Published in final edited form as:

Nurs Res. 2019 ; 68(2): 167–173. doi:10.1097/NNR.0000000000000334.

IL-17A and Chronic Stress in Pregnant Women at 24-28 Weeks Gestation

Tiffany A. Moore, PhD, RN [Assistant Professor],

University of Nebraska Medical Center (UNMC) College of Nursing-Omaha Division

Adam J. Case, PhD [Assistant Professor],

University of Nebraska Medical Center, College of Medicine Department of Cellular and Integrative Physiology Omaha, NE

Therese L. Mathews, Ph.D., APRN-NP, BCBA-D [Associate Professor],

University of Nebraska Medical Center College of Nursing-Omaha Division Omaha, NE

Crystal Modde Epstein, PhD, APRN-NP [Post-Doctoral Scholar],

University of California, San Francisco School of Nursing San Francisco, CA

Katherine Laux Kaiser, PhD, PHCNS, BC [Professor Emeritus], and

University of Nebraska Medical Center College of Nursing-Omaha Division Omaha, NE

Matthew C Zimmerman, PhD [Associate Professor]

University of Nebraska Medical Center, College of Medicine Department of Cellular and Integrative Physiology Director, Free Radicals in Medicine Program Omaha, NE

Abstract

Background: Allostatic Load (AL) is a biopsychosocial model that suggests chronic psychosocial stress leads to physiologic dysregulation and poor outcomes. The purpose of this study was to examine AL in pregnant women operationalized using pro-inflammatory cytokines and psychosocial indicators and perinatal outcomes.

Objectives: In pregnant women, identify relationships between circulating cytokines/chemokines and the Prenatal Distress Questionnaire (PDQ), Maternal Antenatal Attachment Scale (MAAS), Emotional and Quotient Inventory (EQi), Life Experiences Scale (LES), and demographics.

Methods: A cross-sectional design was used to recruit pregnant women between 24–28 weeks gestation. Blood and stress/emotional indicators were obtained after informed consent. Plasma was abstracted to simultaneously measure 29 cytokines/chemokines using a multiplex array. Cytokine/chemokine levels were compared with continuous variables using Spearman's Rho and with categorical variables using Mann-Whitney U.

Corresponding author: Tiffany A. Moore, PhD, RN, University of Nebraska Medical Center, College of Nursing-Omaha Division, 985330 Nebraska Medical Center, Omaha, NE 68198-5330, tamore@unmc.edu.

The authors have no conflicts of interest to report.

Ethical Conduct of Research: This study received IRB approval from the University of Nebraska Medical Center: IRB #069–15-EP and #477–16-EP.

Clinical Trial Registration: n/a

Results: Twenty-five women with medically high-risk ($n = 16$) and low-risk ($n = 9$) pregnancies consented. The majority of women were White (68%) with a mean age of 29 years (5.9). While several cytokines and chemokines showed significant correlations with the stress/emotional indicators, only interleukin-17 (IL-17A) was significantly associated with all of the indicators [PDQ ($r_s = 0.528$; $p = 0.012$); MAAS ($r_s = -0.439$; $p = 0.036$); EQi total ($r_s = -0.545$; $p = 0.007$); LES ($r_s = 0.458$, $p = 0.032$); and birthweight ($r_s = -0.499$; $p = 0.013$), and race ($p = 0.01$).

Discussion: Increased levels of IL-17A, a known cytokine associated with chronic stress and with poor perinatal outcomes, was associated with high prenatal distress, low maternal attachment, and lower emotional intelligence in pregnant women. Increased levels of IL-17A also were associated with lower birthweight and non-White race. Results support the model of AL in pregnant women and highlight IL-17A as a potential biomarker of AL during pregnancy.

Keywords

chronic stress; emotional intelligence; inflammation; perinatal

Chronic psychosocial stress is believed to affect physiological processes and exacerbate multifactorial phenomena as described by McEwen's allostatic load (AL) theory (Juster, McEwen, & Lupien, 2010; McEwen, 1998). AL is a biopsychosocial theory suggesting psychosocial stress affects physiologic dysregulation which eventually leads to "wear and tear" on body systems and results in poor outcomes (McEwen, 1998). Relevant complex phenomena linked to multiple biological mechanisms as well as chronic psychosocial profiles in the perinatal population include preterm birth (PTB) and low birthweight (LBW) (National Center for Health Statistics, 2017). PTB, defined as parturition prior to 37 weeks gestation, and LBW, defined as weighing < 2500g at birth, are perinatal outcomes prioritized as public health concerns (United States Department of Health and Human Services, Office of Disease Prevention and Health Promotion, 2011).

Allostatic load explains how chronic psychosocial stress affects physiologic dysregulation leading to poor health outcomes. Although chronic stress is a challenging concept to quantify, we identified four stress/emotional indicators to measure in pregnant women that may be related to chronic stress: pregnancy distress, maternal attachment, major life events, and emotional intelligence. Pregnancy distress refers to the emotional distress specific to pregnancy and is consistently reported as a negative stress/emotional indicator relating to PTB (Brunton, Dryer, Saliba, & Kohlhoff, 2015; Dunkel Schetter, Niles, Guardino, Khaled, & Kramer, 2016; Guardino & Schetter, 2014; Haas et al., 2015; Liou, Wang, & Cheng, 2016; Rose, Pana, & Premji, 2016; Shapiro, Fraser, Frasch, & Séguin, 2013). Pregnancy distress was used to identify state responses specific to pregnancy but may provide a more global understanding of trait responses to situations. Maternal antenatal attachment also is believed to play an important role in psychosocial stress, albeit as a buffer of stress, affecting infant growth and development in utero and early childhood (Alhusen, Hayat, & Gross, 2013; Branjerdporn, Meredith, Strong, & Garcia, 2017; Pisoni et al., 2016). Attachment to the fetus may provide understanding of a more in-depth trait response of the mother and provides opportunity for future interventional therapies.

