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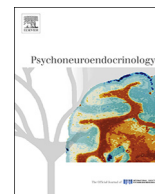
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Pregnancy anxiety predicts shorter gestation in Latina and non-Latina white women: The role of placental corticotrophin-releasing hormone

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ABSTRACT

Objective: Previous research has shown that a woman's anxiety about her pregnancy predicts gestational length. Placental corticotrophin-releasing hormone (CRH) is a stress-responsive peptide proposed as a mechanism. We examined placental CRH as a physiological mediator of the association between pregnancy anxiety and gestational length in Latina and non-Latina White women to replicate evidence of associations between pregnancy anxiety, placental CRH and gestational length; to test whether placental CRH levels or changes mediate effects of pregnancy anxiety on gestational length; to examine ethnic differences in pregnancy anxiety, placental CRH, and gestational length; and to explore whether the effects of pregnancy anxiety on gestational length as mediated by placental CRH vary by ethnicity.

Methods: In a prospective study of 337 pregnant Latina and non-Latina White women, participants completed in-person interviews that included a 10-item measure of pregnancy anxiety and provided blood samples assayed using radioimmunoassay at three timepoints (19, 25, and 31 weeks gestation).

Results: Pregnancy anxiety at 19 and 31 weeks and levels of placental CRH at 31 weeks predicted gestational length. Tests of indirect effects were consistent with mediation such that both pregnancy anxiety at 19 weeks and increases from 19 to 31 weeks predicted placental CRH at 31 weeks, which in turn predicted gestational length. Tests of moderated mediation by ethnicity showed that the mediated effect of placental CRH at 31 weeks was significant for Latinas only.

Conclusions: These findings add to growing evidence of the involvement of pregnancy anxiety in the timing of birth, address mechanisms, and suggest possible ethnic differences.

1. Introduction

Pregnancy anxiety, an emotional state rooted in concerns specific to the current pregnancy, has been implicated in the etiology of preterm birth and shortened length of gestation (Dole et al., 2003; Kramer et al., 2009; Lobel et al., 2008; Rini et al., 1999). Pregnancy anxiety refers to worries and fears experienced by pregnant women about their current pregnancy, including concern about the health of the baby, childbirth, health-care experiences, labor and delivery, and the maternal role (Dunkel Schetter, 2010; Guardino and Dunkel Schetter, 2014). Several large prospective studies have shown that this contextually-rooted form of anxiety reliably predicts shorter length of gestation. For example, one

prospective study of 2000 Black and White pregnant women revealed that pregnancy anxiety predicted spontaneous preterm birth (Dole et al., 2003). Another large study assessed many types of acute and chronic stressors in 5000 pregnant women including relationship strain and job-related stress, and found that only pregnancy anxiety predicted preterm birth in controlled analyses (Kramer et al., 2009).

Although the physiological pathways underlying the associations between pregnancy anxiety and birth outcomes have not been fully determined, the interrelated activities of the hypothalamic-pituitary-adrenal (HPA) axis and especially of placental corticotrophin-releasing hormone (CRH) are potential mechanisms explaining this association (Hobel et al., 1999). In the non-pregnant state, CRH is secreted by the

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hypothalamus and is not detectable in peripheral blood at concentrations of 10–20 pg/ml (McLean et al., 1995; Smith et al., 2009). During pregnancy, however, the placenta synthesizes and secretes CRH (referred to as placental CRH) into maternal and fetal circulation as early as the seventh week of gestation (McLean et al., 1995). As pregnancy progresses, levels of placental CRH increase exponentially, reaching high levels in maternal and fetal compartments during late pregnancy, and peak concentrations of 1000–10,000 pg/ml at term and in labor (Hillhouse and Grammatopoulos, 2002; Lindsay and Nieman, 2005; McLean et al., 1995). Several studies have shown that circulating CRH acts on CRH receptors in the myometrium to influence contractility (Cong et al., 2009; Jin et al., 2007; Zhang et al., 2008; Sandman and Glynn, 2009). Thus, the sharp rise of placental CRH in late pregnancy may initiate a cascade of events ultimately resulting in myometrial activation.

Only one published study has examined whether placental CRH mediates the link between pregnancy anxiety and length of gestation (Mancuso et al., 2004). The results of this study showed indirect effects of pregnancy anxiety reported at 28–30 weeks on length of gestation via levels of placental CRH measured at 28–30 weeks. Similar effects were not observed for measures of perceived stress or state anxiety, suggesting that pregnancy anxiety may be a particularly important construct for understanding stress processes underlying preterm birth. These results are consistent with the premise that pregnancy anxiety accelerates placental CRH trajectories during late pregnancy, thereby increasing risk for preterm birth through the triggering of labor and delivery pathways. However, the study did not collect measures of pregnancy anxiety before the time of placental CRH collection, nor did it examine changes in pregnancy anxiety or placental CRH over pregnancy.

