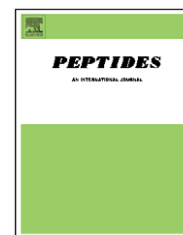


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Ethnic differences in adrenocorticotrophic hormone, cortisol and corticotropin-releasing hormone during pregnancy

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ARTICLE INFO

Article history:

Received 2 January 2007

Received in revised form

11 April 2007

Accepted 11 April 2007

Published on line 19 April 2007

Keywords:

Pregnancy

Ethnicity

Race

Adrenocorticotrophic hormone

(ACTH)

Cortisol

Corticotropin-releasing hormone

(CRH)

Preterm birth

ABSTRACT

Significant ethnic disparities exist in reproductive outcomes. A potential contributing factor may be the functioning of the hypothalamic-pituitary-adrenal (HPA) axis and placenta during pregnancy. In the present study, levels of cortisol, ACTH and CRH were determined longitudinally from the plasma of 310 African American, Hispanic and non-Hispanic White women at 18–20, 24–26 and 30–32 weeks' gestation. During pregnancy, African American women exhibited lower levels of cortisol than non-Hispanic women and higher levels of ACTH than Hispanic women. The trajectory of CRH increase also differed by ethnicity, with African Americans exhibiting the lowest levels both early and late in pregnancy. Higher levels of cortisol at 18–20 weeks were associated with higher levels of CRH at 30–32 weeks among the African American and Hispanic women, but not among non-Hispanic women. Ethnic differences persisted when adjusting statistically for sociodemographic and biomedical factors. The findings are consistent with the possibility that ethnic disparities in adverse birth outcomes may be due, in part, to differences in HPA axis and placental function.

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Ethnic disparities in adverse birth outcomes are substantial and persistent. Among the most dramatic disparities are the particularly high levels of poor reproductive and infant outcomes reported for African American women. The infants of African American women are 75% more likely to be born preterm (<37 weeks' gestation), they are almost twice as likely to be born low birth weight (<2500 g) and more than 2.5 times more likely to die during the fetal, perinatal, neonatal and infant periods than the offspring of non-Hispanic White women [17]. Thus far, the explanation for such differences

remains elusive despite the large number of studies conducted that have addressed this issue. The disparities cannot be fully accounted for by sociodemographic or behavioral factors such as income, education, marital status, parity, maternal age, prenatal care or substance use [3,5,9,16,17,25].

One potential factor that may contribute to the disparities in adverse birth outcomes is differences in the functioning of the hypothalamic-pituitary-adrenal (HPA) axis and placenta. The products and function of the HPA axis and placenta during pregnancy play a critical role both in the timing of onset of

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doi:10.1016/j.peptides.2007.04.005

Table 1 – Sample characteristics

	African American (n = 53)	Hispanic (n = 82)	Non-Hispanic White (n = 175)	F or χ^2
Age at delivery	29.8	29.0	32.1	12.76**
Parity (% nulliparous)	42%	41%	66%	18.98**
Prepregnancy BMI	27.6	26.8	23.6	14.42**
Medical risk (% with no risk factors)	11%	23%	29%	7.09 [†]
Adjusted annual household income	\$18,084	\$15,765	\$32,703	44.31**
Education				65.87**
High school or less	57%	61%	22%	
Associates or vocational degree	13%	21%	12%	
Bachelors degree	24%	13%	38%	
Graduate or professional degree	6%	5%	28%	

BMI = body mass index; adjusted income = total annual household income divided by the number of household members.

[†] $p < .05$.

** $p < .01$.

parturition as well as fetal growth [18,27,29]. Heightened levels of circulating corticotropin-releasing hormone (CRH), a stress-sensitive peptide produced by the placenta, are risk factors for shortened gestational length [12,18,28]. In addition, a recent paper provides evidence that levels of maternal cortisol early in pregnancy may “prime the placental clock”, determining the trajectory of the surge in CRH and affecting the length of gestation [24]. Exposures to higher levels of cortisol early in pregnancy were associated with accelerated CRH trajectories, which were predictive of shortened gestation. One important aspect of the documentation of this relation “in vivo” is that it provides a plausible mechanism through which stress exposure might influence the timing of onset of parturition. Exposure to physical or environmental stress early in pregnancy would increase cortisol levels and these increased levels would result in an altered CRH trajectory and an earlier delivery. To date, no study has explored whether meaningful individual differences exist in the relation between cortisol levels early in gestation and the later surge in CRH.