Major life events, especially negative events, are believed to affect perinatal outcomes, specifically increasing the risk of PTB (Barrios, Sanchez, Qiu, Gelaye, & Williams, 2014; Witt et al., 2014). Quantifying major life events may provide insight for an objective measure of stress. Emotional intelligence is an emerging concept that measures the essential emotional skills and self-awareness used in personal, professional, and public settings and interactions (Shonkoff, 2012). The impact of emotional intelligence on perinatal outcomes is unknown because this concept has received little attention in the perinatal population or as a risk factor of PTB. Theoretically, however, pregnant women with lower emotional intelligence would have decreased self-regulatory mechanisms to confront daily, or even chronic, stressors which may result in more physiologic dysregulation from stress. We chose the concept of emotional intelligence because of the emerging literature of relationships between adverse childhood events and emotional intelligence (Shonkoff, 2012).

Inflammation has been used to identify dysregulation in previous AL studies and is relevant to PTB and LBW. Inadequate responses of the immune system measured at single time points (e.g., exaggerated inflammatory response measured as cytokines) in pregnant women with PTB have been previously identified (Lucaroni et al., 2018). Specifically, a systematic review authored by Lucaroni and colleagues (2018) reported increased interleukin-6 (IL-6) levels measured in maternal serum are associated with increased odds ratio of 2 (95% CI 1–3) and increased likelihood value of 12. As noted by the authors, however, more prospective studies are needed in various subsets of pregnant women to identify if specific cytokine levels are sufficient for the prediction of PTB. Furthermore, inadequate immune responses also have been associated with LBW during the preconception period (Pearce et al., 2016), but no studies to date were identified that investigated prenatal cytokine levels associated with LBW.

The emerging concept of AL is a relevant theoretical framework in the perinatal population, yet, no studies to date have used the AL model to measure prospective prenatal cytokine levels, sociodemographics, and specific stress/emotional indicators. The specific aim of this study was to identify correlations between circulating cytokine and chemokine levels at 24–28 weeks gestation with maternal antenatal attachment, prenatal distress, life events, emotional intelligence, maternal race, gestational age at birth, and birthweight.

Methods

Pregnant women already enrolled in a larger study were recruited during a clinic visit between 24–28 weeks for this pilot study. The clinic is located in an academic perinatal center in the Midwest region. Maternal patients seen by the maternal-fetal-medicine and general obstetrics practice groups were included in the larger study. This study was approved by the institutional review board from the primary investigator's university. Inclusion criteria were women previously enrolled in the larger study and scheduled for routine metabolic/glucose challenge between 24–28 weeks gestation. Although not an exclusion criteria, pregnant women not participating in the metabolic/glucose challenge for clinical reasons (e.g., previous diagnosis were not approached. A member of the research team with ethical access approached eligible pregnant women, obtained informed consent using the teach-back method to verify understanding. After consent, whole blood was obtained, samples

were centrifuged, and the plasma was extracted and frozen at -80°C until analysis. Cytokines and chemokines were assessed using the 30 V-plex™ assay kit and Discovery Workbench® 4.0 from Meso Scale Discovery® (Rockville, Maryland). At time of analysis, the 30 V-plex™ assay kit only included 29 cytokines as MCP-4 was not available from the manufacturer. On the same day as blood collection, stress/emotional indicators also were obtained using validated and reliable tools to measure the four stress/emotional indicators: (a) Revised Prenatal Distress Questionnaire (NuPDQ); (b) Maternal Antenatal Attachment Scale (MAAS); (c) Life Experiences Survey (LES); and (d) Emotional Quotient Inventory 2.0 (EQi 2.0). Demographic data (i.e., birthweight; gestational age, race/ethnicity, maternal age; insurance coverage) were extracted through the electronic health records. Cytokine and chemokine levels were correlated with stress/emotional indicator scores using Spearman's Rho and SPSS v25 (SPSS Inc, Chicago, IL).

The *Maternal Antenatal Attachment Scale* (MAAS; Condon, 1993, Condon & Corkindale, 1997) measures antenatal global maternal attachment using 19 items scored on a 5-point Likert-scale (higher levels indicate higher levels of attachment) with Cronbach's alpha ranging between .69 and .82 (Condon, 1993; Schwerdtfeger & Goff, 2007; Thomas, 2014). The *Revised Prenatal Distress Questionnaire* (NuPDQ; Lobel et al., 2008) includes 17 questions about pregnancy-specific stress using a 3-point Likert scale (higher levels indicate higher distress). Cronbach's alpha ranges from .59 – .79 (Alderice, Lynn, & Lobel, 2012). The *Life Experiences Survey* (LES; Sarason, Johnson, & Siegel, 1978) is a 57-item tool that measures the occurrence of specific events (y/n) experienced in the past year; higher numbers means more major life events occurred. Test-retest reliability ranges from .63 – .64 (Saranson, Johnson, & Seigel, 1978). The *Emotional Quotient Inventory 2.0*® (North Tonawanda, NY) measures social-emotional intelligence using 133 questions and a 5-point Likert scale (higher scores indicate higher levels of emotional intelligence). Test-retest reliability was .92 at 2–4 weeks; Cronbach alpha coefficients range from .77 to .91 (Multi Health Systems, 2011).

Because this was a pilot study, our goal was to recruit 30 pregnant women consistent with sample sizes appropriate for pilot studies (Hertzog, 2008). Birthweight and gestational age were measured as continuous variables to identify significant correlations between birthweight, age, cytokines, and stress/emotional scores in this small sample. Descriptive and correlational statistics were completed using SPSS version 25 (SPSS Inc, Chicago, IL). Nonparametric tests were used because the assumptions of normality were not met; *p*-values were not adjusted for multiple comparisons because of the small sample size and exploratory aim of the study.