Although some of the study samples in prior research on pregnancy anxiety are ethnically diverse, analyses typically adjust for ethnicity rather than examine it as a variable of interest. However, differences in attitudes about child-bearing and motherhood between Latina and non-Latina White women may contribute to differing levels of pregnancy anxiety (Campos et al., 2007; Engle et al., 1990; Fleuriet and Sunil, 2014; Scrimshaw et al., 1997). The authors of one qualitative study on the pregnancy behaviors of Puerto Rican women living in New York and pregnant Mexican immigrant women living in Los Angeles, speculated that Latinas expressed concerns about dying and leaving their babies motherless, and about their infant dying during childbirth (Scrimshaw et al., 1997). However, this study did not investigate these concerns in non-Latina women. In another study, Mexican-immigrant women living in South Texas reported higher levels of pregnancy anxiety compared to Mexican-American women (Fleuriet and Sunil, 2014). The limited available evidence demonstrating that Latinas may experience higher levels of pregnancy anxiety is noteworthy because of the implications for risk of preterm birth¹. However, additional research is needed to better understand how biopsychocultural factors operate in the etiology of preterm birth for the growing subgroup of Latinas in the United States population.

In sum, pregnancy anxiety has been shown to predict the length of gestation and has been shown to be higher among Latinas in a few studies. Furthermore, the physiological mechanisms linking pregnancy anxiety and birth outcomes are under active investigation. The present study examined whether pregnancy anxiety differed between Latina and non-Latina White women, tested indirect pathways (mediation) by placental CRH, and considered whether indirect or mediational

processes differed between these two ethnic groups.

We examined these issues in a sample of pregnant women who identified as Latina or non-Latina White. The first aim was to examine whether pregnancy anxiety, placental CRH, or changes in placental CRH predict the length of gestation. Based on prior research, we hypothesized that higher pregnancy anxiety and higher levels of placental CRH late in pregnancy would predict shorter length of gestation. We further hypothesized that placental CRH in pregnancy (19 and 25 weeks) and rate of change in placental CRH from mid to late pregnancy would predict the length of gestation. Second, we tested for ethnic differences between Latina and non-Latina White women in these variables (pregnancy anxiety, placental CRH at 19, 25, and 31 weeks, and changes in placental CRH from 19 to 31 weeks and 25 to 31 weeks). We expected that Latinas would show higher levels of pregnancy anxiety. No hypotheses were made for ethnic differences in length of gestation or ethnic differences in placental CRH in light of past conflicting evidence (Glynn et al., 2007; Ruiz et al., 2002; Siler-Khodr et al., 2003). Finally, we examined whether there were indirect pathways between pregnancy anxiety and length of gestation via levels of and changes in placental CRH, and whether ethnicity moderated any indirect effects.

2. Materials and methods

2.1. Protocol

This study utilized data from a prospective longitudinal study on psychosocial and behavioral factors in pregnancy. We recruited participants at two large medical centers, and obtained blood samples and interviewed women at three timepoints in pregnancy separated by six week intervals: T1 (M = 19 weeks, SD = .85); T2 (M = 25 weeks, SD = .85); and T3 (M = 31 weeks, SD = .80). Birth outcome data were abstracted from medical charts. Each institution's Institutional Review Board approved all protocols and procedures.

2.2. Subjects

Eligibility criteria were that a woman had to be 18 years of age or older, English speaking, and carrying a singleton intrauterine pregnancy. Exclusion criteria were no current tobacco, alcohol, or drug use, and no medical conditions involving dysregulated neuroendocrine, cardiovascular, hepatic, or renal functioning. The latter were to collect biomarkers that would be unaffected by these medical conditions.

A total of 63% of the 1189 women who were screened for the larger study met the eligibility criteria, and 67% of these women consented to participate in the study (N = 498). The primary reasons for declining to participate were having work or school conflict, scheduling difficulties, childcare issues, and lack of interest. For the present study, we consider only the subset of 337 participants who self-identified as Latina (n = 107) or non-Latina White (n = 230).

Among the 107 Latina women, 34 were foreign-born (32%), mainly born in Mexico (n = 23) but also Guatemala (n = 3), El Salvador (n = 3), Cuba (n = 1), the Dominican Republic (n = 1), Panama (n = 1), and other unspecified Latin American countries (n = 2). Foreign-born Latina women had been living in the United States for an average of 18 years (SD = 8.58, Range = 1–35).