In the non-pregnant state, ethnic differences in functioning of the HPA axis are clearly documented [31–34]. Although a role for differences in functioning of the HPA axis and placenta in ethnic disparities in birth outcomes is plausible, even likely, to date few studies have explored whether or not differences in functioning of the HPA axis and placental CRH during pregnancy exist. Holzman and colleagues have shown that CRH levels are lower among African American women than in White women at 15–19 weeks’ gestation [12]. Lower levels of CRH in Hispanic women compared to non-Hispanic White women during the second trimester also have been reported [23,26].

This study examined differences among African American, Hispanic and non-Hispanic White women in HPA axis products (cortisol, adrenocorticotrophic hormone; ACTH) and CRH longitudinally during pregnancy. Further, it explored the extent to which sociodemographic and biomedical factors, which differ between the ethnic groups, account for any observed differences. The study also assessed whether the documented positive relation between early cortisol and later CRH levels differs between ethnic groups. This study adds to the small existing literature examining ethnic differences in HPA axis and placental function in four critical ways. First, to date no study has assessed differences in the products of the

HPA axis during pregnancy between Hispanic and African American women. Second, no study of ethnic differences has conjointly examined ACTH, cortisol and CRH during pregnancy. Third, the three previous studies documenting ethnic differences in CRH levels have not included potential socio-demographic and biomedical confounds [12,23,26] (with the exception of one study that did include maternal weight as a covariate [26]). Last, for the first time, this study examines whether there are meaningful individual or ethnic differences in the association between cortisol levels early in pregnancy and CRH levels later in pregnancy.

1. Experimental subjects

Participants were English-speaking pregnant women who participated at one of two Southern California sites: Cedars Sinai Hospital in Los Angeles and the University of California, Irvine Medical Center. All of the women were over the age of 18, non-smokers and had a singleton pregnancy. None had systemic disease or were taking corticosteroid medications. Participants were included in the present study if they were African American ($n = 53$), Hispanic ($n = 82$) or non-Hispanic White ($n = 175$) and had complete endocrine data at each of the three data collection points.¹ Ethnicity was self-reported and among the Hispanic women, 82% were fluent in Spanish and the great majority were of Mexican or Central American heritage. Sample characteristics are shown in Table 1.

2. Materials and methods

The study procedures were approved by the Institutional Review Boards of the participating institutions and all participants provided written informed consent. Women were seen longitudinally at three time points during pregnancy: 18–20 weeks’ ($M = 19.3$), 24–26 weeks’ ($M = 24.9$) and 30–32 weeks’ ($M = 30.9$) gestation. Blood was collected at each visit and then

¹ There were additional 62 women of other ethnic groups who were not included in the study sample because there was not enough of any in a single group on which the analyses could be conducted.

assayed to determine plasma levels of cortisol, ACTH and CRH. The study visits were conducted in the afternoon to control for possible circadian influences on the endocrine measures. Despite this methodological control, the ethnic groups did differ slightly in time of draw at the first study assessment (African American $M = 2:43$ p.m., Hispanic $M = 3:28$ p.m.; non-Hispanic White $M = 3:06$ p.m., one-way ANOVA, $p < .05$). The mean draw time did not differ among the ethnic groups at the second or third study visits (one-way ANOVA's, both p 's $> .17$).

Blood (25 ml) was drawn and deposited into siliconized EDTA (purple top) vacutainers, placed on ice, and then centrifuged at $2000 \times g$ for 15 min. The plasma was decanted into polypropylene tubes containing 500 KIU/ml aprotinin (to arrest enzymatic degradation; Sigma Chemical) and stored at -70°C until assayed.

Medical risk for preterm birth was defined a priori as the presence of certain historical risk factors and medical conditions in the index pregnancy including previous history of preterm birth, vaginal bleeding and pregnancy-induced hypertension [11]. Risk conditions were determined through interview and extensive medical chart review. Medical risk was coded as a dichotomous variable with "1" indicating the presence of at least one condition and "0" indicating the absence of any current or historical risk conditions.

