation (Hunt, Langat, McIntire, & Morales, 2006). Early in gestation there is an upregulation of innate immunity as cytokines flood the maternal system, encouraging the activation of both uterine natural killer (NK) cells and macrophages (Chaouat et al., 2007). During the third trimester, the processes of cervical ripening, uterine contractions and the rupture of the amniotic sac are all inflammatory events (Challis et al., 2009).

This inflammatory upregulation occurring in the pregnant uterus also appears to affect systemic immunity as, for instance, interleukin (IL)-6 levels increase across pregnancy (Opsjon et al., 1993). The intense immune activity of pregnancy is carefully controlled by the placenta, and excessive inflammation is associated with adverse pregnancy outcomes (Elovitz et al., 2011; Rusterholz, Hahn, & Holzgreve, 2007). Thus both *excessive* and *less than adequate* inflammation are risk factors for pregnancy success.

Cytokines are often characterized by their secretion from different Th lymphocytes. The Th1 cytokines (e.g., interferon [IFN]- γ and IL-2) are related to cell-mediated immunity (activation of cytotoxic T cells and macrophages) and are considered pro-inflammatory. Cytokines of the Th2 group (e.g., IL-4, IL-5, IL-13) are associated with antibody-mediated humoral immunity. The reciprocal inhibitory relationship between Th1 and Th2 cytokines results in the downregulation of Th2 cytokines by Th1 cytokines and vice versa. Th2 cells are inhibited by IFN- γ , while IL-4 and IL10 inhibit Th1 cells (Fitzgerald, O'Neill, Gearing, & Callard, 2001)

Observation of a predominance of either a Th1 or Th2 cytokine subset has been helpful in explaining the underlying mechanisms of various human diseases. For example, a Th1 dominance is associated with many autoimmune diseases (Balkwill, 2000). In contrast, pregnancy has been long described as a Th2 phenomenon, in that successful pregnancies tend to be associated with higher levels of Th2 cytokines, and elevations in Th1 cytokines may have detrimental effects on pregnancy outcome (Wegmann, Lin, Guilbert, & Mosmann, 1993). This shift toward a Th2 profile in pregnancy may also explain why women with cell-

mediated autoimmune diseases such as rheumatoid arthritis demonstrate a remission of their symptoms during pregnancy.

Cortisol is a major regulator of inflammation and may play a role in keeping inflammation in check (Mastorakos & Ilias, 2003). In the nonpregnant state, stress triggers the release of corticotropin-releasing hormone (CRH; from the hypothalamus), which acts on the pituitary to release adrenocorticotropin hormone (ACTH) and subsequently on the adrenal glands to release cortisol into circulation. This negative feedback loop eventually results in the rise in cortisol influencing the hypothalamus to cease secreting CRH. In the pregnant state, however the placenta also produces CRH (pCRH). The relationship of cortisol to pCRH is in contrast with its relationship to CRH produced in the hypothalamus in that a rise in cortisol during pregnancy increases the production of pCRH (Sandman, Davis, Buss, & Glynn, 2011). There is a steady rise in pCRH and a managed state of hypercortisolemia during pregnancy.

As a result of the upregulation of the hypothalamic-pituitary-adrenal (HPA) axis during pregnancy, cortisol levels rise 3-fold during pregnancy, reaching their peak during the third trimester (Jung et al., 2011). Normative daily cortisol values during pregnancy have not been established, but levels in nonpregnant women range between 6 and 23 mcg/dL in the morning with a decline in afternoon levels to 3-to-16 mcg/dL.

Cortisol elevation above what is expected in normal pregnancy has been noted in women experiencing prenatal depression (Field & Diego, 2008). Prenatal depression may be even more prevalent than postpartum depression (Evans, Heron, Francomb, Oke, & Golding, 2001), with an incidence between 10 and 51% (Evans & Bullock, 2012; Luke et al., 2009; Price & Proctor, 2009). Depressed women are more likely to experience preterm labor, preeclampsia, diabetes, Cesarean section, anemia, and infections during labor (Dunkel Schetter & Tanner, 2012; Nysten, O'Hara, & Engeldinger, 2012). Infants born to depressed women are also at greater risk for fetal growth restriction, abnormalities, distress, and death (Bansil et al., 2010).