2.3. Measures

2.3.1. Pregnancy anxiety

Pregnancy anxiety was measured with the 10-item Pregnancy-Related Anxiety Scale (Rini et al., 1999). This scale has been used in previous studies of pregnant English and Spanish speaking women (e.g., Rini et al., 1999) with good to excellent reliability and validity in both languages. Participants rated the extent to which they worried or felt concerned about their own health, their baby's health, labor and

¹ In a prior study of a subset of the present cohort examining familism, social support, perceived stress, pregnancy anxiety, and infant birthweight, there was an incidental finding on ethnic differences in pregnancy anxiety, which were not the focus of that study (Campos et al., 2008). The present study uses a larger cohort and different predictors and outcomes. Only the analysis of ethnic differences in pregnancy anxiety is common between them.

delivery, and parenting. Sample items are: "I am concerned or worried about how the baby is growing and developing inside me," "I am confident of having a normal childbirth," (reverse scored) "I am worried that the baby might not be normal," "I am concerned or worried about losing the baby", and "I am concerned about taking care of a new baby". Pregnancy anxiety was measured at each timepoint to document changes in levels of pregnancy anxiety throughout pregnancy. Participants responded on a 4-point scale from 1 (*not at all or never*) to 4 (*very much or almost all the time*). The Cronbach alpha coefficients were: T1 $\alpha = 0.81$, T2 $\alpha = 0.82$, T3 $\alpha = 0.84$.

2.4. Hormone assays

Levels of placental CRH were measured in samples of maternal blood (25 mL) drawn through antecubital venipuncture (within 20 s of venipuncture) and assayed through radioimmunoassay (RIA; Bachem Peninsula Laboratories, San Carlos, CA) techniques described in full by Glynn and Sandman (2014). Briefly, withdrawn blood was deposited into siliconized and chilled EDTA (purple top) vacutainers and then centrifuged for 15 min at 2000 g. The plasma was then decanted into polypropylene tubes containing 500-kallikrein inhibitor units/ml of aprotinin (Sigma Chemical) and stored at -70°C until assayed. CRH concentrations (pg/ml) were determined by radioimmunoassay (RIA; Bachem Peninsula Laboratories, San Carlos, CA). CRH was extracted from (1–2 mL) plasma samples with three volumes of ice-cold methanol, mixed, allowed to stand (10 min, 48°C), and then centrifuged (20 min, 1700 g, 4°). Pellets were washed with 0.5 mL of methanol, and the combined supernatants were dried in a concentrator (SpeedVac; Savant Instruments, Holbrook, NY). Samples were incubated (100 mL/assay tube) for 48 h with anti-CRH serum (100 mL/assay tube) for 48 h at 4°C followed by a 24-hour incubation with iodine-125 labeled CRH at 4°C . Both labeled and unlabeled CRH were collected by immunoprecipitation, and the aspirated pellets were counted with a gamma counter (Isoflex Gamma Counter; ICN Biomedical, Costa Mesa, CA). Intra-assay and inter-assay coefficients of variance were 5% and 15%, respectively. The placental CRH values were log transformed to reduce the typical skewness of the distribution.

2.5. Birth outcome variables

Birth outcomes and maternal medical risk factors were obtained from medical records abstracted by skilled research staff. Gestation in weeks was estimated during early prenatal visits by the conventional obstetrics method of reported last menstrual period (LMP) and confirmed by pelvic ultrasound.

2.6. Demographic and medical covariates

Variables were selected for inclusion as covariates based on previous studies showing associations with length of gestation (Behrman and Butler, 2007). They were: years of completed education, total household income adjusted by household size, age at study entry, parity and medical risk factors. Each was obtained from interviews or medical charts. Twenty-one medical risk conditions were coded based on a woman's medical history (e.g., diabetes), ObGyn history (e.g., previous abortion), and current pregnancy complications (e.g., bacterial vaginosis). A medical risk score was calculated as the total number of conditions present, based on prior research (see Hobel et al., 1979; the full list is available from authors).

2.7. Statistical analyses

All analyses statistically controlled for covariates (medical risk factors, level of education completed, adjusted household income, age at study entry, and parity), and gestational week at the time of data collection for the placental CRH and pregnancy anxiety variables. Additionally, multiple

imputation (Rubin, 2004; Enders, 2010) was used to account for missing data in the sample to increase power and reduce bias. The primary reason for missing data was a standard procedure involving placental CRH data removed at the time of assay for cases in which the values were greater than 25% deviation from the standard curve. Given the causes of missing data, we assumed that missing data were missing at random (MAR; Little and Rubin, 2014).