Plasma levels of ACTH were measured by a commercially available direct solid phase two-site immunoradiometric assay (IRMA) with non-significant cross-reactivity with beta-endorphin and ACTH fragments, and with reported detection limits of 1.0 pg/ml (Nichols Institute Diagnostics; San Juan Capistrano, CA). The ACTH immunoassay measures intact ACTH in a radiolabeled soluble sandwich complex bound to two antibodies with high affinity and specificity for ACTH coupled to a solid bead matrix. Briefly, duplicate samples (200 μl /assay tube) were incubated with ACTH ^{125}I -antibody solution (100 μl) and an avidin-coated bead at room temperature for 20 ± 1 h. After washing, the bead with bound radiolabeled antibody complex was quantified using an ICN Biomedical (formerly Micromedex) Isoflex Gamma Counter. The intra- and inter-assay coefficients of variance were 4.4% and 10.8%, respectively.

Plasma levels of cortisol were determined by a competitive antibody coated tube radioimmunoassay (RIA) with reported sensitivity of 0.22 $\mu\text{g}/\text{dl}$ (American Laboratory Products Company, Windham, NH). Plasma samples (25 μl) were incubated with ^{125}I -labeled cortisol (500 μl) in antibody coated tubes for 45 min in a 37°C water bath. The aspirated antibody-bound labeled tubes were counted on an ICN Biomedical (formerly Micromedex) Isoflex Gamma Counter. Cross-reactivities of the cortisol antiserum are $<5\%$ with 11-deoxycortisol, cortisone, prednisone, and $<1\%$ cross-reactivity with other naturally occurring steroids. The intra- and inter-assay coefficients of variance are 6.6% and 10.6%, respectively.

CRH was extracted from 1 to 2 ml plasma with three volumes of ice-cold methanol by the modified method of Linton et al. [14]. The mixture was allowed to stand for 10 min at 4°C and then centrifuged at $1700 \times g$ for 20 min at 4°C . Pellets were washed with 0.5 ml methanol and the combined supernatants were dried in a speed vacuum concentrator (Savant Instruments, Holbrook, NY). CRH was measured by a modified double-antibody commercially available RIA kit

(Bachem Peninsula Laboratories, San Carlos, CA), which specifically detects human CRH without cross-reactivity with CRH precursors and human ACTH, as previously described [24]. Briefly, reconstituted samples were preincubated with anti-CRH serum for 48 h at 4°C followed by a 24-h incubation with ^{125}I -CRH. Labeled and unlabeled CRH was collected by immunoprecipitation and the aspirated pellets were quantified with a gamma counter (ICN Biomedical, formerly Micromedex, Isoflex Gamma Counter). Intra- and inter-assay coefficients of variance ranged from 5% to 15%, respectively.

2.1. Data reduction and analysis

Standard curves were computed by fitting to a four-parameter logistics equation [22]. Differences in ACTH, cortisol and CRH profiles across pregnancy were initially assessed with 3 (ethnicity) \times 3 (weeks' gestation) repeated measures ANOVAs. Those that revealed statistically significant effects of ethnicity were repeated with ANCOVAs in which those variables that differed by ethnic group were entered as covariates (see Table 1 for the list of variables). In addition, because the groups differed in mean blood draw time at the initial study visit, and because cortisol was modestly correlated with draw time at this point ($r = -.20$, $p < .01$), time of draw also was included as a covariate in the ANCOVAs examining group differences in cortisol at 18–20 weeks. All reported repeated-measures results utilized the Greenhouse-Geisser correction. Post hoc comparisons were computed using the Bonferroni correction. The relation between cortisol at 18–20 weeks and CRH at 30–32 weeks was determined within each ethnic group first by zero-order Pearson correlation coefficients and then with partial correlations. The differences between correlation coefficients were tested with the null hypothesis test for the difference between correlation coefficients as recommended by Cohen et al. [4].

3. Results

3.1. ACTH

ACTH levels during pregnancy increased in all three groups (see Fig. 1A; repeated measures ANOVA, main effect of gestation; $F = 193.80$, $p < .01$). In addition, there was a main effect of ethnic group ($F = 4.88$, $p < .01$). The ethnicity \times time interaction was not statistically significant ($p > .22$). The results of an ANCOVA (adjusting for annual income, education, maternal age, parity, body mass index and medical risk) also indicated that ACTH levels differed across pregnancy by ethnic group (see Table 2 for estimated means; $F = 3.89$, $p < .05$). The post hoc comparisons revealed that the African American women had higher adjusted ACTH levels than the Hispanic women ($p < .05$), and that the ACTH levels of the non-Hispanic White women did not differ statistically from either of the other two groups (both p 's $> .39$).

