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Immune Dysregulation and Glucocorticoid Resistance in Minority and Low Income Pregnant Women

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Summary

Chronic prenatal stress contributes to poor birth outcomes for women and infants. Importantly, poor birth outcomes are most common among minority and low income women. To investigate underlying mechanisms, we tested the hypothesis that chronic stress related to minority or low income status is associated with glucocorticoid resistance as indicated by disruption in the cytokine-glucocorticoid feedback circuit. Home visits were conducted during which 3rd trimester pregnant women completed stress and depression surveys and provided blood for pro- and anti-inflammatory cytokines. Saliva was collected 5 times the preceding day for diurnal cortisol levels. For statistical analyses, women were grouped 3 ways, by race, income, and the presence or absence of either of those risk factors; this last group was labeled high or low general risk. Immune regulation was evaluated by evidence of a functioning negative feedback relationship between cytokines and cortisol. Of 96 participants, 18 were minority, 22 of low income, and 29 either minority or low income (high general risk). Pearson partial correlation identified a significant negative relationship between cortisol area under the curve (AUC) and pro- to anti-inflammatory cytokine ratios in the low general risk women (i.e., Caucasian, higher income) including IFN γ /IL10 ($r = -0.73$, $p < 0.0001$), IL6/IL10 ($r = -0.38$, $p = 0.01$), IL1 β /IL10 ($r = -0.44$, $p = 0.004$) and TNF α /IL10 ($r = -0.41$; $p = 0.005$); no such correlations existed in the high general risk women (i.e., minority, low income) for (IFN γ /IL10: $r = -0.25$, $p = 0.43$; IL6/IL10: $r = 0.12$, $p = 0.70$; IL1 β /IL10: $r = 0.05$, $p = 0.87$; TNF α /IL10: $r = 0.10$; $p = 0.75$), suggestive of glucocorticoid resistance. Cortisol levels throughout the day also were higher in minority and high general risk groups ($p < 0.05$). Without cytokine glucocorticoid feedback, a pregnant woman's ability to regulate inflammation is limited, potentially contributing to adverse maternal and infant outcomes.

Keywords

Cytokines, Cortisol, Cytokine-glucocorticoid feedback circuit, Glucocorticoid resistance, Pregnancy, Minority, Health disparity, Psychoneuroimmunology

Chronic prenatal stress contributes to adverse perinatal outcomes, including preterm birth (Institute of Medicine, 2007), intrauterine growth retardation (Nordentoft et al., 1996), and spontaneous miscarriage (Institute of Medicine, 2007). Infants born premature may experience mental and physical disabilities that last a lifetime (Calkins and Devaskar, 2011). Even infants born at or near term whose mothers were exposed to prenatal stress have increased risk of abnormal neurological development (Davis et al., 2011, Talge et al., 2007), infectious disease (Tegethoff et al., 2011), congenital malformation (Tegethoff et al., 2011), poor executive functioning (Buss et al., 2011), and mood or

behavioral disturbance (Wadhwa, 2005). Although progress has been made to clarify key mechanisms underlying the associations between prenatal stress and adverse pregnancy outcomes (Karrow, 2006, Meaney et al., 2007, Sandman et al., 2011, Weaver, 2007), additional research is required to determine how perturbations in stress-related biological responses conspire to influence poor birth outcomes in high-risk populations (Kramer et al., 2011)

With mental or physical stress, a complex neuroendocrine-immune response is initiated (Sapolsky et al., 2000) that includes activation of the hypothalamic-pituitary-adrenal (HPA) axis and stimulation of the innate immune response, leading to the increased release of pro-inflammatory cytokines (Steptoe et al., 2007, Yang and Glaser, 2002). This response carries benefits as well as risks for a pregnant woman and her offspring. Acute inflammation offers protection from infection and supports healing. However, even acute inflammation increases the risk of premature delivery (Romero et al., 2006) while chronic inflammation carries additional complications, including gestational hypertension (Freeman et al., 2004) and diabetes (Richardson and Carpenter, 2007). Fetal exposure to prenatal inflammation is also under investigation for contributions to fetal growth restriction (Almasry et al., 2012) and childhood diagnosis of autism (Angelidou et al., 2012). Finally, pro-inflammatory cytokines are associated with sickness symptoms, that include fatigue, decreased sleep, poor cognitive function, and depressed mood (Dantzer and Kelley, 2007), each having the potential to impact maternal health.