Results

Twenty-five women with medically high-risk ($n = 16$) and low-risk ($n = 9$) pregnancies were enrolled in the study. Missing data include blood ($n = 1$), EQi ($n = 1$), MAAS ($n = 1$), PDQ ($n = 2$), and LES ($n = 2$). Demographic data identifies the majority of women were White ($n = 17$; 68%) and all 25 women were self-identified as non-Hispanic. Perinatal outcomes include preeclampsia ($n = 4$), gestational diabetes ($n = 4$), and diagnosis of morbidly obese

($n = 5$). Newborn data include median birthweight of 3240 grams (ranging from 2,010–4,051 grams) and median gestational age at birth of 38.9 weeks (ranging from 34–41.3 weeks).

Table 1 shows the correlations between cytokine/chemokine levels, stress/emotional indicators, and birthweight. Several of the cytokines and chemokines were significantly correlated with stress/emotional questionnaires and birthweight. Notably, IL-17A levels were significantly correlated with *all* stress scales and birthweight suggesting that pregnant women with high levels of IL-17A were more likely to have lower emotional intelligence scores EQi total ($r_s = -0.545$; $p = 0.007$), lower antenatal attachment scores MAAS ($r_s = -0.439$; $p = 0.036$), higher prenatal distress scores PDQ ($r_s = 0.528$; $p = 0.012$), more major life events in the past year LES ($r_s = 0.458$, $p = 0.032$) and deliver a newborn with a lower birthweight ($r_s = -0.499$; $p = 0.013$). Table 2 identifies significant differences in cytokine/chemokine levels based on race (White vs. non-White). Several cytokines and chemokines, including IL-17A, were significantly different based on race suggesting that pregnant women with higher levels of these specific proteins were more likely to be non-White ($p = 0.01$). No significant differences were found with gestational age.

Pregnant women diagnosed with gestational diabetes ($n = 4$) had significantly higher IL-10 ($p = 0.025$) and IL-6 ($p = 0.036$) levels and the newborn infants had significantly higher birthweights ($p = 0.009$). Pregnant women diagnosed with morbid obesity had significantly higher TNF- α ($p = 0.02$) and IL-6 ($p = 0.001$) levels. No other significant differences were found between the stress/emotional questionnaires, cytokine levels, race, or birthweight in pregnant women diagnosed with preeclampsia, gestational diabetes, or morbid obesity.

Discussion

Herein, we used the AL model to examine stress/emotional indicators on a subset of pregnant women and identify associations between inflammatory biomarkers and psychosocial stress. These stress/emotional indicators were administered on the same day as a clinical blood draw obtained between 24–28 weeks gestation. Several correlations were identified between cytokines/chemokines and scores for the stress/emotional indicators. The most interesting finding was IL-17A and the significant relationships with birthweight, maternal race, and all of the stress/emotional indicators administered for the current study.

Briefly, IL-17A is a member of a subfamily of pro-inflammatory cytokines that is composed of six (i.e. A-F) unique IL-17 ligands (Onishi & Gaffen, 2010). Recently, elevated IL-17A has been shown to be associated with various psychological diseases, suggesting a possible mechanistic role in driving behavioral changes. For example, in a cohort of patients with rheumatoid arthritis, IL-17A levels were positively correlated with the severity of comorbid anxiety (Liu, Ho, & Mak, 2012). Additionally, IL-17A was associated with poorer cognitive status in patients with depressive symptoms following stroke (Swardfager et al., 2014), and IL-17A has been demonstrated to directly cause depressive-like behavior in rodent models (Nadeem et al., 2017). Furthermore, patients with posttraumatic stress disorder (PTSD) have been demonstrated to have increased IL-17A (Wang, Mandel, Levingston, & Young, 2016; Zhou et al., 2014). One hallmark of many psychological disorders is dysregulation of the autonomic nervous system, and our group was the first to demonstrate that elevated levels of

norepinephrine directly lead to increased production of IL-17A from T-lymphocytes (Case, Roessner, Tian, & Zimmerman, 2016). Elevations in sympathetic tone could suggest a possible mechanism in these pregnant mothers that may explain the observed increases in IL-17A, but further studies are needed to examine this hypothesis. Herein, we demonstrate that IL-17A showed significant correlations with all stress evaluations as well as with birthweight and race, suggesting a possible new pathogenic role for IL-17A in the etiology of LBW.

Indeed, IL-17A also has been implicated in the etiology of PTB and other pregnancy complications (Barnie, Lin, Liu, Xu, & Su, 2015; Gargano et al., 2008; Ito et al., 2010; Marquardt et al., 2016). In a study authored by Darmochwal-Kolarz (2017), pregnant women with placental insufficiency ($n = 34$), specifically fetal growth restriction and preeclampsia, had higher levels of circulating IL-17 compared to healthy pregnant women ($n = 35$). Ito et al. (2010) measured IL-17 in the amniotic fluid of pregnant women undergoing amniocentesis between 22–34 weeks gestation ($n = 150$). Their results identified increased levels of IL-17 in the amniotic fluid, primarily produced by T-lymphocytes, was associated with PTB. Methods used in these studies have different specimen sources and timing of measurements compared to our study, results warrant further investigation of IL-17A as a specific cytokine of interest in PTB and LBW.

Previous literature on cytokine activity related to PTB and LBW have reported significant relationships between (a) IL-6 and PTB (Lucaroni et al., 2018); and (b) IL-13 and IFN γ with LBW (Pearce et al., 2016). In our study, IL-6 showed a trend for a significant relationship with birthweight ($r_s = 0.388$, $p = 0.062$) but did not show any significant correlations with the stress/emotional indicators. In contrast, IL-13 and IFN γ did not show any relationship with birthweight but did show several significant correlations with the stress/emotional indicators. These results highlight the complexity of PTB, LBW, and chronic stress and emphasize the need to measure multiple factors for these perinatal phenomena.

