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Influence of prenatal maternal stress on umbilical cord blood cytokine levels

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Abstract

Purpose—Prenatal maternal stress (PNMS) is known to influence fetal programming and development. Thus far, the effects of PNMS on the developing immune system have mainly been documented in animal studies. This study aimed to examine the association between PNMS and immune cytokine profiles in the umbilical cord blood of newborn human infants.

Methods—PNMS, including perceived stress, numbers of stressful life events experiences (both partner and health related), and state and trait anxiety, was assessed with five questionnaires and interviews from 43 pregnant women during the second trimester. Seven key cytokines important for immune function, i.e., IL-12, IL-1β, IL-4, IL-5, IL-6, IL-8, and TNF-α, were analyzed in cord

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Compliance with ethical standards

The study was approved by the Institutional Review Boards at Icahn School of Medicine at Mount Sinai and Queens College, City University of New York.

Conflict of interest

The authors have no conflicts of interest to declare.

blood by bead-based ELISA method (Luminex 200). Logistic regression was used to estimate the associations of PNMS scores and cytokine levels.

Results—Increased levels of IL-1β, IL-4, IL-5, IL-6, and IL-8 were significantly associated with at least one of the maternal stress assessments, while the levels of IL-12 and TNF-α were not significantly associated with any of the PNMS measurements examined.

Conclusion—These preliminary findings suggest that PNMS may influence cytokine levels in newborn infants, in particular Th2-related cytokines. This report supports previous findings in animal studies and could suggest that newborns born to mothers with elevated PNMS have a predisposition to immune-related disorders.

Keywords

Prospective birth cohort outcomes; Prenatal maternal stress; Depression and anxiety; Stressful life events; Umbilical cord blood; Cytokines

Introduction

The prenatal period plays a critical role in the fetal development and postnatal health of offspring through adulthood (Dipietro 2012). Emerging evidence supports a link between prenatal maternal stress (PNMS), including stressful life events and psychological distress/state, and increased risk of adverse birth and fetal development outcomes, such as preterm delivery, low birth weight, fetal growth retardation, and cognitive deficits in offspring later in childhood (Dunkel Schetter 2011; Kinsella and Monk 2009; Littleton et al. 2010; Rice et al. 2007). While the precise mechanisms for these associations are poorly understood, psychological stress is thought to exert influence on human health through inflammation and immunity (Cohen et al. 2007; Glover 2015; Sapolsky 2004). However, due to unique biological features of the maternal-fetal ensemble during pregnancy, including changes in immune and neuroendocrine function, prior findings on psychological stress and immune dysregulation in most human studies may not be easily translated to the special period of pregnancy or prenatal period (Christian 2012).

The effects of PNMS on the developing immune system of the fetus have mainly been documented in animal studies (Veru et al. 2014); current human studies have almost exclusively focused on the behavioral and neuroendocrine effects of prenatal stress. Only one human study has investigated the association between prenatal stress and cytokine profiles in umbilical cord blood (UCB) as an indicator of the effects on the immune system, and their findings suggest that stressful life events altered both innate and adaptive immune responses (Wright et al. 2010). This demonstrates the need for further examination of the influence of prenatal stress on inflammatory and immune processes in the offspring (Chen et al. 2014; Christian 2012; Glover 2014). Moreover, as immune dysregulation has been found to increase the risk of a wide range of chronic immune-mediated disorders such as asthma, various atopic disorders, autoimmune diseases, and cardiovascular conditions, further validation and exploration of the PNMS and fetal immune system relationship are urgently needed (Akdis et al. 2011; Andersson et al. 2016; Cohen et al. 2007; Ridker 2007; Sapolsky 2004).

The current study seeks to examine the influence of PNMS on cytokine profiles of UCB from a still ongoing birth cohort study. We focused on seven cytokines, IL-12, IL-1β, IL-4, IL-5, IL-6, IL-8, and TNF-α, which represent diverse immune processes. IL-4 induces IgE class switching and is a major stimulus of Th2 (i.e., supporter of humoral immunity) as well as suppressor of Th1 development and response (i.e., cellmediated immunity); it is often associated with inflammatory and autoimmune disease (Akdis et al. 2011; Cameron and Kelvin 2003). IL-5 and IL-6 are main secretory cytokines of Th2 cells (IL-6 also being part of innate immune response) and are associated with allergy and chronic inflammatory disease. TNF-α is a prototypic Th1 cytokine and, with IL-12, is involved with the induction of Th1 development and maintenance including the production of IFN-γ (Pincus-Knackstedt et al. 2006). IL-8 is a broad functioning chemokine required in the recruitment of neutrophils to sites of infection or injury; IL-1β is a pro-inflammatory pyrogenic cytokine involved with Th2 cell differentiation to regulatory T-cells; both are associated with various inflammatory disease (Akdis et al. 2011). The diverse selection of cytokines allows us to observe specific patterns in cytokine levels, especially in those related to either Th1 or Th2 immunity, because a skewing toward predominance of Th2 immunity have been implicated to predispose offspring to various immunologic disorders, including atopic disorder, in animal studies.