3.2. Cortisol

Fig. 1B displays the cortisol levels for the three ethnic groups during pregnancy. The repeated measures ANOVA revealed a

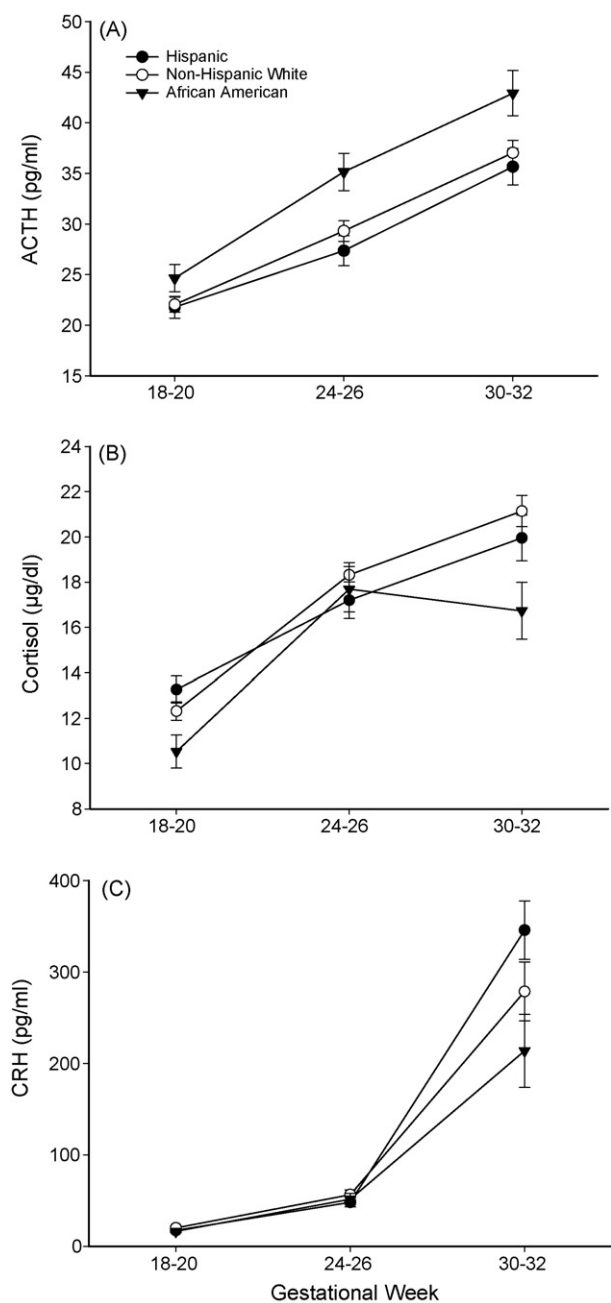


Fig. 1 – Levels of ACTH, cortisol and CRH in African American, Hispanic and non-Hispanic White women during pregnancy.

main effect of ethnic group ($F = 3.78, p < .01$). There also was a statistically significant interaction between ethnicity and gestational week ($F = 2.88, p < .05$). All groups showed an increase in cortisol from 18–20 weeks' to 24–26 weeks' gestation. However, from the second visit to the 30–32 weeks visit, the Hispanic and the non-Hispanic White women showed an increase while the African American women showed a decrease in cortisol levels. The ANCOVA confirmed a main effect of ethnic group (see Table 2 for estimated means; $F = 3.2, p < .05$) and the post hoc tests revealed that, although the cortisol levels of Hispanic women did not differ

from the other two groups (both p 's $> .2$), African American women displayed lower adjusted levels than the non-Hispanic White women ($p < .05$). There also was a statistically significant interaction between ethnic group and gestation (ANCOVA; $F = 3.50, p < .05$). Separate one-way ANCOVAs at each gestational time point indicated that the groups did not differ statistically at the first two visits (both p 's $> .06$), but they did differ at the 30–32 weeks assessment ($F = 5.07, p < .01$). Post hoc comparisons indicated that the African American women had lower cortisol levels than the non-Hispanic White women ($p < .01$) and that the Hispanic women did not differ from the other two groups at this third study visit (both p 's $> .20$).