Chronic stress is a difficult concept to operationalize and objectively measure. AL is one theoretical framework to quantify the effects of chronic stress by identifying dysregulation of physiologic mechanisms, including inflammation. Our results warrant further investigation into using an AL index tool composed of multiple cytokines and psychosocial variables, to quantify AL and identify those at risk for a disease or phenomenon such as PTB.

Limitations of the study include small sample size and the accessible population used for the study. Type I error may be affected in this pilot study and future studies will use the false rate discovery method to account for multiple comparisons in a fully powered study. This pilot study included both medically high-risk and low-risk pregnant women which may be a confounding factor when interpreting data. Obtaining blood consistent with the clinical metabolic/glucose challenge measured between 24–28 weeks gestation also may have affected cytokine levels. However, this was a prospective design with stress/emotional indicators obtained on the same day as the blood used to measure inflammation. Previous literature and our current results support further investigation into IL-17A as a potential

biomarker to quantify chronic psychosocial stress and identify pregnant women at-risk for poor perinatal outcomes. Measuring several cytokines increases probability of a significant correlation but it is the significant correlations of IL-17A with birthweight and all of the stress/emotional indicators, as well as implications of IL-17A in previous literature, that emphasizes the relevance and importance of IL-17A in future research in this population. This study also demonstrates the necessity of incorporating biological, psychological, and sociodemographic factors together in perinatal research. Future studies should incorporate a biopsychosocial theoretical approach, such as AL.

Conclusion

Increased levels of IL-17A, a known cytokine associated with chronic stress and with poor perinatal outcomes, measured at 24–28 weeks gestation was associated with lower birthweight, non-White race, lower emotional intelligence, lower antenatal maternal attachment, higher prenatal distress, and higher number of life events in pregnant women. This exploratory study supports the biopsychosocial model of AL suggesting individualized responses to stress/emotions may lead to physiologic dysregulation of inflammatory processes associated with poor perinatal outcomes.

Acknowledgment:

Research reported in this publication was supported by the National Institute of Nursing at the National Institutes of Health under award number K01NR014474 and a University of Nebraska Medical Center's Edna Ittner Pediatric Support grant. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors wish to thank the staff and patients at Nebraska Medicine and Olson Center, Dr. Margaret M Kaiser, and Dr. Jonathon Buhrman from Mesoscale Discovery.

References

- Alderdice F, Lynn F, & Lobel M (2012). A review and psychometric evaluation of pregnancy-specific stress measures. *Journal of Psychosomatic Obstetrics and Gynecology*, 33(2), 62–77. doi: 0.3109/0167482X.2012.673040 [PubMed: 22554138]
- Alhusen JL, Hayat MJ, & Gross D (2013). A longitudinal study of maternal attachment and infant developmental outcomes. *Archives of Women's Mental Health*, 16, 521–529. doi:10.1007/s00737-013-0357-8
- Barnie PA, Lin X, Liu Y, Xu H, & Su Z (2015). IL-17 producing innate lymphoid cells 3 (ILC3) but not Th17 cells might be the potential danger factor for preeclampsia and other pregnancy associated diseases. *International Journal of Clinical and Experimental Pathology*, 8, 11100–11107. [PubMed: 26617829]
- Barrios YV, Sanchez SE, Qiu C, Gelaye B, & Williams MA (2014). Risk of spontaneous preterm birth in relation to maternal experience of serious life events during pregnancy. *International Journal of Women's Health*, 6, 249–257. doi:10.2147/IJWH.S54269
- Branjerdporn G, Meredith P, Strong J, & Garcia J (2017). Associations between maternal-foetal attachment and infant developmental outcomes: A systematic review. *Maternal and Child Health Journal*, 21, 540–553. doi:10.1007/s10995-016-2138-2 [PubMed: 27456309]
- Brunton RJ, Dryer R, Saliba A, & Kohlhoff J (2015). Pregnancy anxiety: A systematic review of current scales. *Journal of Affective Disorders*, 176, 24–34. doi:10.1016/j.jad.2015.01.039 [PubMed: 25687280]
- Case AJ, Roessner CT, Tian J, & Zimmerman MC (2016). Mitochondrial superoxide signaling contributes to norepinephrine-mediated T-lymphocyte cytokine profiles. *PloS One*, 11, e0164609. doi:10.1371/journal.pone.0164609 [PubMed: 27727316]