Mechanisms are in place, during pregnancy (Elenkov et al., 2001) and at other times, to regulate inflammation including a key cytokine-glucocorticoid negative feedback circuit (Besedovsky and del Rey, 2006, Elenkov et al., 2005). Pro-inflammatory cytokines are potent activators of the hypothalamic-pituitary-adrenal (HPA) axis, and contribute to stress-induced elevation in cortisol secretion. Cortisol in turn, is not only important in mobilizing resources to respond to the stressor, but also plays a fundamental role in limiting the inflammatory response and the further production of cytokines (Anisman and Merali, 2003, Besedovsky and del Rey, 2006, Yang and Glaser, 2002). This occurs through synergistic, organized mechanisms (Pace and Miller, 2009), initiated by cortisol binding to glucocorticoid receptors present on immune cells that are critical for regulation of the inflammatory response, such as monocytes and lymphocytes. Considerable evidence suggests that activation of the glucocorticoid receptor attenuates activity of inflammatory signaling pathways, including those that promote production of pro-inflammatory cytokines, while activating pathways that promote production of anti-inflammatory cytokines.

In the case of chronic stress, it has been suggested that prolonged activation of the stress response can promote a state of glucocorticoid resistance that involves an inability of cortisol to inhibit pro-inflammatory signaling pathways, leading to a loss of the normal negative association between cortisol concentration and various indicators of inflammatory immune activation (Pace et al., 2007, Stark et al., 2001). For example, the negative correlation between plasma cortisol concentration and circulating leukocyte subsets seen in non-stressed individuals was lost in subjects experiencing a major chronic stressor during the preceding year, a finding identified as consistent with glucocorticoid resistance (Cohen et al., 2012). Among the mechanisms hypothesized for glucocorticoid resistance include the impact of stress-induced pro-inflammatory cytokine production on glucocorticoid receptor function (Engler et al., 2008, Raison and Miller, 2003) and that sustained elevations in cortisol in response to chronic stress lead to functional resistance to GR signal transduction (Miller et al., 2008). Ultimately,

pro-inflammatory cytokine production can become dysregulated regardless of cortisol levels. Glucocorticoid resistance in response to chronic stress has been identified in caregivers of persons with cancer (Miller et al., 2008), parents of children with cancer (Miller et al., 2002), adults with a history of low early-life social class (Miller et al., 2009), and in women suffering post-traumatic stress syndrome (Pace et al., 2012a).

Although most research on stress and inflammation has focused on non-pregnant individuals, Coussons-Read et al. (2005), in a study of twenty-six pregnant women, reported a positive correlation between self-reported stress and maternal serum levels of pro-inflammatory cytokines interleukin-6 (IL-6) and tumor-necrosis factor-alpha (TNF- α), and a negative correlation between stress and the anti-inflammatory cytokine interleukin-10 (IL-10). These findings suggested a mechanism by which chronic prenatal stress could be linked to adverse pregnancy outcomes. Subsequent reports by the same researchers furthered these findings (Coussons-Read et al., 2007), including most recently a report identifying a linkage between elevated serum cytokines and preterm birth (Coussons-Read et al., 2012). Others, however, have not confirmed a linkage between prenatal stress and either pro-or anti-inflammatory cytokines during pregnancy or preterm birth (Blackmore et al., 2011, Christian et al., 2010).

The relationship between chronic prenatal stress and adverse pregnancy outcome appears to be moderated by race and social class, with minority and low income women disproportionately affected (Institute of Medicine, 2007). After controlling for other variables (e.g., body mass index, smoking), minority and low income women experience worse pregnancy outcomes, including a 64% increase in preterm birth in African American women compared to white women (Institute of Medicine, 2007), and their offspring fare worse in developmental, behavioral, and physical outcomes than infants born to non-minority women (Reichman et al., 2008). Reproductive-age African American and low income women also report increased levels of stress (Paul et al., 2008), a phenomenon these authors and others (Dominguez, 2011, Rich-Edwards and Grizzard, 2005) ascribe to race and class discrimination.

Identifying the underlying mechanisms by which minority status and low income adversely affect pregnant women and their offspring is essential. Based on the previous discussion and evidence of increased inflammatory responses in other populations exposed to chronic stress, we tested the hypothesis that minority status or low income during pregnancy (possible sources of chronic stress) may be associated with dysregulation in the feedback relationship between pro-inflammatory cytokines and cortisol. In addition, because of the effect of chronic stress on the HPA axis and the inflammatory response, we also hypothesized that minority status or low income would be associated with both increased plasma pro-inflammatory cytokine and salivary cortisol levels.

1. Methods

1.1. Subjects recruitment and inclusion/exclusion criteria

The subjects were 96 women in the second or early third trimester of pregnancy who responded to ads placed in prenatal clinics and on community billboards. Subjects who met inclusion criteria during an initial phone conversation were scheduled for a home visit during their 32–36th week of pregnancy. Inclusion criteria were that each subject was between the ages of 18–40 years, anticipating a vaginal birth of a singleton fetus, in good health without pregnancy restrictions, a non-smoker, not afflicted by

any disease that might affect the immune or endocrine systems and not taking any chronic medications including anti-inflammatory agents. These criteria were established to reduce to the extent possible conditions that might themselves be associated with inflammation or endocrine disorder. Subjects also were required to live within a 20 miles of the laboratory, to minimize the time biological samples were in transport, thereby preserving the validity of the biomarkers examined.