One-way repeated measures analyses of covariance (ANCOVA) were conducted to determine if levels of pregnancy anxiety, placental CRH, and change in placental CRH differed between Latina and non-Latina White participants. Next, using eight separate multiple regression analyses, gestational length was regressed on: (a) pregnancy anxiety at each of three times in pregnancy; (b) placental CRH at each of three timepoints; and (c) changes in placental CRH from 19 to 31 weeks gestation and from 25 to 31 weeks gestation of gestational length. All ANCOVAs and regression analyses were performed in R using multiply imputed data². In these analyses, first, we estimated models with the independent variable (pregnancy anxiety, placental CRH, change in placental CRH), covariates, ethnicity, and the interaction between ethnicity and the corresponding independent variable. If the interaction term was significant, we retained the term in the final models. If the interaction term was not significant, we removed it from the model. For the models without the interaction term, ethnicity was included as a covariate.

Primary Analyses. We then tested the hypothesis that placental CRH, and change in placental CRH, mediate the association between pregnancy anxiety and length of gestation. First, we tested whether ethnicity significantly moderated the hypothesized indirect effects of pregnancy anxiety on the length of gestation via placental CRH, or changes in placental CRH. If significant moderation was found, we then used the moderated mediation model to test the simple mediated effects for Latina and non-Latina White women. Otherwise, we dropped the moderation component from the model and estimated the mediated effect in the full sample with ethnicity included as a covariate. This process was repeated for four separate mediators: placental CRH at 25 weeks, placental CRH at 31 weeks, change in placental CRH from 19 to 31 weeks, and change in placental CRH from 25 to 31 weeks. Additionally, we replicated the mediation analyses presented in Mancuso et al. (2004) using pregnancy anxiety at 31 weeks as the predictor and placental CRH at 31 weeks as the mediator in predicting length of gestation. Each effect was judged to be significant if the corresponding bias-corrected 95% confidence interval did not include zero. The mediation and moderated mediation analyses were conducted in each imputed dataset using the PROCESS macro in SPSS (Preacher and Hayes, 2008) and the bootstrapped estimates and confidence intervals were calculated in R³.

3. Results

3.1. Sample demographics

Table 1 presents the descriptive statistics and tests of ethnic differences for demographic characteristics for the full sample. Women in

²The R package mice (R Core Team, 2016; Buuren and Groothuis-Oudshoorn, 2011) was used to generate 100 imputations using regression imputation for continuous variables and logistic/multinomial imputation for categorical variables. To account for slight differences in gestational week at the time of placental CRH measurement, gestational week at the time of placental CRH measurement was included as an auxiliary variable for imputation (Enders, 2010). Unless otherwise noted, all parameter estimates, standard errors, and significance tests were calculated by pooling the model results across imputations in R using Rubin's pooling rules (Rubin, 2004), and all F tests used the D1 multiple imputation significance test (Enders, 2010).

³Bias-corrected bootstrapped confidence intervals were used to test the mediated effects and index of moderated mediation. We adapted the approach described in Schomaker and Heumann (2016), which calculates confidence intervals based on the bootstrapped estimates from all imputations.

Table 1
Descriptive Statistics for key variables in the full sample and by ethnicity.

Variable	Full Sample			Latina			Non-Latina White			F or χ^2	p
	(N = 337)			(N = 107)			(N = 230)				
	n	M	SD	n	M	SD	n	M	SD		
Age at Study Entry	333	30.01	5.44	105	27.80	5.68	228	31.03	5.01	25.22	< .001
Adjusted Income	332	25.80	16.75	105	14.69	12.26	227	30.97	16.05	104.08	< .001
Medical Risk	329	2.45	1.63	103	2.65	1.79	226	2.36	1.54	1.97	.081
Parity (% multiparous)	337	57%		107	39%		230	65%		19.04	< .001
Education	337			107			230			67.65	< .001
High School or less		16%			32%			9%			
Some college		37%			53%			30%			
Bachelor's degree		27%			11%			34%			
Graduate degree		19%			4%			27%			
Married or cohabitating (% yes)	337	75%		107	59%		230	83%		20.73	< .001

Note. Adjusted household income was calculated as total annual household income divided by household size, in units of thousands of dollars. Estimates and results for maternal age at study entry, adjusted income, medical risk, and length of gestation are based on multiple imputation.

the present study were on average 30 years old (SD = 5.44) and the majority of the sample was either married to the baby's father (76%) or cohabitating with him (15%). Compared to the 230 non-Latina White women, the Latina women were significantly younger, had lower adjusted household income and less education, and were more likely to have had a prior birth and to be married or cohabitating with the baby's father. There were no significant differences between these groups on medical risk.