- Condon JT (1993). The assessment of antenatal emotional attachment: Development of a questionnaire instrument. *British Journal of Medical Psychology*, 66, 167–183. doi/10.1111/j.2044-8341 [PubMed: 8353110]
- Condon JT & Corkindale C (1997). The correlates of antenatal attachment in pregnant women. *British Journal of Medical Psychology*, 70, 359–372. doi/10.1111/j.2044-8341. [PubMed: 9429755]
- Dunkel Schetter C, Niles AN, Guardino CM, Khaled M, & Kramer MS (2016). Demographic, medical, and psychosocial predictors of pregnancy anxiety. *Paediatric and Perinatal Epidemiology*, 30, 421–429. doi:10.1111/ppe.12300 [PubMed: 27221458]
- Gargano JW, Holzman C, Senagore P, Thorsen P, Skogstrand K, Hougaard DM, . . . Chung H (2008). Mid-pregnancy circulating cytokine levels, histologic chorioamnionitis and spontaneous preterm birth. *Journal of Reproductive Immunology*, 79, 100–110. doi:10.1016/j.jri.2008.08.006 [PubMed: 18814919]
- Guardino CM, & Schetter CD (2014). Understanding pregnancy anxiety: Concepts, correlates, and consequences. *Zero to Three*, 34, 12–21.
- Haas DM, Parker CB, Wing DA, Parry S, Grobman WA, Mercer BM, . . . Reddy UM (2015). A description of the methods of the nulliparous pregnancy outcomes study: Monitoring mothers-to-be (nuMoM2b). *American Journal of Obstetrics & Gynecology*, 212, 539.e1–539.e24. doi: 10.1016/j.ajog.2015.01.019 [PubMed: 25648779]
- Hertzog MA (2008). Considerations in determining sample size for pilot studies. *Research in Nursing & Health*, 31, 180–191. 10.1002/nur.20247 [PubMed: 18183564]
- Ito M, Nakashima A, Hidaka T, Okabe M, Bac ND, Ina S, . . . Saito S (2010). A role for IL-17 in induction of an inflammation at the fetomaternal interface in preterm labour. *Journal of Reproductive Immunology*, 84, 75–85. doi:10.1016/j.jri.2009.09.005 [PubMed: 19969371]
- Juster RP, McEwen BS, & Lupien SJ (2010). Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neuroscience and Biobehavioral Reviews*, 35, 2–16. doi:10.1016/j.neubiorev.2009.10.002 [PubMed: 19822172]
- Liou SR, Wang P, & Cheng CY (2016). Effects of prenatal maternal mental distress on birth outcomes. *Women and Birth*, 29, 376–380. doi:10.1016/j.wombi.2016.03.004 [PubMed: 27079210]
- Liu Y, Ho RC, & Mak A (2012). The role of interleukin (IL)-17 in anxiety and depression of patients with rheumatoid arthritis. *International Journal of Rheumatic Diseases*, 15, 183–187. doi: 10.1111/j.1756-185X.2011.01673.x [PubMed: 22462422]
- Lobel M, Cannella DL, Graham JE, DeVincent C, Schneider J, & Meyer BA (2008). Pregnancy-specific stress, prenatal health behaviors, and birth outcomes. *Health Psychology*, 27(5), 604–615. doi: 10.1037/a0013242 [PubMed: 18823187]
- Lucaroni F, Morciano L, Rizzo G, D' Antonio F, Buonomo E, Palombi L, & Arduini D (2018). Biomarkers for predicting spontaneous preterm birth: An umbrella systematic review. *Journal of Maternal-Fetal & Neonatal Medicine*, 31, 726–734. doi:10.1080/14767058.2017.1297404 [PubMed: 28274163]
- Marquardt N, Ivarsson MA, Sundström E, Åkesson E, Martini E, Eidsmo L, . . . Michaëlsson J (2016). Fetal CD103+ IL-17-producing group 3 innate lymphoid cells represent the dominant lymphocyte subset in human amniotic fluid. *Journal of Immunology*, 1502204. doi:10.4049/jimmunol.1502204
- McEwen BS (1998). Protective and damaging effects of stress mediators. *New England Journal of Medicine*, 338, 171–179. doi:10.1056/NEJM199801153380307 [PubMed: 9428819]
- Multi Health Systems (2011). Emotional Quotient Inventory 2.0: Users Handbook. Retrieved from <http://www.mhs.com>.
- Nadeem A, Ahmad SF, Al-Harbi NO, Fardan AS, El-Sherbeeney AM, Ibrahim KE, & Attia SM (2017). IL-17A causes depression-like symptoms via NFκB and p38MAPK signaling pathways in mice: Implications for psoriasis associated depression. *Cytokine*, 97, 14–24. doi:10.1016/j.cyto.2017.05.018 [PubMed: 28570931]