1.2. Procedure

At the start of the first home visit, the study protocol was reviewed, and participants provided informed consent for their participation; as a result, all procedures were carried out with the adequate understanding and written consent of the subjects. Participants then completed a demographic questionnaire detailing age, marital status, height, pre-pregnancy weight, race/ethnicity, and whether or not they currently were receiving government financial assistance. Self-reported height and weight were used to estimate pre-pregnancy body mass index (BMI). Participants were also trained to collect saliva samples using Salivette swabs (Sarstedt, Numbrecht, Germany). Instructions included being directed to rinse their mouths out with water and then place the roll-shaped saliva swab in their mouth, roll it around for 60 s then remove the swab and place it in the labeled tube, cap the tube, and place it in their home refrigerator, inside the small, padded tote provided to them. Subjects were additionally instructed not to eat or brush their teeth for at least half an hour before collecting saliva. Subjects practiced the technique with a sample swab under the observation of the research nurse, and then were provided the saliva collection kit. At the end of this training visit, a second home visit was arranged for sample collection and completion of questionnaires; this visit typically occurred within 7-days of the training visit and lasted approximately 30 min. All sample collection visits were conducted by registered nurses between 3:30 and 4:30 PM to control for diurnal variability in both cortisol and cytokines. Subjects were compensated for both home visits.

During the sample collection home visit, subjects provided a fresh saliva sample after which they completed the Perceived Stress Scale (PSS), the Edinburgh Postnatal Depression Scale (EPDS), and a questionnaire asking about their current health, including whether they were experiencing any symptoms of infection. Lastly, blood was drawn from the antecubital vein into EDTA-containing tubes for later measurement of plasma pro-inflammatory cytokines IL-6, IL-1 β , TNF- α , and interferon-gamma (IFN- γ), and anti-inflammatory cytokine IL-10. In addition, on the day preceding the home visit, each woman collected salivary samples upon awakening, 30-min later, and at 11:00 AM, 4:00 PM, and 8:00 PM. To encourage compliance with and accuracy of diurnal salivary collections, each subject was provided a study phone programmed to receive in-coming calls only, and was called the night before the collections were to occur, and the next day, approximately 5-min prior to each of the scheduled saliva collections. Subjects were compensated additionally each time they answered the phone. To verify the times of sample collections, the saliva swabs were kept in Medical Electronic Monitoring System [[MEMS[®]], Apex Corp., Fremont, Calif.]] containers. Each time a sample was taken, the participant would have to remove the MEMS[®] cap, thereby recording the time of the event. Subjects whose sample collections were shown to have been taken at the correct times when the MEMS[®] cap data were read later in the lab, also received additional compensation. Accurate sample collection was defined by MEMS[®] cap readings within 60 min of the designated time, except for the 30-min post-awakening sample. During the 8:00 PM phone call, subjects were reminded of the next day's visit. All samples were kept on ice until reaching the laboratory where they were processed as described below.

1.3. Questionnaires

Questionnaires included the 14-item Perceived Stress Scale (PSS) which was used to provide information on participants' perception of stress (Cohen et al., 1983). The responses are based on a Likert-scale from 0 to 4, or from "never" to "very often." Each question asks the individual how she has been feeling during the past month. The final score is a simple sum of each item response, with some items reverse coded. In Cohen's original report, internal consistency reliability was high (Cronbach's alpha coefficients ranged from 0.84–0.86) as was test-retest correlation (0.85). Evidence for concurrent and predictive validity was significant at $p < 0.05$ ($r = 0.49$). Scores on the PSS have been shown to correlate with measures of HPA axis function during pregnancy and the postpartum period (Ruiz et al., 2003).

The 10-item EPDS was used for self-report of symptoms of depression (Cox et al., 1987). It is an easy to administer and effective screening tool that has been validated for both antepartum and postpartum use. Answers to questions such as "I have looked forward with enjoyment to things" are scored from 0 ("As much as I ever did") to 4 ("Hardly at all"). After completion, a woman's score is summed to provide information on the likelihood of clinical depression. Validation of the EPDS against a diagnostic clinical interview identified a specificity of 78%, a sensitivity of 86%, and a positive predictive value of 73% for women scoring >10 (Cox et al., 1987).

1.4. Biomarker measurement

Upon reaching the laboratory, blood samples were centrifuged at 4 °C for 8 min at 2000 rpm. Plasma aliquots were placed into 1.5 cc polypropylene microtubes and stored separately in the study lab, at –70° C, until assayed using a Human Pro-inflammatory Ultra-Sensitive assay and quantitative multiplex array technology (Meso Scale Discovery, Gaithersburg, Maryland). Intra-assay coefficient of variation was $<5\%$ and inter-assay coefficient of variation was $<10\%$. The level of each cytokine is reported as well as the ratio of each pro-inflammatory cytokine to anti-inflammatory cytokine (e.g., IL-6/IL-10). Measuring the pro- to anti-inflammatory ratio is a sensitive means by which to identify cytokine equilibrium or disequilibrium (Petrovsky and Harrison, 1997).