High levels of pro-inflammatory cytokines have been positively associated with depressive symptoms and psychosocial stress in many studies of nonpregnant individuals (Raison, Capuron, & Miller, 2006). However, the nature of the relationships among stress, depression, cytokine levels and plasma cortisol throughout pregnancy has not been well explicated. Given that pregnancy is a state of controlled inflammation, loss of control of the inflammatory processes in either direction might be deleterious. A greater understanding of these relationships could thus help to improve pregnancy outcomes. Therefore the purpose of this study was to explore the relationships among perceived stress, depression, and levels of plasma cortisol and cytokines during the second trimester of pregnancy.

Materials and Methods

Participants and Setting

We obtained Institutional Review Board approval at both the university and clinical sites. The research involved participants enrolled in a larger study of stress, immunity and thyroid

function. While the parent study involved collection of blood samples from 631 women to test for thyroid antibodies, perceived stress and dysphoric moods, we examined a subset of participants' ($N = 105$) plasma samples for cytokines and cortisol. Data from that subset are included in this analysis. We made no attempt to recruit equal numbers of women based on race, socioeconomic status, or other variables for the parent study or the current analysis. We selected a sample size based on feasibility rather than on a power analysis. We conceptualized the present pilot study after the parent study was underway; therefore several aspects of the study present limitations to the interpretation of the data. Nevertheless, we viewed the opportunity to explore the posited relationships in the sample as worthwhile.

Healthy pregnant women were recruited from two prenatal clinics affiliated with a large university practice in the southeastern United States. Data were collected between 16 and 26 weeks' gestation after documentation of informed consent was obtained. Criteria for exclusion included age less than 18 and greater than 45 years; body mass index (BMI) less than 20 kg/m² at time of venipuncture; problem with drugs or alcohol; current use of immunosuppressant, hormonal or anticoagulant medications; personal history of thyroid disease; serious mental illness; chronic disease; use of in-vitro fertilization for current pregnancy; hyperemesis; anemia; and known genetic abnormalities in the developing fetus.

Demographic, Stress and Depression Measurements

Participants completed a brief demographic survey collecting information about age, race, education, income, marital status, employment status, and pregnancy history. We also calculated BMI prior to pregnancy and at the time of blood collection.

The Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983) was used to measure levels of self-reported stress. The 14-item version of the scale measures how often the individual felt or thought a certain way with Likert-type responses ranging from 0 (*never*) to 4 (*very often*). Scores range from 0 to 56, with higher scores indicating greater stress. The internal consistency reliability was .84–.86 in a young adult population. Congruent and criterion validity for the scale has been shown to be excellent, although predictive validity falls with time (Cohen et al., 1983). Cronbach's alpha was .89 in our population.

Participants also completed the Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1992), a 65-item adjective-rating scale measuring how often the respondent experienced a feeling in the past week, including the day of measurement. The POMS has a total mood disturbance score and six subscales: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. Responses range from 0 (*not at all*) to 4 (*extremely*). We used only the depression-dejection scale (POMS-D), scored as the sum of 15 items on the scale, in the current analysis as none of the other subscales describing additional dysphoric moods had any relationship with cytokines or plasma cortisol levels in our sample. Scores range between 0 and 60 on this subscale, with a higher score indicating a greater disturbance in this area. The POMS-D has an internal consistency reliability of .84–.95 in an antepartum population (Heaman, 1992). The validity of the scale (face validity, factorial validity, predictive validity, and construct validity) is

reported to be excellent (McNair et al., 1992). The Cronbach's alpha in our study population was .92.

Cytokine and Cortisol Measures

Venipuncture was completed at the participant's regularly scheduled prenatal visit and therefore took place at any time throughout the clinic day, although the majority of the data were collected before noon. While it would have been ideal to have all women's data collected at the same time of day, this was not possible because of the clinic schedule. Also, salivary samples would have given a better approximation of free cortisol, but salivary sampling was not a practice in the parent study and therefore results were not available. Blood samples were collected concurrently with the written surveys.