3.2. Ethnic differences in pregnancy anxiety, length of gestation, and placental CRH

Table 2 presents descriptive statistics for pregnancy anxiety, placental CRH (19, 25, and 31 weeks), change in placental CRH (from 19–31 weeks and 25–31 weeks), and length of gestation, along with correlations among these measures in the full sample, univariate descriptive statistics of these measures by ethnicity, and tests of ethnic

differences in these measures. After applying an experiment-wise Bonferroni correction ($\alpha = .0063$ for eight tests), and after adjustment for covariates, Latina women reported significantly higher pregnancy anxiety at each timepoint in pregnancy compared to non-Latina White women (T1 $F(1, 336.6) = 14.47, p < .001, d = 0.66$; T2 $F(1, 335.2) = 9.43, p = .002, d = 0.61$; T3 $F(1, 335.9) = 10.60, p = .001, d = 0.62$). After adjustment for covariates, there were no ethnic differences in levels of placental CRH, changes in placental CRH, or length of gestation (all F 's < 1.33, p 's > .250). There were also no significant differences between US-born Latinas and foreign-born Latinas in length of gestation, pregnancy anxiety, placental CRH, or change in placental CRH ($F < .67, p > .41$) after adjustment for covariates.

3.3. Predictors of length of gestation

Table 3 presents regression coefficients from eight different models predicting gestational length from pregnancy anxiety (one model each

Table 2
Variances, Covariances, Correlations, and Comparisons by Ethnicity of Pregnancy Anxiety, pCRH (ln), and Δ pCRH (ln).

Bivariate Statistics		Pregnancy Anxiety			pCRH (ln)			ΔpCRH (ln)		Gestation Length
		19 wks	25 wks	31 wks	19 wks	25 wks	31 wks	19-31 wks	25-31 wks	
Pregnancy Anxiety	19 wks	0.26	.70	.69	.05	.21	.19	.14	.00	-.02
	25 wks	0.16	0.20	.76	.03	.10	.08	.06	-.01	.05
	31 wks	0.16	0.16	0.22	.02	.08	.14	.12	.06	-.06
pCRH (ln)	19 wks	0.01	0.01	0.00	0.28	.35	.19	-.48	-.14	-.07
	25 wks	0.07	0.03	0.03	0.13	0.47	.44	.17	-.49	-.07
	31 wks	0.07	0.03	0.05	0.07	0.22	0.53	.77	.57	-.25
ΔpCRH (ln)	19-31 wks	0.06	0.02	0.04	-0.21	0.09	0.46	0.67	.59	-.18
	25-31 wks	0.00	0.00	0.02	-0.05	-0.25	0.31	0.37	0.56	-.17
Gestation Length		-0.01	0.04	-0.05	-0.06	-0.08	-0.30	-0.24	-0.21	2.71
Latina	n	107	95	95	79	41	69	52	33	104
	M	2.05	1.89	1.88	2.87	3.71	5.28	2.41	1.57	38.92
	Min	1.00	1.00	1.10	2.03	2.36	3.67	0.82	-0.39	32.71
	Max	3.60	3.10	3.30	4.65	5.44	7.90	4.72	3.05	42.29
Non-Latina White	n	227	203	204	175	82	128	92	68	217
	M	1.83	1.73	1.71	2.87	3.73	5.22	2.35	1.49	39.32
	Min	1.00	1.00	1.00	1.63	2.44	3.65	0.32	-0.18	31.86
	Max	3.60	3.30	3.40	4.64	5.04	6.64	4.57	3.82	42.14
	F	14.47	9.43	10.60	0.78	0.60	0.33	0.06	0.06	1.33
	p	.000	.002	.001	.377	.439	.567	.811	.802	.250
	d	.66	.61	.62	-.20	-.16	-.11	.04	.04	-.15

Note. Numbers on the diagonal are variances, those below the diagonal are covariances, and those above the diagonal (italicized) are correlations. Statistical tests of group differences account for maternal age at study entry, parity, medical risk, adjusted income, education, and gestational age(s) at each time point for each dependent variable. Descriptive statistics were not adjusted for covariates. pCRH data were log transformed. Number of non-missing observations (n), minimum (Min) and maximum (Max) are based on the raw data, all other statistics are based on multiple imputation. Effect sizes were estimated using the pooled standard deviation.