Upon reaching the laboratory, salivary samples were centrifuged at 4 °C for 3 min at 3000 rpm and aliquoted into 1.5 cc polypropylene microtubes for storage at the study lab at –70°C until assayed. Salivary cortisol levels were determined using an expanded range high sensitivity EIA kit (No. 1-3002/1-3012, Salimetrics, State College, PA). The cortisol detection limit of the kit is .018 mg/dl and shows minimal cross reactivity (4% or less) with other steroids. Intra-assay coefficient of variation was 4.3% and inter-assay coefficient of variation was 5.2%. All samples were measured in duplicate. Area under the curve (AUC) was calculated with respect to ground (Pruessner et al., 2003). The cortisol awakening response was determined based on the difference in salivary cortisol concentration between that measured at awakening to that measured 30-min post-awakening according to the following formula: [30-min post-awakening – awakening]/awakening.

2. Statistical analysis

For comparative analyses, women were grouped three ways; first, as either Caucasian or of a racial/ethnic minority (Race), and second, as being either of high or low income (Income). These categories were determined by self-report of race/ethnicity and by self-report of participation in WIC

or other government assistance programs respectively. For the third group, women were separated based on the presence or absence of either of the two risk factors: being minority or low income. This category is identified in analyses as being of high or low general risk (General Risk). Demographic and clinical characteristics were compared between the race, income and the general risk groups. Continuous variables were compared using the independent sample Student *t*-test. Categorical variables were compared using the Chi-square test or Fisher's exact test when appropriate.

Multiple linear regression was used to assess the difference in the plasma concentrations of cytokines and pro- and anti-inflammatory cytokine ratios between each of the three subject groups (Race, Income, General Risk). Demographic and clinical variables that were significantly related to these groups were controlled for in the multiple linear regressions. Model-based mean and standard error for the cytokine measurements were derived for each subgroup.

Linear mixed (hierarchical) models were performed on the salivary cortisol samples collected upon awakening, 11:00 AM, 4:00 PM, and 8:00 PM to compare the overall temporal pattern in salivary cortisol across the day between subject's groups. Linear mixed models were also performed on the salivary cortisol samples collected upon awakening and 8:30 AM to compare the cortisol awakening response between subject groups. An unstructured variance–covariance form in repeated measurements within a woman was assumed, which provides the most flexible modeling of the covariance structure. Subject-specific random effects were included in the mixed models to accommodate between-subject variation in the cortisol level. The fixed effects in the mixed models include subject group (Race, Income, General Risk), collection time of the sample and the interaction between group and the collection time. The models also include demographic and clinical variables that were found to be significant related to the group variable. The fitted mixed models provided model-based estimates for mean cortisol level at each collection time point for different subject groups. The differences in the temporal pattern of the cortisol between subject groups were evaluated by testing the significance of the interaction term between group and time.

Pearson partial correlation coefficients were used to evaluate the association between daily average salivary cortisol (area under the curve [AUC], calculated using awakening, 11:00 AM, 4:00 PM, and 8:00 PM samples) and pro- and anti-inflammatory cytokine ratios in each subject group while controlling for relevant demographic and clinical variables. Probability values for the partial correlations were computed to test the significance of the association.

In addition to evaluating the independent effects of race and income on the levels of cytokines and salivary cortisol, we also performed additional statistical analyses to evaluate the interaction effects between race and income on the outcome measures. Specifically, we examined the significance of the interaction term between race and income in the multiple linear regression analyses of the plasma concentrations of cytokines and pro- and anti-inflammatory cytokine ratios, controlling for demographic and clinical variables that were significantly related to these groups. We also examined the significance of the interaction term between race and income on salivary cortisol in the linear mixed (hierarchical) models, controlling for relevant demographic and clinical variables. When there were significant interaction effects between race and income, model-based hypothesis tests were applied to evaluate the effect of income for each race group separately.

Because the cytokine and cortisol data were right-skewed, natural log transformations were performed prior to the analysis and results were reported based on back transformation of the log values to the original scale. Statistical analysis was performed using SAS (version 9.2; SAS Institute, Cary, NC) and SPSS 20. All statistical tests were two-sided and a p value of <0.05 was considered statistically significant.

3. Results

Demographic data for the 96 pregnant women in this study are included in Table 1. As shown, 18 participants self-reported minority racial or ethnic status, 11 of whom self-identified as African American and 7 as Hispanic. Twenty two participants reported receiving government aid. Twenty-nine were of minority status or reported receiving government aid and were categorized as the high general risk group; 66 participants were Caucasian and did not receive government aid and were categorized as the low general risk group. None of the participants reported or demonstrated symptoms of infection or illness on the day of the home visit, although four reported a physical complaint: anemia, swelling, allergies, or sciatica for which that woman had taken acetaminophen. With regards to birth outcomes, 7 women delivered by Cesarean section, (7.3%); one of whom was a minority and none of whom were of low income; 2 women required a transfusion after delivery, both were Caucasian and neither of low income; and one Caucasian, non-low income woman gave birth to an infant prematurely. There were no statistically significant differences based on either race/ethnicity or income in these outcomes.