Blood was collected in three 5-ml heparinized tubes and transported to the lab in a chilled cooler. Upon receipt in the lab, plasma was collected by centrifugation. The plasma was aliquoted and stored at -80°C until cytokine and cortisol analyses were completed in batches. All analyses were completed in duplicate.

Plasma cortisol levels ($\mu\text{g/dl}$) were measured with ELISA assay kits from ALPCO Immunoassays (Salem, NH) per kit instructions. Standards and controls were completed with the samples for each plate. Intra-assay coefficients of variation were under 10%. This assay measures both free and bound cortisol, the active form being the unbound portion.

A 12-plex panel of cytokines with potential roles in pregnancy was multiplexed in the parent study and consisted of signature pro-inflammatory and anti-inflammatory cytokines as well as chemokines of importance to immune responses. Cytokines (pg/ml) measured were tumor necrosis factor alpha ($\text{TNF-}\alpha$), interferon gamma ($\text{IFN-}\gamma$), and the following interleukins: IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, and IL-13. A 12-plex bead-based assay was completed with Milliplex Map kits (Billerica, MA) and analyzed on a Luminex-200. The samples were prepared per kit instructions and incubated in duplicate in filter bottom plates with beads overnight at 4°C . The plates were washed and incubated with detection antibodies at room temperature. Streptavidin-Phycoerythrin was added to each well and the samples were incubated for an additional 30 min. Standards and low and high controls were run for every plate. Median fluorescence intensity was converted into picograms per milliliters. Intra-assay coefficients of variation were under 10%.

Statistical Analysis

Log-10 transformation was used to normalize the cytokine values before comparison. Pearson's correlation coefficients and partial correlations were used to identify whether there were significant relationships among the demographic variables, psychological factors, and biological data. Linear regressions were performed to identify the predictors of depression in these women. Statistical analyses were conducted using SPSS statistical software (SPSS 20).

Race was a potentially important variable to investigate since previous research has identified that prenatal depression is higher in women of color (Gavin, Chae, Mustillo, & Kiefe, 2009) and that there are differences in the distribution of cytokines by race (Velez et

al., 2008). In the current study, however, results of ANOVA showed that race did not have a significant effect on the variables under investigation. Therefore, no attempt to control for race was indicated.

Gestational age at the time of data collection was also important to consider as cortisol is known to rise across pregnancy. Researchers have reported, however, that plasma cortisol levels at 16 and 26 weeks' gestation are identical, with the steep rise in plasma cortisol beginning at 25 weeks (Carr, Parker, Madden, MacDonald, & Porter, 1981). Although our data showed the same effect, we thought it prudent to control for gestational age at blood draw while completing partial correlation analyses between variables.

Separate hierarchical linear regressions were carried out on each cytokine correlated with depression. Gestational age at blood draw, gravidity, ethnicity, and race were controlled in the model, and POMS-D scores and plasma cortisol were entered as a block.

Results

Demographic information has been summarized in Table 1. Mean scores on the POMS-D and PSS were 6.13 ($SD = 8.82$) and 23.22 ($SD = 6.61$), respectively. Of the 105 participants, 8 (7.6%) met the protocol's screening criteria for possible clinical depression with a POMS-D score greater than 20. Following study protocol, the primary obstetrician or midwife was notified if POMS-D scores were greater than 20 so that follow-up could be arranged. Because this number was small, we did not do statistical comparisons between depressed and nondepressed individuals.

Biological Measures

The mean time of day for blood drawn was 11:25 a.m. and the mean gestational age was 20 weeks (range 16–26 weeks). The plasma cortisol mean was 16.92 $\mu\text{g/dl}$ ($SD = 7.4$), with a range of 5.19–43.54, and a scatter plot of early-morning and afternoon cortisol samples over time showed a mild circadian rhythm. Cortisol's circadian rhythm is known to be blunted during pregnancy (Cousins et al., 1983). These values reflect the expected hypercortisolemia of pregnancy as the mean is higher than published normal, nonpregnant ranges. The cytokines did not show circadian rhythms over this limited time-of-day span. The cytokine values are presented in the last row of Table 2.