- National Center for Health Statistics. (2017). Peristats. Retrieved from www.marchofdimes.org/peristats
- Onishi RM, & Gaffen SL (2010). Interleukin-17 and its target genes: Mechanisms of interleukin-17 function in disease. *Immunology*, 129, 311–321. doi:10.1111/j.1365-2567.2009.03240.x [PubMed: 20409152]

- Pearce BD, Nguyen PH, Gonzalez-Casanova I, Qian Y, Omer SB, Martorell R, & Ramakrishnan U (2016). Pre-pregnancy maternal plasma cytokine levels and risks of small-for-gestational-age at birth. *Journal of Maternal-Fetal & Neonatal Medicine*, 29, 4065–4069. doi: 10.3109/14767058.2016.1156669 [PubMed: 26902393]
- Pisoni C, Garofoli F, Tzialla C, Orcesi S, Spinillo A, Politi P, . . . Stronati M (2016). Complexity of parental prenatal attachment during pregnancy at risk for preterm delivery. *Journal of Maternal-Fetal & Neonatal Medicine*, 29, 771–776. doi:10.3109/14767058.2015.1017813 [PubMed: 25747945]
- Rose MS, Pana G, & Premji S (2016). Prenatal maternal anxiety as a risk factor for preterm birth and the effects of heterogeneity on this relationship: A systematic review and meta-analysis. *BioMedical Research International*, 1–18. doi:10.1155/2016/8312158
- Sarason IG, Johnson JH, & Siegel JM (1978). Assessing the impact of the life experiences survey. *Journal of Consulting and Clinical Psychology*, 46, 932–946. doi: 10.1037/0022-006X.46.5.932 [PubMed: 701572]
- Schwerdtfeger KL, & Goff BSN (2007). Intergenerational transmission of trauma: Exploring mother–infant prenatal attachment. *Journal of Traumatic Stress*, 20, 39–51. doi:10.1525/jer.2009.4.4.39 [PubMed: 17345647]
- Shapiro GD, Fraser WD, Frasch MG, & Séguin J.R. (2013). Psychosocial stress in pregnancy and preterm birth: Associations and mechanisms. *Journal of Perinatal Medicine*, 41, 631–645. doi: 10.1515/jpm-2012-0295 [PubMed: 24216160]
- Shonkoff JP (2012). Leveraging the biology of adversity to address the roots of disparities in health and development. *PNAS Proceedings of the National Academy of Sciences*, 109, 17302–17307. doi:10.1073/pnas.1121259109
- Swardfager W, Herrmann N, Andreazza AC, Swartz RH, Khan MM, Black SE, & Lanctôt KL (2014). Poststroke neuropsychiatric symptoms: Relationships with IL-17 and oxidative stress. *BioMed Research International*. 10.1155/2014/245210
- Thomas N, Komiti A, & Judd F (2014). Pilot early intervention antenatal group program for pregnant women with anxiety and depression. *Archives of women's mental health*, 17(6), 503–509. 10.1007/s00737-014-0447-2
- United States Department of Health and Human Services, Office of Disease Prevention and Health Promotion. (2011). Healthy People 2020 (No. Maternal, infant, and child health objectives MICH-8 and MICH-9). Washington, DC: Retrieved from <https://www.healthypeople.gov/2020/topics-objectives/topic/maternal-infant-and-child-health/objectives>
- Wang Z, Mandel H, Livingston CA, & Young MR (2016). An exploratory approach demonstrating immune skewing and a loss of coordination among cytokines in plasma and saliva of veterans with combat-related PTSD. *Human Immunology*, 77, 652–657. doi:10.1016/j.humimm.2016.05.018 [PubMed: 27216157]
- Witt WP, Cheng ER, Wisk LE, Litzelman K, Chatterjee D, Mandell K, & Wakeel F (2014). Preterm birth in the United States: The impact of stressful life events prior to conception and maternal age. *American Journal of Public Health*, 104, S73–S80. doi:10.2105/AJPH.2013.301688 [PubMed: 24354830]
- Zhou J, Nagarkatti P, Zhong Y, Ginsberg JP, Singh NP, Zhang J, & Nagarkatti M (2014). Dysregulation in microRNA expression is associated with alterations in immune functions in combat veterans with post-traumatic stress disorder. *PloS One*, 9. doi:10.1371/journal.pone.0094075