Table 1. Demographic and clinical characteristics of subjects.

	Race		Income		General risk	
	Minority	Caucasian	Low	High	High risk	Low risk
	(<i>N</i> = 18)	(<i>N</i> = 78)	(<i>N</i> = 22)	(<i>N</i> = 73)	(<i>N</i> = 29)	(<i>N</i> = 66)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age	25.9(5.0)	29.6(4.9)**	24.1(4.5)	30.3(4.5)***	25.7(4.8)	30.3(4.6)***
BMI	25.1(4.8)	23.7(3.9)	26.1(5.4)	23.4(3.4)*	25.4(5.1)	23.4(3.4)*
PSS	20.9(7.6)	19.6(6.4)	21.6(6.6)	19.3(6.6)	21.9(7.5)	19.0(6.1)*
EPDS	4.7(4.1)	4.4(3.3)	5.1(4.3)	4.3(3.1)	5.2(4.3)	4.2(2.9)
Marital status	<i>N</i> (%)	<i>N</i> (%) $p = 0.10$	<i>N</i> (%)	<i>N</i> (%) $p < 0.0001$	<i>N</i> (%)	<i>N</i> (%) $p = 0.001$
Other	1(5.6)	1(1.3)	2(9.1)	0(0)	2(6.9)	0(0)
Single	3(16.7)	9(11.5)	7(31.9)	5(6.9)	7(24.1)	5(7.6)
Married	11(61.1)	65(83.3)	10(45.5)	65(89.0)	16(55.2)	59(89.4)
Partner	3(16.7)	3(3.9)	3(13.6)	3(4.1)	4(13.8)	2(3.0)

Notes: values presented are mean and standard deviation (SD) or percentages (%).

* $p < 0.05$.

** $p < 0.001$.

*** $p < .0001$.

As shown in Table 1, the minority group was significantly younger than the Caucasian group ($p = 0.005$) but was similar in BMI and marital status. Compared to the high income group, the low income group was significantly younger ($p < 0.0001$), had higher BMI ($p = 0.04$) and had significantly lower

proportions of being married ($p < 0.0001$). Between the general risk groups, the high risk group was significantly younger ($p < 0.0001$), had higher BMI ($p = 0.05$) and had significantly lower proportions of being married ($p = 0.001$). Mean scores on the PSS were not significantly different between racial/ethnic groups ($p = 0.47$) or income groups ($p = 0.17$). PSS was, however, elevated in the high general risk group ($p = 0.04$).

3.1. Salivary cortisol

Of the more than 300 salivary samples collected, all but 2 were collected within the designated time and both of those were inaccurate at the 8:00 PM sampling. All analyses were run with and without those two samples; there were no differences in results so all samples were included in the reported analyses.

Results from the linear mixed models of the salivary cortisol level are presented in Table 2 and Fig. 1. Subjects with low income had a significantly different temporal pattern in cortisol across the day than subjects with high income ($p = 0.04$; see Fig. 1B). There was no significant difference in the temporal pattern of cortisol between Caucasian and minority women, however, minority women showed a significantly higher level of cortisol than Caucasian women ($p = 0.01$; see Fig. 1A), especially in the time points of 11 AM ($p = 0.01$), 4 PM ($p = 0.04$) and 8 PM ($p = 0.06$). There was likewise no significant difference in the temporal pattern of cortisol between high general risk and low general risk groups. However, high general risk women showed a significantly higher level of cortisol than low risk women ($p = 0.01$; see Fig. 1C), again, especially in the time points of 11 AM ($p = 0.001$), 4 PM ($p = 0.01$) and 8 PM ($p = 0.02$). The change in cortisol from morning awakening to 30 min after was not significantly different between the race groups, the income groups, or the general risk groups (Fig. 1).

Table 2. Results of linear mixed models of salivary cortisol samples ($\mu\text{g/dL}$) for race, income and general risk groups.