Relationships

While controlling for gestational age at blood draw, partial correlation analyses identified inverse correlations of POMS-D scores with IL-1 β , IL-7, and TNF- α levels. Plasma cortisol level was inversely correlated with several cytokine levels including IL-1 β , IL-4, IL-5, IL-7, IL-10, IL-13, and TNF- α . Cytokine levels were not directly correlated with perceived stress. Perceived stress and POMS-D scores were highly correlated with each other. These correlations are presented in Table 2. The hierarchical linear regression models presented in Table 3 indicate that cortisol and depression contributed to the levels of plasma cytokines IL-1 β , TNF- α , and IL-7.

Discussion

The aim of the present analysis was to examine the relationships among depressive symptoms, perceived stress, cytokines, demographic variables and cortisol during the second trimester of pregnancy. The results suggest that second-trimester prenatal depressive symptom scores are highly correlated with perceived stress and are also inversely associated with plasma levels of two of the three major plasma pro-inflammatory cytokines (IL-1 β and TNF α) associated with innate immunity, which are secreted mostly by macrophages. Cortisol may potentially play a role in the decreased levels of these cytokines, as plasma cortisol values were also inversely correlated with these levels.

Although studies of cortisol levels in pregnancy are fairly common in recent literature (see, for example, Buss et al., 2009; Hompes et al., 2012), there have been just a few studies of depression, stress and cytokines in pregnancy. In one study of 60 women at approximately 15 weeks' gestation, 57% of whom were African American, depressive symptoms (using the Center for Epidemiologic Studies Depression Scale [CES-D]) were associated with higher levels of IL-6, but there were no relationships with perceived stress (Christian, Franco, Glaser, & Iams, 2009). The gestational age of the pregnancy in Christian et al.'s study was earlier than in the study reported here. In another study, increased stress was associated with decreased IL-10 and increased IL-6 in the first and third trimesters of pregnancy (Coussons-Read, Okun, & Nettles, 2007). In an earlier study of 30 participants in which data were collected at three time points between 16 and 36 weeks of gestation, levels of TNF- α and IL-6 were reported to increase and IL-10 decrease with increasing stress (Coussons-Read, Okun, Schmidt, & Giese, 2005). Consistent with the results presented here, neither of these studies found relationships between stress and cytokines in mid-pregnancy. In both studies, the stress measure was a life-events stress scale rather than a perceived stress scale, as was used in the current study, and depression was not measured in either. Studies have shown that depression may be associated with hypercortisolemia in both pregnant and nonpregnant women (Field & Diego, 2008; O'Keane et al., 2011). The absence of a correlation between depression and cortisol in the current analysis may be due to the small number of women reporting depressive symptoms. There may have not been enough variation in the depression scores to identify a relationship with cortisol.

Cortisol has general anti-immune properties and can downregulate both Th1 and Th2 cytokine release (Sun, Yu, Yang, & Zhang, 2011), suggesting that higher-than-normal levels of cortisol might downregulate the inflammatory cytokine balance that is so important for normal pregnancy. Maternal cortisol levels may also have both short- and long-term effects on the development and responsiveness of the infant's HPA, as reported by Monk et al. (2011).

In view of the changing endocrine and immune environment across gestation, the differences between the current findings and those of other published reports could be related to a variety of issues, with gestational age at time of measurement being perhaps the most critical. However, differences in assay methods, instruments and number of participants may also play a role in the different results. The POMS-D is not the ideal instrument for measuring depression because it is a dysphoric moods questionnaire.

Cytokines were measured by ELISA in other studies, whereas in the current work we employed Luminex multiplexing. The current study has the largest number of participants reported so far in the literature among studies of the relationships among depression, stress, cortisol and cytokines in pregnancy.

Perceived stress had a positive, but nonsignificant, relationship with cortisol in the present analysis. Previous research has shown relationships between prenatal stress and cortisol (Field & Diego, 2008). In addition, Glynn, Schetter, Wadhwa, and Sandman (2004) demonstrated that multiparous women describe more stress in pregnancy, using a life-events scale, than women experiencing their first pregnancy. Likewise, in the present study, we found a positive correlation between PSS score and the number of living children a woman reported. Multiparous women are usually parenting other children, which may lead to increased worries about finances and resources for caring for the enlarging family. These worries, in turn, may affect the stress axes and increase serum cortisol to levels that suppress the inflammatory responses compared to women who have not yet reproduced.