3.3. CRH

Levels of CRH for each of the groups showed a dramatic increase by the 32nd week of gestation (see Fig. 1C; repeated measures ANOVA; $F = 180.41, p < .01$). Mean differences of ethnic group across pregnancy did not achieve statistical significance ($F = 2.83, p = .06$). The largest separation of means occurred at 30–32 weeks' gestation and this was reflected in a statistically significant interaction between ethnicity and gestation ($F = 3.66, p < .05$). Repeating the analyses with an ANCOVA yielded a significant main effect of ethnicity (see Table 2; $F = 3.13, p < .05$). However, post hoc analyses did not indicate statistically significant group differences in the average adjusted levels of CRH across pregnancy (all p 's $> .06$). The ethnicity by gestation interaction remained statistically significant with the introduction of the biomedical and sociodemographic covariates (ANCOVA; $F = 3.98, p < .05$). This interaction was explored with three one-way ANCOVAs. At the 18–20 weeks visit there was an effect of ethnicity ($F = 3.39, p < .05$), with the African American women showing lower levels of CRH than the non-Hispanic women (post hoc test, $p < .05$). None of the groups differed at the second visit at 24–26 weeks ($F = .20, p = .82$). Differences again emerged at the final study visit ($F = 3.75, p < .05$). Again, African American women had the lowest levels. They exhibited lower levels of CRH compared to the Hispanic women (post hoc test, $p < .05$), and the CRH levels of the non-Hispanic White women fell in between (both p 's $> .12$).

3.4. Relation between cortisol and CRH

Table 3 shows the relation between early cortisol and later CRH among the three ethnic groups. For both the African American and Hispanic women, there was a positive relation between cortisol at 18–20 weeks' gestation and CRH at 30–32 weeks (both r 's $> .35, p$'s $< .01$). In contrast, this association was not present among the non-Hispanic White women ($r = .13; p = .13$). The null hypothesis test for the difference between correlation coefficients confirmed that the relation between cortisol and CRH for the African American and Hispanic women differed statistically from that in the non-Hispanic White women (both p 's $< .05$). Reanalysis with partial correlations, adjusting for the effects of the sociodemographic and biomedical covariates, revealed the same pattern of findings: there was a positive association between early cortisol and later CRH among the African American and

Table 2 – Raw and adjusted means for HPA products and CRH during gestation by ethnic group

	African American		Hispanic		Non-Hispanic White	
	Mean	Estimated mean	Mean	Estimated mean	Mean	Estimated mean
ACTH (pg/ml)						
18–20 weeks	24.7	24.2	21.8	21.6	22.1	22.3
24–26 weeks	35.2	33.7	27.4	26.5	29.3	30.2
30–32 weeks	42.9	41.5	35.7	34.6	37.0	38.0
Cortisol (µg/dl)						
18–20 weeks	10.5	10.8	13.3	13.4	12.3	12.2
24–26 weeks	17.7	17.8	17.2	17.3	18.3	18.2
30–32 weeks	16.7	16.4	19.9	19.4	21.1	21.5
CRH (pg/ml)						
18–20 weeks	16.3	15.5	17.7	17.3	19.9	20.4
24–26 weeks	51.5	53.8	48.1	50.9	56.4	54.4
30–32 weeks	213.7	229.0	345.8	360.6	278.7	267.1

Estimated means are adjusted for adjusted annual income, education, maternal age, body mass index, parity and medical risk.

Hispanic women, but not among the non-Hispanic White women (see Table 3; both *p*'s < .01).

4. Discussion

During the course of pregnancy, African American women exhibited lower levels of cortisol than non-Hispanic White women and higher levels of ACTH than Hispanic women. In addition, the trajectory of CRH increase during pregnancy differed depending on ethnic group, with the African American women showing the lowest levels both at 18–20 weeks and at 30–32 weeks. Ethnic differences also were seen in the relation between early cortisol and later CRH. High levels of cortisol at 18–20 weeks were associated with higher levels of CRH at 30–32 weeks' gestation among the African American and Hispanic women, whereas this relation was near zero among the non-Hispanic White women. These data document, for the first time, that group differences may exist in the extent to which cortisol “primes the placental clock” or determines later CRH levels that are predictive of length of gestation. All of these differences persisted when adjusting statistically for income, education, maternal age, body mass index, parity and medical risk for preterm birth. Other than three published studies examining circulating CRH levels (described below), we are unaware of studies examining the heterogeneity of placental hormones across ethnic groups. In light of the ethnic disparities in birth outcomes and these new findings documenting ethnic differences in HPA axis products

and CRH levels during pregnancy, further examination of placental hormones is warranted.