	Awake	11:00 AM	4:00 PM	8:00 PM	Group	Time	Group \times time
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	p value	p value	p value
Minority							
Yes	0.43(0.06)	0.41(0.04)	0.23(0.03)	0.17(0.02)	0.01	<0.0001	0.64
No	0.41(0.03)	0.31(0.01)	0.18(0.01)	0.13(0.01)			
p value for yes vs. no	$p = 0.79$	$p = 0.01$	$p = 0.04$	$p = 0.06$			
Income							
High	0.42(0.04)	0.30(0.03)	0.17(0.02)	0.13(0.01)	0.52	<0.0001	0.04
Low	0.33(0.05)	0.38(0.04)	0.20(0.02)	0.15(0.02)			
p value for high vs. low	$p = 0.14$	$p = 0.05$	$p = 0.29$	$p = 0.36$			
GenRisk							
Low	0.39(0.04)	0.27(0.02)	0.16(0.01)	0.12(0.01)	0.01	<0.0001	0.10
High	0.37(0.05)	0.38(0.03)	0.21(0.02)	0.16(0.02)			

p value for high vs. low	$p = 0.69$	$p = 0.001$	$p = 0.01$	$p = 0.02$			
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Note: values presented are model-based mean and standard error (SE) of the salivary cortisol levels ($\mu\text{g/dL}$). Potential confounding factors were controlled for in the linear mixed models.

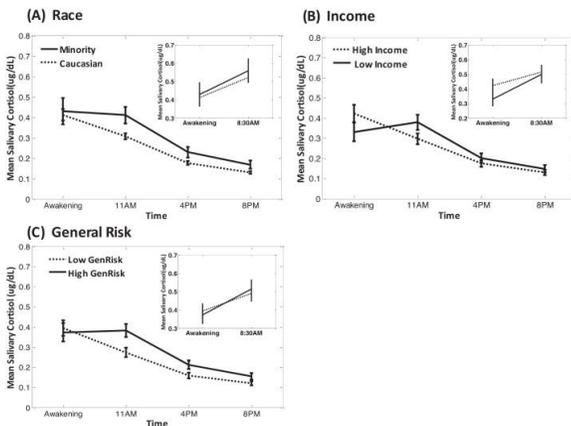


Figure 1. Model-based mean salivary cortisol ($\mu\text{g/dL}$) at each time point for subject subgroups. Error bars represent standard error of the mean.

After controlling for the appropriate demographic and physical variables, the cortisol concentration in the salivary sample collected immediately upon arrival at the subject's homes was elevated in the minority women ($p = 0.01$) compared to the Caucasian women, in women of low compared to high SES ($p = 0.02$), and in women in the high general risk group compared to the low general risk group ($p = 0.004$). These findings were concordant with the results based on cortisol samples collected by the women on their own, on the day preceding the home visit.

3.2. Pro- and anti-inflammatory cytokines

Results based on multiple linear regression of the plasma cytokine measurements are presented in Table 3. After controlling for age, marital status and BMI, there were no significant differences in cytokine levels or cytokine ratios between the low versus high income group or between the low general risk versus high general risk group. When considering minority race/ethnicity, the anti-inflammatory cytokine IL-10 was marginally lower ($p = 0.09$) in minority compared to Caucasian women.

Table 3. Cytokine profile of subjects Mean (SE) (pg/ml).

	Race			Income			General risk		
	Minority	Caucasian	<i>p</i> -value	Low	High	<i>p</i> -value	High risk	Low risk	<i>p</i> -value
	(<i>N</i> = 12)	(<i>N</i> = 52)		(<i>N</i> = 15)	(<i>N</i> = 48)		(<i>N</i> = 20)	(<i>N</i> = 43)	
IL-1 β	1.53(0.20)	1.56(0.10)	0.88	1.55(0.21)	1.22(0.17)	0.16	1.40(0.17)	1.36(0.18)	0.84
IL-6	2.27(0.23)	2.35(0.11)	0.78	2.37(0.25)	2.37(0.26)	0.99	2.33(0.22)	2.43(0.25)	0.68
TNF α	5.53(0.88)	7.29(0.54)	0.13	7.65(1.17)	5.94(1.06)	0.24	6.68(1.06)	6.93(1.19)	0.84
IFN γ	1.86(0.25)	2.20(0.14)	0.28	2.02(0.30)	1.98(0.30)	0.93	1.97(0.27)	2.04(0.30)	0.80
IL-10	3.19(0.96)	5.75(0.80)	0.09	4.51(1.45)	5.55(1.85)	0.61	4.34(1.27)	5.93(1.87)	0.34
Pro- to anti-inflammatory ratios									
IL-1 β /IL10	0.17(0.08)	0.10(0.02)	0.31	0.15(0.07)	0.06(0.03)	0.13	0.11(0.05)	0.08(0.04)	0.48
IL-6/IL-10	0.55(0.17)	0.34(0.04)	0.16	0.40(0.14)	0.38(0.12)	0.85	0.42(0.13)	0.36(0.12)	0.63
TNF α /IL10	1.73(0.49)	1.27(0.17)	0.32	1.70(0.51)	1.07(0.33)	0.22	1.54(0.43)	1.17(0.35)	0.37
IFN γ /IL-10	0.40(0.20)	0.22(0.05)	0.26	0.27(0.13)	0.18(0.09)	0.48	0.26(0.12)	0.18(0.09)	0.46

Notes: values presented are model-based mean and standard error (SE) for cytokine measurements, controlling for relevant demographic and clinical variables. Natural log transformations were performed on the cytokine measurements prior to the analysis and results reported in the table were back transformation of the log values to the usual arithmetic scale.