Table 1

Correlations Between Maternal Circulating Cytokine and Chemokine Levels at 24-28 Weeks Gestation with Stress/Emotional Indicators

	EQI					MAAS		PDQ		LES		BW	
	Total	I. Self-Perception	II. Inter-personal	III. Decision Making	IV. Self-Expression	V. Stress Management	Total	I. Quality of Attachment	II. Time in Attachment	Total	Total	Newborn Birthweight	
IL-17A	$r_s = -.545$ $p = .007$	$r_s = -.467$ $p = .025$	$r_s = -.519$ $p = .011$	$r_s = -.523$ $p = .010$	$r_s = -.336$ $p = .117$	$r_s = -.664$ $p = .001$	$r_s = -.439$ $p = .036$	$r_s = -.417$ $p = .048$	$r_s = -.355$ $p = .096$	$r_s = .528$ $p = .012$	$r_s = .458$ $p = .032$	$r_s = -.499$ $p = .013$	
IFN- γ	$r_s = -.350$ $p = .101$	$r_s = -.328$ $p = .127$	$r_s = -.534$ $p = .009$	$r_s = -.277$ $p = .201$	$r_s = -.137$ $p = .533$	$r_s = -.408$ $p = .054$	$r_s = -.341$ $p = .111$	$r_s = -.282$ $p = .193$	$r_s = -.288$ $p = .183$	$r_s = .521$ $p = .013$	$r_s = .130$ $p = .563$	$r_s = -.200$ $p = .349$	
IL-10	$r_s = -.220$ $p = .314$	$r_s = -.276$ $p = .203$	$r_s = -.190$ $p = .386$	$r_s = -.278$ $p = .199$	$r_s = -.192$ $p = .380$	$r_s = -.401$ $p = .058$	$r_s = -.233$ $p = .284$	$r_s = -.038$ $p = .862$	$r_s = -.228$ $p = .295$	$r_s = .037$ $p = .870$	$r_s = .184$ $p = .401$	$r_s = -.253$ $p = .233$	
IL-1b	$r_s = -.204$ $p = .351$	$r_s = -.077$ $p = .728$	$r_s = -.086$ $p = .697$	$r_s = -.325$ $p = .130$	$r_s = -.074$ $p = .736$	$r_s = -.396$ $p = .061$	$r_s = -.141$ $p = .522$	$r_s = -.248$ $p = .255$	$r_s = .014$ $p = .950$	$r_s = .353$ $p = .107$	$r_s = .100$ $p = .657$	$r_s = .030$ $p = .889$	
IL-6	$r_s = -.079$ $p = .721$	$r_s = -.016$ $p = .943$	$r_s = -.240$ $p = .271$	$r_s = -.043$ $p = .845$	$r_s = .139$ $p = .526$	$r_s = -.154$ $p = .484$	$r_s = .004$ $p = .986$	$r_s = .210$ $p = .336$	$r_s = -.099$ $p = .652$	$r_s = .280$ $p = .207$	$r_s = -.119$ $p = .599$	$r_s = .388$ $p = .061$	
IL-8	$r_s = -.536$ $p = .008$	$r_s = -.368$ $p = .084$	$r_s = -.455$ $p = .029$	$r_s = -.537$ $p = .008$	$r_s = -.383$ $p = .071$	$r_s = -.582$ $p = .004$	$r_s = -.229$ $p = .292$	$r_s = -.368$ $p = .084$	$r_s = -.207$ $p = .343$	$r_s = .348$ $p = .112$	$r_s = .293$ $p = .185$	$r_s = -.053$ $p = .806$	
TNF α	$r_s = -.439$ $p = .036$	$r_s = -.242$ $p = .266$	$r_s = -.460$ $p = .027$	$r_s = -.497$ $p = .016$	$r_s = -.167$ $p = .446$	$r_s = -.407$ $p = .054$	$r_s = -.120$ $p = .584$	$r_s = -.246$ $p = .259$	$r_s = -.118$ $p = .591$	$r_s = .388$ $p = .074$	$r_s = .284$ $p = .201$	$r_s = -.097$ $p = .654$	
Eotaxin	$r_s = -.565$ $p = .005$	$r_s = -.433$ $p = .039$	$r_s = -.272$ $p = .209$	$r_s = -.572$ $p = .004$	$r_s = -.464$ $p = .026$	$r_s = -.553$ $p = .006$	$r_s = -.211$ $p = .335$	$r_s = -.182$ $p = .405$	$r_s = -.150$ $p = .496$	$r_s = .457$ $p = .033$	$r_s = .132$ $p = .559$	$r_s = .035$ $p = .872$	
Eotaxin-3	$r_s = -.266$ $p = .220$	$r_s = -.093$ $p = .672$	$r_s = -.020$ $p = .929$	$r_s = -.240$ $p = .270$	$r_s = -.265$ $p = .222$	$r_s = -.285$ $p = .187$	$r_s = -.109$ $p = .619$	$r_s = -.118$ $p = .592$	$r_s = -.059$ $p = .790$	$r_s = .231$ $p = .301$	$r_s = .235$ $p = .292$	$r_s = -.199$ $p = .351$	
IL-8-ha	$r_s = -.148$ $p = .501$	$r_s = .135$ $p = .539$	$r_s = -.088$ $p = .689$	$r_s = -.287$ $p = .184$	$r_s = -.006$ $p = .977$	$r_s = -.136$ $p = .535$	$r_s = .075$ $p = .734$	$r_s = -.129$ $p = .558$	$r_s = .214$ $p = .326$	$r_s = .428$ $p = .047$	$r_s = .201$ $p = .369$	$r_s = -.155$ $p = .469$	
IP-10	$r_s = -.506$ $p = .014$	$r_s = -.372$ $p = .081$	$r_s = -.343$ $p = .109$	$r_s = -.513$ $p = .012$	$r_s = -.399$ $p = .059$	$r_s = -.516$ $p = .012$	$r_s = -.189$ $p = .389$	$r_s = -.110$ $p = .617$	$r_s = -.150$ $p = .496$	$r_s = .418$ $p = .053$	$r_s = .135$ $p = .549$	$r_s = -.102$ $p = .636$	
MCP-1	$r_s = -.522$ $p = .011$	$r_s = -.425$ $p = .043$	$r_s = -.203$ $p = .353$	$r_s = -.496$ $p = .016$	$r_s = -.469$ $p = .024$	$r_s = -.501$ $p = .015$	$r_s = -.175$ $p = .425$	$r_s = -.132$ $p = .550$	$r_s = -.148$ $p = .500$	$r_s = .387$ $p = .075$	$r_s = .017$ $p = .940$	$r_s = .021$ $p = .923$	
MDC	$r_s = -.575$ $p = .004$	$r_s = -.414$ $p = .050$	$r_s = -.394$ $p = .063$	$r_s = -.549$ $p = .007$	$r_s = -.457$ $p = .028$	$r_s = -.542$ $p = .008$	$r_s = -.294$ $p = .174$	$r_s = -.270$ $p = .213$	$r_s = -.198$ $p = .364$	$r_s = .342$ $p = .120$	$r_s = .155$ $p = .492$	$r_s = -.006$ $p = .977$	
MIP-1a	$r_s = -.357$ $p = .095$	$r_s = -.258$ $p = .235$	$r_s = -.217$ $p = .320$	$r_s = -.407$ $p = .054$	$r_s = .187$ $p = .392$	$r_s = -.357$ $p = .095$	$r_s = -.085$ $p = .701$	$r_s = -.023$ $p = .916$	$r_s = -.102$ $p = .642$	$r_s = .253$ $p = .257$	$r_s = .019$ $p = .932$	$r_s = -.208$ $p = .330$	
MIP-1b	$r_s = -.514$ $p = .012$	$r_s = -.455$ $p = .029$	$r_s = -.310$ $p = .050$	$r_s = -.484$ $p = .019$	$r_s = -.415$ $p = .049$	$r_s = -.540$ $p = .008$	$r_s = -.304$ $p = .159$	$r_s = -.299$ $p = .166$	$r_s = -.163$ $p = .459$	$r_s = .484$ $p = .022$	$r_s = .107$ $p = .637$	$r_s = .077$ $p = .719$	
TARC	$r_s = -.520$ $p = .011$	$r_s = -.344$ $p = .108$	$r_s = -.225$ $p = .301$	$r_s = -.525$ $p = .010$	$r_s = -.468$ $p = .024$	$r_s = -.527$ $p = .010$	$r_s = -.217$ $p = .319$	$r_s = -.187$ $p = .392$	$r_s = -.173$ $p = .430$	$r_s = .271$ $p = .222$	$r_s = .009$ $p = .968$	$r_s = .003$ $p = .987$	