Materials and methods

Study population

This study utilizes the first 50 women enrolled in the Stress in Pregnancy (SIP) Study, an on-going birth cohort study, at the Icahn School of Medicine at Mount Sinai and Mount Sinai Hospital. Pregnant women were recruited during the second trimester of their pregnancy at the prenatal obstetrics and gynecological (OB/GYN) clinic at Mount Sinai Hospital, which draws patients from East Harlem and the South Bronx in New York City, where the majority of the residents are low-income ethnic minorities. Exclusion criteria for participation included HIV infection, maternal psychosis, maternal age <15 years, life-threatening medical complications of the mother, and congenital or chromosomal abnormalities of the fetus. Demographic information, including maternal age, ethnicity, education level, welfare status, marital status, health condition, and previous obstetric histories, was obtained through self-administered questionnaires during the second trimester, and diagnostic outcomes of depression and anxiety disorders among mothers during pregnancy were ascertained by the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al. 2002) in the third trimester. Of the 50 women enrolled, 43 (86 %) completed prenatal psychosocial stress assessment. The study was approved by the Institutional Review Boards at Icahn School of Medicine at Mount Sinai and Queens College, City University of New York.

UCB collection

UCBs were collected at birth; once the baby was delivered, the cord was clamped, cord blood was collected in red top vacutainer (no additive) tube for serum extraction, and serum aliquots were stored in an ultra-freezer at −80 °C before being analyzed.

Assessment of stress during pregnancy

The study included five relevant and distinct measurements of PNMS: (1) prenatal perceived stress via the Perceived Stress Scale (PSS-14)(Cohen et al. 1983) that assessed mothers' feelings and degree in which situations were considered unpredictable, uncontrollable, and burdensome during the past month; (2) state and (3) trait anxiety via a State-Trait Anxiety Inventory (STAI) that evaluated the temporary condition of "state anxiety" which refers to a person's temporary feeling in time of a perceived threat (e.g., nervousness, or fear) and the long-standing quality of "trait anxiety" which denotes a person's feelings during every day experiences (e.g., stress or worry) (Spielberger 1989; Spielberger and Sydeman 1994); (4) number of stressful life events experienced during the prior trimester related to the quality of relationship with their partner; and (5) number of stressful life events related to medical health problems experienced during the first trimester of the pregnancy via the Life Experience Interview (Dohrenwend et al. 2002).

Cytokines analyses

All cytokines, chemokines, and growth factors were analyzed by the Human Immune Monitoring Core Shared Resource Facility at Icahn School of Medicine at Mount Sinai. Analyses and assays were based on a bead-based ELISA method that employs by Milliplex xMAP technology (Millipore, Billerica, MA, USA) using a Luminex 200 (Luminex Corporation, Austin, TX, USA). Data was analyzed using Milliplex Analyst™ software. Each sample was run in duplicate with the average CV ranged between 0.069 and 0.70 % for seven analyses. The level of detection (LOD) was 1.98, 1.81, 2.00, 0.80, 1.43, 1.57, and 0.77 pg/mL for IL-12, IL-1β, IL-4, IL-5, IL6, IL-8, and TNF-α, respectively.

Statistical analysis

Logistic regression was used to estimate the association of PNMS scores (independent variables) and the levels of cytokines (dependent variables) with reported odds ratios (ORs) and 95 % confidence intervals (CIs). Prenatal perceived stress, state anxiety, and trait anxiety were continuous variables; the number of stressful life events was categorized into two groups (0 or >0). For cytokines IL-12, IL-1β, IL-4, IL-5, and IL-6, of which more than 50 % of samples had levels below the LOD, samples were dichotomized into <LOD or ≥LOD groups. For the remaining two cytokines, IL-8 and TNF-α, samples were dichotomized at the median. Gestational age (continuous) was included in the final model. Adjustment for the other variables (i.e., maternal age, marital status, maternal education level, maternal race, preeclampsia, hypertension, delivery method, number of prior full-term birth, and diabetes) did not result in substantial changes (<10 %) for the observed associations and therefore were not included in the final model (Greenland 1989). All statistical analysis was performed using RStudio Version 0.97.551 statistical software (RStudio, Inc., 2009–2012). Statistical tests were two-sided, and $p \leq 0.05$ was considered statistically significant.