3.3. Correlation between pro-inflammatory cytokine and cortisol

After controlling for relevant demographic and physical characteristics, we identified significant differences in the correlations between cortisol and cytokines between women within the general risk group. Fig. 2 graphically displays the different patterns of association between cortisol AUC and pro- to anti-inflammatory cytokine ratios in this group. As shown, there were significant negative correlations in the low general risk women – as indicated by the negative slope (solid circles, blue lines) – between daily average salivary cortisol AUC and pro- to anti-inflammatory cytokine ratios including IFN γ /IL-10 (Pearson's partial $r = -0.73$, $p < 0.0001$), IL6/IL-10 ($r = -0.38$, $p = 0.01$), IL1 β /IL-10 ($r = -0.44$, $p = 0.004$), and TNF α /IL-10 (Pearson's partial $r = -0.41$; $p = 0.005$). In contrast, there were no negative correlations between any pro- to anti-inflammatory cytokine ratio and cortisol in the high general risk women (IFN γ /IL10: Pearson's partial $r = -0.25$, $p = 0.43$; IL6/IL10: Pearson's partial $r = 0.12$, $p = 0.70$; IL1 β /IL10: Pearson's partial $r = 0.05$, $p = 0.87$; TNF α /IL10: Pearson's partial $r = 0.10$; $p = 0.75$), as indicated by the relatively flat slopes (open circles, red lines) in Fig. 2.

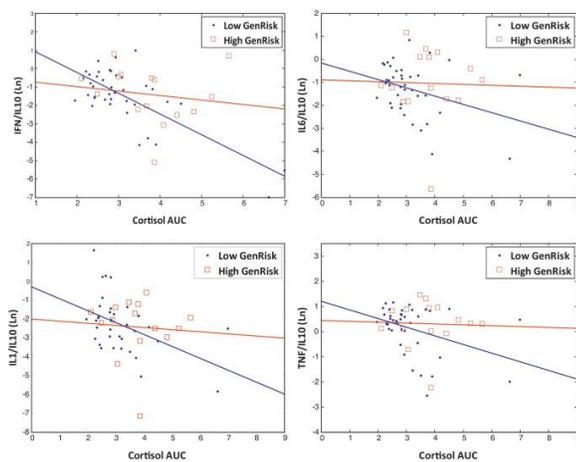


Figure 2. Different patterns of association between cytokine and salivary cortisol in general risk groups (the blue/red lines represent low/high general risk groups).

3.4. Interaction effects between race and income

After controlling for relevant demographic and physical characteristics, we found significant interaction effects between race and income on IL1/IL10 ratio ($p = 0.05$). Specifically, the IL1/IL10 ratio was significantly higher for those with low income vs. those with high income in the minority group ($p = 0.02$). But this significant difference in IL1/IL10 ratio between low and high income women was not found in the Caucasian group ($p = 0.66$). No significant interaction effects between race and income were found on the salivary cortisol, controlling for relevant demographic and clinical variables

4. Discussion

In this report, we describe the effects of chronic social stress on the relationship between cortisol and the pro-inflammatory cytokines in a uniquely vulnerable population, pregnant women. The most significant finding is that chronic stress related to minority status or low income was associated with elevated cortisol without a compensatory decrease in pro-inflammatory cytokine concentration; such a diminished negative feedback relationship between cortisol and pro-inflammatory cytokines is indicative of glucocorticoid resistance. Without negative feedback, an individual's ability to regulate

inflammation is limited. Although similar findings have been reported previously in patients with high lifetime trauma exposure (O'Donovan et al., 2012), in caregivers of family members with cancer (Miller et al., 2008, Miller et al., 2002) and in individuals with a lifetime exposure to low socioeconomic status (Miller et al., 2009), to our knowledge, this is the first report to identify diminished negative feedback as occurring in pregnant minority or low-income women.

Diminished regulation of the inflammatory response related to chronic stress in other populations has been linked to glucocorticoid resistance (Cohen et al., 2012, Miller et al., 2009, Pace et al., 2012b, Rohleder, 2012). Normally, binding of cortisol to the glucocorticoid receptor reduces WBC production of pro-inflammatory cytokines by inhibiting NF-kappaB (NF- κ B), a transcription factor that regulates expression of pro-inflammatory genes (Pace et al., 2007, Pace et al., 2012a, Rohleder, 2012). With chronic stress, this feedback circuit becomes disrupted (Besedovsky and del Rey, 2006). Since we did not measure NF- κ B activity we are unable to determine whether transcription factor activity was increased in the minority and/or low income pregnant women compared to the white or more economically advantaged women. The findings in this study highlight, however, the significant impact of poverty and minority race/ethnicity on psychoneuroimmune functioning in pregnant women and emphasize the need for future research in this important area.