	EQi							MAAS		PDQ		LES		BW	
	Total	I. Self-Perception	II. Inter-personal	III. Decision Making	IV. Self-Expression	V. Stress Management	Total	I. Quality of Attachment	II. Time in Attachment	Total	Total	Total	Total	Newborn Birthweight	
IL-12p40	$r_s = -.283$ $p = .191$	$r_s = -.064$ $p = .772$	$r_s = -.223$ $p = .306$	$r_s = -.356$ $p = .096$	$r_s = -.314$ $p = .145$	$r_s = -.193$ $p = .377$	$r_s = -.021$ $p = .923$	$r_s = -.007$ $p = .975$	$r_s = -.014$ $p = .950$	$r_s = -.096$ $p = .671$	$r_s = .171$ $p = .448$	$r_s = .141$ $p = .511$			
IL-15	$r_s = -.161$ $p = .463$	$r_s = -.148$ $p = .500$	$r_s = -.253$ $p = .244$	$r_s = -.217$ $p = .319$	$r_s = .020$ $p = .927$	$r_s = -.165$ $p = .452$	$r_s = .060$ $p = .785$	$r_s = .105$ $p = .633$	$r_s = -.005$ $p = .980$	$r_s = .470$ $p = .027$	$r_s = .209$ $p = .351$	$r_s = -.249$ $p = .241$			
IL-16	$r_s = -.151$ $p = .492$	$r_s = .004$ $p = .984$	$r_s = .086$ $p = .696$	$r_s = -.268$ $p = .216$	$r_s = -.154$ $p = .483$	$r_s = -.111$ $p = .614$	$r_s = .129$ $p = .556$	$r_s = -.191$ $p = .382$	$r_s = .222$ $p = .308$	$r_s = .107$ $p = .634$	$r_s = .208$ $p = .353$	$r_s = .132$ $p = .538$			
IL-1a	$r_s = .182$ $p = .405$	$r_s = .098$ $p = .656$	$r_s = -.125$ $p = .571$	$r_s = .353$ $p = .098$	$r_s = .178$ $p = .418$	$r_s = .111$ $p = .613$	$r_s = -.216$ $p = .321$	$r_s = -.051$ $p = .816$	$r_s = -.153$ $p = .485$	$r_s = -.022$ $p = .922$	$r_s = -.064$ $p = .779$	$r_s = .079$ $p = .713$			
IL-7	$r_s = -.452$ $p = .030$	$r_s = -.279$ $p = .198$	$r_s = -.357$ $p = .095$	$r_s = -.448$ $p = .032$	$r_s = -.362$ $p = .090$	$r_s = -.541$ $p = .008$	$r_s = -.194$ $p = .375$	$r_s = -.116$ $p = .598$	$r_s = -.173$ $p = .431$	$r_s = .442$ $p = .040$	$r_s = .120$ $p = .596$	$r_s = .109$ $p = .613$			
TNF-b	$r_s = -.103$ $p = .640$	$r_s = .103$ $p = .640$	$r_s = -.107$ $p = .626$	$r_s = -.207$ $p = .343$	$r_s = -.081$ $p = .713$	$r_s = -.198$ $p = .366$	$r_s = .085$ $p = .699$	$r_s = .122$ $p = .579$	$r_s = .126$ $p = .566$	$r_s = .242$ $p = .278$	$r_s = -.026$ $p = .910$	$r_s = -.110$ $p = .610$			
VEGF	$r_s = .048$ $p = .830$	$r_s = -.023$ $p = .918$	$r_s = -.186$ $p = .395$	$r_s = .177$ $p = .418$	$r_s = .152$ $p = .488$	$r_s = .039$ $p = .861$	$-r_s = -.311$ $p = .149$	$r_s = -.164$ $p = .453$	$r_s = -.289$ $p = .181$	$r_s = .044$ $p = .846$	$r_s = -.054$ $p = .812$	$r_s = .231$ $p = .277$			

Note: significant correlations ($p < .05$) for Spearman's Correlations (r_s) are **bolded**. IFN=interferon; IL=interleukin; TNF= tumor necrosis factor; IP= inducible protein; MCP= monocyte chemoattractant protein; MDC= macrophage-derived chemokine; MIP= macrophage inflammatory protein; TAR= thymus and activation-regulated chemokine; GM-CSF=granulocyte-macrophage colony-stimulating factor; VEGF=vascular endothelial growth factor; EQi=Emotional and Quotient Inventory for social-emotional maturity; MAAS=Maternal Antenatal Attachment Score; PDQ=Prenatal Distress Questionnaire; LES=Life Events Scale; BW=Birthweight;

* $n = 22-24$ from incomplete study questionnaires for 2 of the subjects. IL-12p70, IL-13, IL-2, IL-4, IL-5, and GM-CSF had median values of 0.1 or less from many sample below the lower level of detection and thus were not included in the table.

Table 2

Means and Standard Deviations (SD) for Maternal Circulating Cytokine and Chemokine Levels By Race

	White (<i>n</i> = 17) Mean(SD)	Non-White (<i>n</i> = 7) Mean(SD)
IL-17A *	.8 (.6)	2.1 (2.1)
IFN- γ	5.7 (5.1)	6.9 (3.3)
IL-10	.3 (.1)	.3 (.1)
IL-1b *	.04 (.1)	1.1 (2.7)
IL-6	.9 (.7)	1.3 (1.3)
IL-8	2.3 (1.2)	3.6 (2.2)
TNF α	1.8 (.5)	2.2 (.7)
Eotaxin ***	31.8 (17.3)	94.7 (52.8)
Eotaxin-3 **	12.8 (12.9)	37.4 (23.7)
IL-8-ha **	10.0 (23.9)	82.8 (55.3)
IP-10 ***	67.6 (62.5)	216.9 (89.6)
MCP-1 **	19.7 (15.9)	72.5 (43.6)
MDC **	485.6 (287.0)	1138.1 (470.7)
MIP-1a **	7.29 (4.58)	15.87 (7.77)
MIP-1b **	21.9 (14.7)	67.4 (15.0)
TARC **	11.7 (13.3)	40.5 (43.0)
IL-12p40	83.9 (46.9)	87.0 (29.6)
IL-15	2.4 (.4)	2.8 (.9)
IL-16	350.4 (558.2)	1439.2 (2960.2)
IL-1a	4.3 (11.7)	.8 (.6)
IL-7 *	1.6 (1.1)	4.1 (2.6)
TNF-b	.3 (.1)	.3 (.1)
VEGF	16.4 (24.7)	8.0 (7.3)

Note. IFN=interferon; IL=interleukin; TNF= tumor necrosis factor; IP= inducible protein; MCP= monocyte chemoattractant protein; MDC= macrophage-derived chemokine; MIP= macrophage inflammatory protein; TARC= thymus and activation-regulated chemokine; GM-CSF=granulocyte-macrophage colony-stimulating factor; VEGF=vascular endothelial growth factor.

IL-12p70, IL-13, IL-2, IL-4, IL-5, and GM-CSF had median values of 0.1 or less from many sample below the lower level of detection and thus were not included in the table.

* $p < .05$ between White vs Non-White using Mann Whitney-U tests

** $p < .01$ between White vs Non-White using Mann Whitney-U tests

*** $p < .001$ between White vs Non-White using Mann Whitney-U tests