In the present study, we found that cortisol levels and depression both contributed to the levels of plasma cytokines IL-1 β , TNF- α , and IL-7. Little is known about the role of IL-7 in normal pregnancy, though in general it is thought to be important in lymphopoiesis, in supporting naive T-cell populations, and in homeostatic cycling of naive and memory cells (Fry & Mackall, 2005). In mice, decreases in IL-7 were associated with decreased B-cell lymphopoiesis (Bosco, Ceredig, & Rolink, 2008). We discovered no studies related to behavior, stress, pregnancy and IL-7 in our literature review.

The cross-sectional view of cytokine levels at approximately 20 weeks' gestation presented by the current findings offers a small clue about how the immunomodulation of pregnancy is influenced by depression and stress. Work by Sandman et al. (2006) showing that elevated cortisol levels at 15–19 weeks' gestation are associated with changes in placental endocrine function in the late-second and third trimesters points toward a possible explanation for these decreased cytokine levels, suggesting that there are downstream effects to stress exposures in the second trimester.

The lower cytokine levels seen in the present study in women with depressive symptoms could be viewed as an exaggeration of the normal immunomodulation of pregnancy. Perhaps stress exposure or mood disorders in the second trimester trigger HPA activation that is meant to enforce the immune quiescence of the second trimester but actually ends up overshooting the normal cytokine balance, downregulating them to a point below normal levels. This downregulation might promote fetal and maternal risks in the third trimester and contribute to adverse birth outcomes such as preterm birth, low birth weight, intrauterine growth restriction and disrupted sleep–wake cycles in newborns (Davalos, Yadon, & Tregellas, 2012; Sandman et al., 2006).

The growing placenta provides evolving opportunities for maternal–placental interaction, and this can, in part, account for the changing immune milieu throughout the advancing trimesters of pregnancy. Three broad activities summarize the nature of the relationship between the placenta and the pregnant host's immune system: the placenta recruits immune

cells, controls immune cell differentiation, and influences the cytokine and chemokine responses of those immune cells (Mor et al., 2011). Immune cell type, pro- and anti-inflammatory cytokine balance, complement activity and other acute-phase reactants, and antigen presentation are aspects of the immune system that undergo modulation as gestation advances (Derzsy, Prohaszka, Rigo, Fust, & Molvarec, 2010; Fest et al., 2007; Hunt et al., 2006; Southcombe, Tannetta, Redman, & Sargent, 2011). This modulation affects the way the maternal host responds to external threats and internal signaling (Mor et al., 2011).

The timing of cytokine changes across pregnancy needs to be addressed in future research. Does decreased or muted production of cytokines predispose a woman to depression in pregnancy, or does the depression or its causes have some impact on the way trophoblasts engage the maternal immune system? Even as investigation into the normal endocrine and immune modulation of pregnancy continues, it is important to investigate the factors that may disrupt these normal immune processes. Normal systemic changes reflect placental physiology and represent discrete protective responses for the pregnant woman. Understanding how psychosocial processes such as prenatal depression or stress exposure inhibit or exacerbate this endocrine and immune modulation will lead to a better understanding of how to prevent adverse pregnancy and birth outcomes.

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Table 1Demographic Variables ($N = 105$).

Variable	M (SD)	Min/Max
Age (years)	27.6 (5.4)	18/41
BMI (kg/m ² ; pre-pregnancy)	27.0 (6.5)	17.2/47.7
BMI (kg/m ² ; at blood draw)	28.9 (6.3)	18.7/47.2
Number of pregnancies	2.4 (1.5)	1/9
Number of living children	.89 (1.1)	0/6
	<i>n</i>(%)	
Race		
Caucasian/White	74 (70.5)	-
African American/Black	23 (21.9)	-
Asian/Pacific Islander	3 (2.9)	-
Other	5 (4.8)	-
Ethnicity		
Not Hispanic	78 (74.3)	-
Hispanic	27 (25.7)	-
Education		
Grammar school	1 (1.0)	-
Middle school	11 (10.5)	-
High school	42 (40.0)	-
College graduate	31 (29.5)	-
Postgraduate	5 (4.8)	-
No response	15 (14.3)	-
Marital status		
Single	44 (41.9)	-
Married	58 (55.2)	-
Divorced	1 (1.0)	-
No response	2 (1.9)	-
Household income		
Under \$4,999	5 (4.8)	-
\$5,000–\$14,999	4 (3.8)	-
\$15,000–\$24,999	6 (5.7)	-
\$25,000–\$39,999	4 (3.8)	-
\$40,000–\$69,999	14 (13.3)	-
\$70,000+	14 (13.3)	-
No response	58 (55.2)	-