Also not addressed in this study is whether dysregulated inflammation was present in the minority or low income women before they became pregnant. Because all subjects were required to be non-smokers with no chronic health conditions and not taking any medications or herbs on a regular basis, we conclude that the indicators of dysregulated inflammation likely reflect a pre-existing vulnerability, and are not due to disease or specific to pregnancy. This is in line with the concept of weathering proposed by Geronimus to explain the unique and cumulative damage to the health of African American women posed by racism and discrimination (Geronimus et al., 2006). In the data provided in this report, a biological underpinning of weathering may be visible.

Likewise, our finding that minority status or low income was associated with elevated cortisol levels during pregnancy is troubling at many levels. First, chronically elevated cortisol contributes to adverse health conditions in non-pregnant individuals including obesity, hypertension, diabetes mellitus, and cancer (Seeman et al., 2010), all disproportionately present in socially and economically disadvantaged women (Arbour et al., 2012). In regard to pregnancy, a systematic review of the literature has identified clear evidence of a relationship between premature birth and elevated maternal cortisol levels (Giurgescu, 2009). In the current study, despite the high levels of salivary cortisol present throughout the day in the high risk women, pro-inflammatory cytokine levels were not decreased, which is explained by the finding of glucocorticoid resistance. This may be the "weathered state" that is a vulnerability for disease. In addition, fetal exposure to elevated HPA activity may predispose offspring to adulthood hypertension, obesity, and insulin resistance (Calkins and Devaskar, 2011). Whether these adverse effects result from fetal exposure to neuroendocrine, cardiovascular, or inflammatory stimuli or from epigenetic modification of the fetal brain remains under investigation (Sandman et al., 2011).

Coussons-Read and colleagues (Coussons-Read et al., 2007, Coussons-Read et al., 2005) reported that chronic stress is associated with elevated serum IL-6 and TNF- α in pregnant women, and subsequent risk of preterm birth (Coussons-Read et al., 2012). Data from the present study did not find such

elevations in cytokines after controlling for appropriate demographic and physical variables. However, we did find a trend toward lower levels of IL-10 in the minority women and an increase in the ratio of IL-1/IL-10 in the minority group only. Ultimately, given the range of biologic, behavioral, and socioeconomic factors that may affect cytokine levels, a larger sample size may be needed to provide sufficient statistical power for detecting differences in cytokine levels between groups of pregnant women.

The linkages between minority status, low income, chronic social stress, and the regulation of inflammation, raise a host of implications when considering clinical strategies to promote health and the prevention of illness. If an individual is affected physiologically simply due to the fact that he or she is a member of a racial or ethnic minority or by being of low income, the benefits of typical prevention and intervention strategies may be limited. This may explain why adding a behavioral intervention to reduce or manage stress in African Americans with chronic disease significantly improves outcomes compared to usual care (Schneider et al., 2005). Lastly, since chronic inflammation has been linked to long term adverse health outcomes, if immune dysregulation exists outside pregnancy in minority and low income women, their future health may be compromised as well.

As with all studies, there are important limitations to our findings. First, the sample was not a random one, but a convenience sample. Inclusion was limited to only relatively healthy women between the ages of 18–40 who did not smoke and were taking no chronic medications, making it difficult to generalize to other groups of pregnant women. Likewise, only women motivated to contact the research team, to follow the somewhat burdensome saliva collection protocol, and to allow a member of the research team to come to their homes were included. Second, only one self-report measure of stress was used (the PSS) that may not reflect perceived stress similarly across groups. Additionally, social economic status of the subjects was assessed using the dichotomized measure of whether or not subjects were participating in WIC, a government support program. A continuous scale of income may have provided a more accurate measure of the social economics status of subjects. Third, although we attempted to verify timing of salivary cortisol samples, and the MEMS caps' records suggested accuracy for nearly all of the women nearly all of the time, there is no absolute guarantee that subjects did indeed collect their saliva samples at the correct time. There was, however, no indication, that members of one race/ethnicity or income category were more or less likely to have accurate collections. Fourth, the number of minority and low income participants was small, increasing the risk of Type 2 error. Finally, the rates of surgical births were low and there were no differences in perinatal outcomes between groups, both perhaps reflecting the bias of the study toward the inclusion of only generally healthy pregnant women. This may also reflect the younger age of the minority and low income women; the weathering hypothesis suggests that, at least for minority women, younger age is associated with lower accumulated health burden and thus better pregnancy outcomes (Geronimus, 1996).

In summary, our findings suggest that pregnant minority or low-income women experience dysregulation in the cytokine-glucocorticoid feedback circuit reflective of glucocorticoid resistance. Such dysregulation carries the potential for significant health risks for less advantaged women and their infants. Further mechanistic and interventional research into this critical area is required.

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Conflict of interest

All authors report no conflict of interest to disclose, including that related to any financial, personal or other relationships with other people or organizations within three years of beginning the work submitted.

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