Table 3
Regression coefficients of separate models predicting length of gestation from pregnancy anxiety, pCRH, and ΔpCRH.

	Interaction				Full Sample				β _x	Latina				Non-Latina White					
	b	SE	F	p	b	SE	F	p		b	SE	F	p	β _x	b	SE	F	p	β _x
T1 Pregnancy Anxiety	-0.99	0.35	8.01	.005						-0.64	0.27	5.75	.017	-.371	0.35	0.23	2.28	.132	.161
T2 Pregnancy Anxiety	-0.80	0.42	3.75	.054	0.03	0.21	0.02	.883	.014										
T3 Pregnancy Anxiety	-1.14	0.39	8.35	.004						-0.93	0.30	9.62	.002	-.492	0.20	0.25	0.64	.425	.086
T1 pCRH (ln)	-0.13	0.42	0.10	.754	-0.11	0.20	0.30	.586	-.057										
T2 pCRH (ln)	-0.10	0.40	0.06	.812	-0.14	0.20	0.52	.474	-.096										
T3 pCRH (ln)	-0.51	0.28	3.23	.074	-0.58	0.16	12.54	.000	-.420										
T1-T3 ΔpCRH (ln)	-0.36	0.27	1.84	.176	-0.39	0.15	6.37	.013	-.318										
T2-T3 ΔpCRH (ln)	-0.53	0.35	2.31	.130	-0.37	0.19	3.89	.050	-.275										

Note. β_x = partially standardized regression coefficient, standardized using the predictor only. All analyses account for maternal age at study entry, parity, medical risk, adjusted income, education, and gestational age(s) at each time point for the independent variable. pCRH data were log transformed.

for 19 weeks, 25 weeks, and 31 weeks), placental CRH (one each for 19 weeks, 25 weeks, and 31 weeks), and change in placental CRH (one each for 19 to 31 weeks and 25 to 31 weeks). After applying an experiment-wise Bonferroni correction (α = .0063 for eight tests), the interaction of ethnicity with T1 and T3 pregnancy anxiety as predictors of length of gestation was found to be statistically significant. Comparing the simple effects of T1 and T3 pregnancy anxiety for each racial/ethnic group and after applying an experiment-wise Bonferroni correction (α = .0125 for four tests), a significant effect of T3 pregnancy anxiety was identified in Latinas only (F (1, 328.8) = 9.62, p = .002, β_x = -0.492). That is, one standard deviation increase in pregnancy anxiety at 31 weeks was associated with 0.492 weeks (3.444 days) shorter gestation in the Latina sample after accounting for covariates. As indicated in Table 3, levels of placental CRH at T1, T2, and T3, and changes in placental CRH from T1 to T3 and from T2 to T3 did not predict the length of gestation after adjusting for covariates. Fig. 1 displays placental CRH across three data collection occasions.

3.4. Mediation and moderated mediation analyses

Table 4 shows the full results of the moderated mediation analyses, with ethnicity moderating the mediated effect of pregnancy anxiety at 19 weeks on length of gestation, mediated by (a) placental CRH at 25 weeks, (b) placental CRH at 31 weeks, (c) change in placental CRH from 19 to 31 weeks, or (d) change in placental CRH from 25 to 31 weeks. When placental CRH at 31 weeks was used as the mediator, the difference in the mediated effects for Latina and non-Latina White women

was consistent with moderated mediation, CI = (-0.83, -0.05). However, when placental CRH at 25 weeks, or change in placental CRH from 19 to 31 weeks or from 25 to 31 weeks, was tested as the mediator, the index of moderated mediation was not significant, indicating that there was no difference between the mediated effects for Latina and non-Latina White women for those mediators.

Fig. 2 displays the model and path coefficients for moderated association between pregnancy anxiety and length of gestation mediated by placental CRH at 31 weeks. Follow-up analyses using the moderated mediational model indicated that placental CRH at 31 weeks mediated the effect of pregnancy anxiety at 19 weeks on the length of gestation for Latina women CI = (-0.86, -0.09), Est_x = -0.24. In this model, the conditional direct effect of pregnancy anxiety at 19 weeks on length of gestation for Latina women, which quantifies the direct effect of pregnancy anxiety at 19 weeks on length of gestation after controlling for placental CRH at 31 weeks and covariates, was not statistically significant (b = 0.49, F(1, 1065.5) = 3.13, p = .077). The calculated effect size indicates that one standard deviation increase in pregnancy anxiety at 19 weeks, as partially mediated by placental CRH at 31 weeks, was associated with 0.24 weeks (1.68 days) shorter gestation in Latina women. No such mediated effect was observed for non-Latina White women, CI = (-0.16, 0.05), Est_x = 0.01. These results for Latinas remained significant after controlling for place of birth (US-born vs. foreign-born).