Note. BMI = body mass index

Table 2

Correlations of Key Variables, Controlling for Gestational Age at Enrollment, r (df)

	POMS-D	PSS	Cortisol	IL-1 β	IL-2	IL-4	IL-5	IL-6	IL-7	IL-8	IL-10	IL-12	IL-13	IFN- γ	TN F- α
PSS	.56** (102)														
Corti sol	.15 (101)	.18 (101)													
IL-1 β	-.21* (102)	-.13 (102)	-.25** (101)												
IL-2	-.17 (102)	-.08 (102)	-.16 (101)	.63** (102)											
IL-4	-.11 (102)	-.04 (102)	-.36** (101)	.60** (102)	.24* (102)										
IL-5	-.16 (102)	.02 (102)	-.22* (101)	.64** (102)	.42** (102)	.54** (102)									
IL-6	-.13 (102)	.02 (102)	-.17 (101)	.54** (102)	.64** (102)	.33** (102)	.46** (102)								
IL-7	-.23* (102)	-.02 (102)	-.18 (101)	.53** (102)	.25** (102)	.71** (102)	.53** (102)	.31** (102)							
IL-8	-.06 (102)	.01 (102)	-.19 (101)	.28** (102)	.21* (102)	.39** (102)	.34** (102)	.39** (102)	.36** (102)						
IL-10	-.15 (102)	-.03 (102)	-.30** (101)	.60** (102)	.23* (102)	.78** (102)	.61** (102)	.43** (102)	.64** (102)	.38** (102)					
IL-12	-.09 (102)	-.11 (102)	-.05 (101)	.43** (102)	.50** (102)	.12 (102)	.26** (102)	.53** (102)	.18 (102)	.17 (102)	.30** (102)				
IL-13	-.12 (102)	.07 (102)	-.20* (101)	.66** (102)	.61** (102)	.51** (102)	.68** (102)	.75** (102)	.44** (102)	.43** (102)	.53** (102)	.42** (102)			
IFN- γ	-.13 (102)	-.12 (102)	-.13 (101)	.61** (102)	.64** (102)	.32** (102)	.45** (102)	.65** (102)	.24** (102)	.28** (102)	.37** (102)	.61** (102)	.71** (102)		
TNF- α	-.25** (102)	-.16 (102)	-.26** (101)	.29** (102)	.24* (102)	.28** (102)	.32** (102)	.33** (102)	.31** (102)	.58** (102)	.28** (102)	.19 (102)	.35** (102)	.29** (102)	1
M (SEM)	6.13 (.86)	23.22 (.65)	16.92 (.69)	3.32 (.74)	13.16 (3.70)	43.04 (13.60)	1.68 (.39)	14.02 (3.60)	26.80 (5.90)	22.97 (5.80)	8.59 (1.80)	10.72 (3.70)	20.05 (9.50)	4.27 (1.50)	5.71 (.87)

Note. IFN = interferon; IL = interleukin; POMS-D = Profile of Mood States, depression subscale; PSS = Perceived Stress Scale; TNF = tumor necrosis factor.

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* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

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Table 3

Hierarchical Multiple Regression Analysis Predicting Inflammatory Cytokines from Profile of Mood States (POMS)-Depression scores and Plasma Cortisol

	IL-1 β	TNF- α	IL-7
R^2	.09	.12	.07
β	-.23	-.23	-.15
df	2,101	2,101	2,101
F	5.19	6.59	4.06
p	.01	.00	.02

Note. Control variables of race, ethnicity, gravidity, and gestational age at blood draw were entered as a block and did not significantly alter the R^2 produced by the combination of depression and cortisol. IL = interleukin; TNF = tumor necrosis factor.