Results

Descriptive statistics of the study population are displayed in Table 1. The mean maternal age was 27.6 years (±5.5), and mean gestational age was 39.0 weeks (±2.6). The majority of

our participants were either Black or Hispanic/Latino (86 %), single or divorced/separated (77 %), and with a high school education or less (56 %).

For self-reported PNMS, the mean scores were 37.4 (±6.5) for prenatal perceived stress, 39.8 (±12.0) for the state anxiety, and 39.4 (±11.4) for the trait anxiety. Ten participants reported at least one stressful life event related to their partner, and nine participants reported one stressful life event related to own health.

The association between PNMS and the level of cytokines is shown in Table 2. All but one PNMS measurements (i.e., state anxiety) were significantly associated with at least one of the cytokines under investigation. Higher prenatal perceived stress was significantly associated with higher levels of IL-6 (OR= 1.23; 95 % CI=1.02–1.48) and IL-8 (OR=1.19; 95 % CI= 1.05–1.35). Significant associations were found between the trait anxiety and both IL-1β (OR=1.11; 95 % CI= 1.01–1.22) and IL-4 (OR=1.09; 95 % CI= 1.01–1.17). Having experienced at least one stressful life events related to partner was significantly associated with higher levels of IL-1β (OR= 8.18; 95 % CI= 1.13–59.02), while events related to health were associated with higher levels of IL-5 (OR= 9.08; 95 % CI = 1.46–56.52), IL-6 (OR = 7.73; 95 % CI = 1.06–56.62), and IL-8 (OR = 6.09; 95 % CI = 1.05–35.37). State anxiety was not associated with any cytokines. Overall, IL-1β, IL-4, IL-5, IL-6 and IL-8, were significantly associated with at least one of the maternal stress measures. Among the seven cytokines examined, the IL-12 and TNF-α were not associated with any PNMS measurement.

Discussion

This short report suggests a link between psychological stress experienced by a mother during pregnancy (i.e., PNMS) and alteration of cytokine profile in offspring at birth. Specifically, higher levels of IL-4, IL-5, IL-6, IL-8, and IL-1β were associated with at least one index of the PNMS factors. Though these findings are preliminary and should be replicated in other studies, they support and extend previous work in humans by showing an association between psychological-related PNMS, such as perceived stress and anxiety, and changes in cytokine profile. This underlines the potential impact of PNMS on the health of the offspring in their postnatal period, especially in relation to altered immunity, which may predispose them to dysregulated immune response and subsequent risk of related disorders such as atopic and chronic inflammatory disorders (Andersson et al. 2016; Cohen et al. 2007; Glaser and Kiecolt-Glaser 2005; McEwen 2007).

The only other human study on UCB cytokine profile in relation to PNMS examined the relationship between the cumulative effect of adverse life events/environmental stressors (such as economic strain, housing worries, neighborhood and community conditions, and difficult life circumstances) and cord blood cytokine response to specific innate and adaptive immune stimulants (such as peptidoglycan and dust mite stimulation) (Wright et al. 2010). The authors found PNMS to alter the cytokine profile and immune response in UCB, which corroborated with our findings that PNMS was significantly associated with IL-1β, IL-6, and IL-8, cytokines that all are involved in the pro-inflammatory innate immune response, as well as IL-5 and IL4 that are prototypic cytokines of the adaptive humoral immune response.

Another study found similar changes in infants at 6 months of age, where prenatal maternal anxiety was associated with an increase of IL-4 and decrease of IFN-γ in response to antigens exposure (O'Connor et al. 2013). Entringer et al., for example, compared peripheral blood mononuclear cells from young women (ages 24–25 years; $n = 62$) whose mothers had or had not experienced negative life events during pregnancy (Entringer et al. 2008). Their findings were consistent with our results, as they found PNMS to be significantly associated to higher levels of IL-4, IL-10, and IL-6 as well as a significant Th2 skewness of immune response. These findings collectively suggest that PNMS may have prolonged impact on immune functioning.