In the full sample, the mediation results were also consistent with mediation by placental CRH at 31 weeks of the effect of pregnancy anxiety at 19 weeks on the length of gestation, CI = (-0.36, -0.13), Est_x = -0.07, and by change in placental CRH from 19 to 31 weeks, CI = (-0.20, -0.06), Est_x = -0.03. Our results were also consistent with placental CRH at 31 weeks mediating the effect of pregnancy anxiety at 31 weeks on the length of gestation, CI = (-0.242, -0.076), Est_x = -0.046, replicating the finding of Mancuso et al. (2004). As with the previous results, the direct effect of pregnancy anxiety on length of gestation, adjusting for placental CRH and covariates, was not significant in either model (F < 0.79, p > .373). There were no significant mediated effects of placental CRH at 25 weeks or change in placental CRH from 25 to 31 weeks in the full sample, nor was there evidence of moderated mediation for those mediators.

4. Discussion

In this prospective and longitudinal study of pregnant women, we tested a biopsychosocial model with pregnancy anxiety as the psychological predictor, placental CRH (a stress-responsive peptide) as the biological mediator, length of gestation as the outcome, and ethnicity as the moderator of the indirect or mediated effect. We found that pregnancy anxiety at 19 and at 31 weeks and levels of CRH of placental origin at 31 weeks each significantly predicted length of gestation. These results are consistent with prior research and make an important contribution given the specifics of this sample and study design.

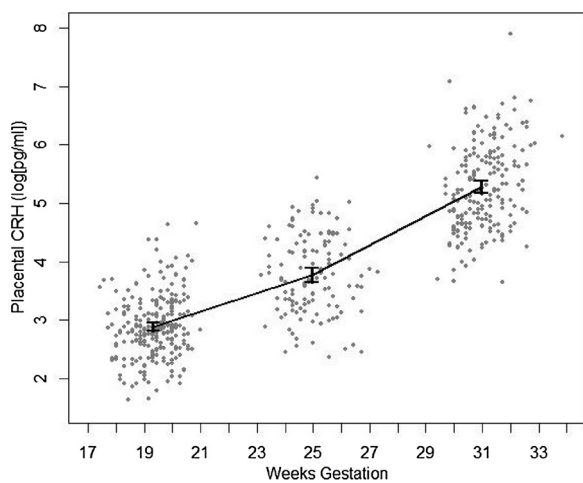


Fig. 1. Placental CRH across three data collection occasions: 17–21 weeks gestation, n = 252; 23–29 weeks gestation, n = 123; 29–34 weeks gestation, n = 197. Error bars indicate 95% confidence intervals (± 1.96 * SE) for each measurement occasion.

Table 4
 Bootstrapped analyses of mediation and moderated mediation predicting length of gestation from T1 pregnancy anxiety.

Mediator	Index of Moderated Mediation			Indirect Effect Full Sample				Indirect Effect White			Indirect Effect Latina				
	Est	LLCI	ULCI	Est	LLCI	ULCI	Est _x	Est	LLCI	ULCI	Est _x	Est	LLCI	ULCI	Est _x
T2 pCRH (ln)	0.03	-0.28	0.35	-0.05	-0.15	0.04	-0.02								
T3 pCRH (ln)	-0.39	-0.84	-0.06	-0.14	-0.28	-0.13	-0.07	-0.03	-0.16	0.05	-0.01	-0.42	-0.86	-0.10	-0.24
ΔpCRH (ln) T1-T3	-0.18	-0.52	0.04	-0.07	-0.18	-0.06	-0.03								
ΔpCRH (ln) T2-T3	-0.19	-0.64	0.05	0.01	-0.01	0.09	> 0.01								

Note. LLCI = lower limit of confidence interval; ULCI = upper limit of confidence interval; Est_x = partially standardized indirect effect, standardized using the predictor only. Confidence intervals are bias-corrected and based on 5000 bootstrapped samples for each of 100 imputed datasets. Significant mediating relationships bolded and indicated by 95% confidence intervals that do not include zero. All analyses account for maternal age at study entry, parity, medical risk, adjusted income, education, and gestational age(s) at each time point for pregnancy anxiety and pCRH.