Two studies have documented previously that levels of CRH differed between non-Hispanic White and Hispanic women during the second trimester [23,26]. We did not reproduce these results. Future research will have to reconcile this inconsistency. However, it is worth considering that our study included sociodemographic and biomedical covariates that vary systematically between these two ethnic groups and that also affect HPA axis function and the other two studies did not, providing one possible interpretation of the disparate findings. On the other hand, the present findings were consistent with the findings of Holzman et al. [12] demonstrating lower levels of CRH in African American compared to White women during the first half of the second trimester. Further, these data suggest for the first time that meaningful differences in circulating CRH levels may exist between Hispanic women and African American women during the third trimester of pregnancy.

Our findings regarding ethnic variation in levels of cortisol and ACTH during pregnancy are consistent with studies documenting differences in the HPA function of healthy non-pregnant African American and White women. When exposed to physical exercise or the administration of ovine CRH, African American women exhibited higher levels of ACTH than White women [31,33,34]. However, for both challenges, these higher ACTH levels were not associated with higher levels of total or free cortisol [31,33,34]. This same ACTH/cortisol pattern in response to CRH stimulation also is found in pre- and early pubescent African American girls [32]. In non-pregnant women it is in the presence of a stressor or under stimulation when ethnic differences in HPA function emerge. This contrasts with our findings in which baseline levels of cortisol during pregnancy differ between African American and White women in the apparent absence of a specific stressor. This is not necessarily surprising because pregnancy represents a period of endocrine change that is almost identical to that seen during prolonged periods of stress (with an exception being the high levels of circulating CRH during pregnancy, which are not present in the non-pregnant state). In addition, it has been proposed that physiological demands of pregnancy represent a “medical stress test” through which

Table 3 – Correlations between cortisol levels at 18–20 weeks' and CRH levels at 30–32 weeks' gestation within ethnic groups

	<i>r</i>	<i>p</i> -Value	Partial <i>r</i> ^a	<i>p</i> -Value
African American	.39	.00	.38	.01
Hispanic	.35	.00	.31	.01
Non-Hispanic White	.13	.13	.09	.22

^a Partial correlations are adjusted for adjusted annual income, education, maternal age, body mass index, parity and medical risk.

a woman's physiological vulnerabilities and likelihood of development of disease later in life can be revealed [30].

We note that the relatively low cortisol levels seen among the African American women are consistent with a pattern of HPA axis dysregulation present in those exposed to traumatic and prolonged stress. Combat veterans, victims of sexual abuse, holocaust survivors and those who suffer from PTSD, among others, exhibit hypocortisolemia [2,10,13,35,36]. It is possible that a lifetime of exposure to increased stress, adverse socioeconomic circumstances and racism results in HPA axis dysregulation characterized by decreased expression of cortisol among African American women during pregnancy. African American women may enter pregnancy with a latent vulnerability to stress that is expressed as gestation progresses. The existence of such a preexisting vulnerability is consistent with proposals that lifelong exposures to stress among African American women may increase the likelihood of poor reproductive outcomes even before a pregnancy is conceived [21] and also that fetal programming may contribute to adult reproductive health [1,16].

The lower levels of CRH exhibited by the African American women in our sample might appear to argue against the role of CRH as a risk factor for the increased incidence of preterm birth they experience. However, it has been demonstrated that although levels of CRH are lower on average than levels among White women, African American women may be more sensitive to their effects [12]. Specifically, Holzman et al. reported that although elevations in CRH were lower within African Americans, those women whose levels of CRH were greater than 1.5 multiples of their group median were more than twice as likely to deliver preterm (OR = 5.0) than were White women whose levels of CRH were more than 1.5 multiples of their group median (OR = 2.3). Our new finding that there is a stronger association of cortisol at 18–20 weeks with CRH later in pregnancy among the African American women provides further evidence of susceptibility to the effects of stress and the role of the HPA axis and placental CRH in their increased rates of preterm birth. For these women, stress exposure may be more likely to translate into a preterm delivery because stress induces increased cortisol levels that are more likely to result in higher levels of CRH and shortened gestation [18,27,28]. An increased susceptibility to the effects of stress exposure in pregnancy due to a more responsive feed-forward loop between cortisol and CRH could be particularly important because African American women are exposed both to more stress and to unique stressors such as racism [6–8,15,19,20].

Acknowledgments

This work was supported by National Institutes of Health Grants R01 HD-40967 to L. Glynn and R01 HD-28413 and NS-41298 to C. Sandman.

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