Effects of PNMS on immune functioning have also been found in animal studies. Evidence from rats, swine, and macaques indicates that PNMS affects innate immunity as reflected by altered NK cell and macrophage function (Coe et al. 2007; Kay et al. 1998; Tuchscherer et al. 2002). Also, several animal studies suggest a stress-induced immune imbalance: selectively skewing the system toward suppressed Th1-mediated cellular and/or enhanced Th2-mediated humoral, immune responses (Pincus-Knackstedt et al. 2006; Veru et al. 2014). These alterations are thought to occur via direct influence on cytokine production, which has been supported by observed dampening of TNF-α and IL-12 production and/or enhanced IL-4 and IL-5 production (reflecting Th1 and Th2 patterns, respectively). Our data also suggest that PNMS affects Th2 immunity, with increased IL-4 and IL-5 production, which would normally be accompanied by increased serum levels of IgE as well as eosinophil counts, and thus predisposing to atopic conditions. Previous studies have also shown lower Th1 response through lower IFN-γ levels, which has been linked to higher risk of atopic disorders including asthma (Li-Weber and Krammer 2003; Prescott et al. 1999). However, we did not find any significant association between PNMS and Th1 immunity indicated by lack of association between IL-12 levels (an inducer of IFN-γ production and Th1 cells) and TNF-α. Continued follow-up on this birth cohort, possibly by assessing a wider range of cytokines, will serve to further elucidate the potential relationship between dysregulated immunity and increased susceptibility to the on-set of atopic disorders.

The biological framework for how PNMS influence immune functioning in offspring is not completely understood. Thus far, evidence has linked stress to prolonged stimulatory effects on neuroimmunoregulatory pathways (such as sympathetic nervous system and hypothalamic-pituitary-adrenal axis), which subsequently contribute to an alteration in immuno-development and functioning (Dunkel Schetter 2011; McEwen 2007; Sapolsky 2004). Children are considered particularly vulnerable to unfavorable stressing of these pathways, especially in early life, including the fetal state, during the development and growth of these systems (Dipietro 2012). Our understanding of the transition of stress-response in mother to fetus still lacks causality, though several explanatory mechanisms have been suggested in literature, including transplacental transfer of stress mediators and maternal stress-response activation of placental release of neuroendocrine stress transmitters in the fetus (Glover 2015). Gaining further knowledge of the potential modulatory involvement of placenta could be important steps for future work. For example, Chen et al. found PNMS to influence the expression of genes in placenta tissues that are involved with these physiological pathways of stress response and neurodevelopment (Chen et al. 2014).

Further elucidation of the biological transduction is needed and could be important for future intervention and management of PNMS.

Our study has several methodological strengths. The chosen method for assessing stress during pregnancy has multiple advantages. First, the prospective design minimizes recall biases. Second, self-reporting of PNMS through questionnaire incorporates the subjective perception of an event or condition to be stressful, which is considered the best way to capture actual psychological stress (Eisenberger and Cole 2012). Third, the applied stress questionnaires are recently recommended as highly reliable and validated instruments for measuring PNMS (Nast et al. 2013). Fourth, to the best of our knowledge, this is one of the first studies to assess the association between psychological conditions in mother and UCB cytokine profile. Depressive and anxiety disorders have gained much attention as they are considered major factors for the effects of PNMS on fetal development, and thus, this study contributes to and continues this previous work (Glover 2014, 2015; O'Donnell et al. 2014). Furthermore, UCB provides access to specific cell lineages and is suggested to be ideal for studies that seek to examine the influence of environmental exposures such as psychological stressors on the immune response of cytokines (Chen et al. 2014). Assessing immune functioning through UCB also benefits by solely addressing exposures during prenatal period as opposed to later in life blood-sampling (e.g., during adolescents), which could be influenced by stressful states or events during upbringing (e.g., Entringer et al. blood sampled at 26 years of age, which creates a need for thorough covariates adjusting such as child-hood adversities).

Because of the explorative nature of the study with its small sample size, results from this study should be interpreted with caution. We are currently following up with the entire study cohort, which will provide better understanding for future clinical implications of the present results as children grow and experience negative health outcomes. For example, PNMS has been associated with various atopic outcomes, and a better understanding of the link between perinatal UCB cytokine profiles and risk for the onset of these atopic disorders could be helpful insights to generate test or biomarkers, which could capture these disorders earlier in life. Present findings could have further policy implications with clinical and societal initiative and interventions to reduce stress during pregnancy.

Conclusion

In summary, while preliminary, our results support the notion that PNMS influences the regulation of the immune system, likely through altering cytokines related to Th2 immunity. Continued follow-up with our birth cohort will provide important insights to the understanding of PNMS influence on the alteration and disruption of child immunity and its subsequent importance for susceptibility to the onset of disease.

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Table 1

Demographic and stress characteristics of the study population (*N*=43)

Demographics	Number (%)
Mother's ethnicity	
Black	15 (35)
Hispanic/Latino	22 (51)
Asian	2 (5)
White	2 (5)
Others	2 (5)
Mother's educational attainment	
<High school/drop-out	11 (26)
High school graduate or GED	13 (30)
College degree	17 (40)
Graduate degree	2 (5)
Mother's marital status at delivery	
Married	10 (23)
Single	30 (70)
Divorced/separated	3 (7)
Preeclampsia	
No	38 (88)
Yes	5 (12)
Hypertension	
No	42 (98)
Yes	1 (2)
Current diabetes	
No	41 (95)
Yes	2 (5)
Allergy status	
No	42 (98)
Yes	1 (2)
Delivery method	
Vaginal	31 (72)
C-section	12 (28)
Number of prior full-term birth	
0	17 (40)
>0	26 (60)
Maternal age (years), Mean (SD)	27.6 (5.5)
Gestational age at birth (weeks), Mean (SD)	39.0 (2.6)
Antenatal stress, self-reported	Mean (SD)
Prenatal perceived stress (range 24~53)	37.4 (6.5)
State anxiety (range 20~66)	39.8 (12.2)
Trait anxiety (range 20~63)	39.4 (11.4)

Demographics	Number (%)
Stress life event—partner (negative)	0.5 (0.9)
0	33
1	5
2	2
3	3
Stress life event—health (negative)	
0	34
1	9

Table 2

Influence of maternal stress on the immune biomarkers in umbilical cord blood

Maternal stress	IL-12		IL-β		IL-4		IL-5		IL-6		IL-8		TNF-α	
	Below/ above[a]	OR, 95 % CI	Below/ above	OR, 95 % CI	Below/ above	OR, 95 % CI	Below/ above	OR, 95 % CI	Below/ above	OR, 95 % CI	Below/ above	OR, 95 % CI	Below/ above	OR, 95 % CI
Prenatal perceived stress														
Continuous	30/13	1.11,0.99–1.25	37/6	1.10,0.96–1.27	30/13	1.05,0.95–1.17	35/8	1.09, 0.95–1.24	37/6	1.23, 1.02–1.48	22/21	1.19, 1.05–1.35	23/20	1.06,0.96–1.16
State anxiety														
Continuous	30/13	1.01, 0.95–1.06	37/6	1.08,0.99–1.17	30/13	1.05,0.99–1.11	35/8	1.03,0.96–1.10	37/6	1.02,0.94–1.10	22/21	1.06, 1.00–1.12	23/20	1.01, 0.96–1.07
Trait anxiety														
Continuous	30/13	1.04,0.98–1.11	37/6	1.11, 1.01–1.22	30/13	1.09, 1.01–1.17	35/8	1.07,0.99–1.16	37/6	1.09,0.99–1.19	22/21	1.05,0.99–1.11	23/20	1.00 0.95–1.05
Stress life event – partner (negative)														
0	24/9	1.00	31/2	1.00	25/8	1.00	26/7	1.00	28/5	1.00	19/14	1.00	18/15	1.00
>0	6/4	2.12,0.46–9.76	6/4	8.18, 1.13–59.02	5/5	3.42, 0.75–15.52	9/1	0.49, 0.05–4.72	9/1	0.76, 0.07–7.68	3/7	3.83, 0.80–18.45	5/5	1.10,0.26–4.64
Stress life event—health (negative)														
0	25/9	1.00	31/3	1.00	25/9	1.00	30/4	1.00	31/3	1.00	20/14	1.00	20/14	1.00
>0	5/4	2.68, 0.56–12.86	6/3	4.02,0.61–26.51	5/4	2.38,0.51–11.23	5/4	9.08, 1.46–56.52	6/3	7.73, 1.06–56.62	2/7	6.09, 1.05–35.37	3/6	2.68, 0.56–12.83

Logistic regression model used and adjusted by gestational age

OR odds ratio, *95 % CI* 95 % confidence interval

[a] Below/above: number of <LOD and ≥LOD