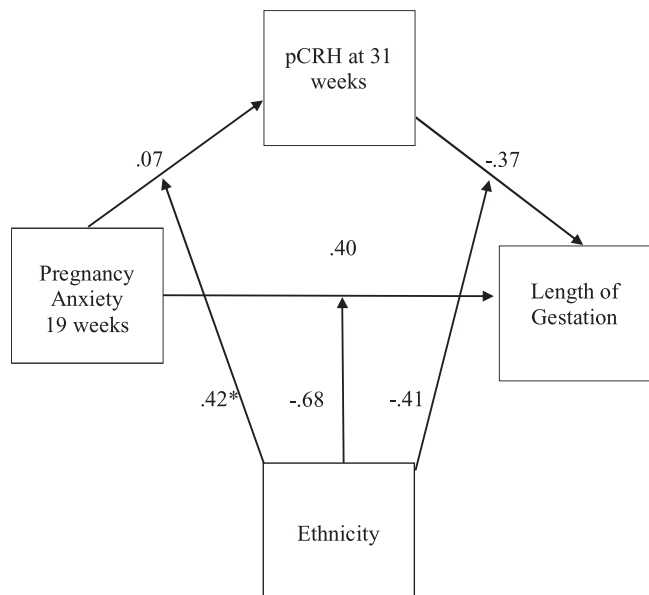


Fig. 2. (a) Path model of pregnancy anxiety (19 weeks), pCRH (31 weeks), and length of gestation, moderated by ethnicity (*n* = 337).
 * *p* < .05.

The tests of indirect effects of pregnancy anxiety at 19 weeks on gestational length via placental CRH at 31 weeks in the full sample were consistent with partial mediation. These results replicate and extend an earlier finding from the only other study to test these specific processes (Mancuso et al., 2004), which found that anxiety tied to fears and worries surrounding a woman's current pregnancy predicts the timing of delivery is at least partially explained by altered neuroendocrine function. However, the current study measured pregnancy anxiety and placental CRH at different times in pregnancy than the previous study. Taken together, these two studies on separate cohorts with assays of placental CRH done in separate labs strengthen the evidence that CRH plays a role in stress processes during pregnancy that have been shown to influence timing of delivery. These results also suggest that mid- to late pregnancy may be a sensitive period during which the effects of pregnancy anxiety and placental CRH are particularly salient for effects on gestational length. Further research can further probe the issue of timing.

In addition, this study extends the previous findings by examining whether changes in placental CRH during pregnancy might mediate the relationship between pregnancy anxiety and gestational length. We found evidence consistent with partial mediation in that changes in placental CRH from 19 to 31 weeks partially mediated the association between pregnancy anxiety at 19 weeks and the length of gestation in the full sample. These findings are the first to indicate that levels of pregnancy anxiety at mid-pregnancy are associated with changes in

placental CRH from mid to late pregnancy, with implications for the timing of delivery. Further experimental evidence of changes in this neuropeptide and the effects would be valuable.

Placental CRH has been associated with maturation of the human fetus and with postnatal child behavioral and brain development, highlighting the importance of testing this specific biomarker (Class et al., 2009; Howland et al., 2016; Sandman et al., 2018). Although the full physiological pathways explaining the association between pregnancy anxiety and placental CRH have not been fully identified, evidence points to a potential direct or indirect association of maternal stress with activation of the HPA axis during gestation (Kane et al., 2014). It is hypothesized that prenatal maternal stress is related to stress-induced secretion of catecholamines by brain arousal and sympathetic systems, which is thought to lead to maternal cortisol secretion, which in turn stimulates the production of placental CRH (Goldstein, 2003; Valsamakis et al., 2017).

Understanding the mechanisms through which maternal stress disrupts the normative physiological processes of pregnancy may have implications for identification of women who might benefit from intervention. For example, assessment of placental CRH levels might be used as an indicator of risk for impending preterm delivery (Hill et al., 2008; Korebrits et al., 1998), which could then be used to guide clinical decision making, ensuring that antenatal glucocorticoids are administered in the optimal time frame (Kamath-Rayne et al., 2016).

This is also the first study to explore whether ethnicity moderates the indirect pathways from pregnancy anxiety to placental CRH and to gestational length at birth. Tests of moderated mediation by ethnicity indicated significant moderation; that is, pregnancy anxiety at 19 weeks predicted CRH at 31 weeks, which predicted timing of birth for Latina women and not for the non-Latina White women. The indirect effect via changes in placental CRH from 19 to 31 weeks was not significantly moderated by ethnicity. It is important to note that placental CRH level at 31 weeks and change in placental CRH from 19 to 31 weeks were strongly correlated (*r* = 0.77) which makes it difficult to compare the two sets of tests and calls for additional research on larger samples. Taken together, these findings contribute to the growing body of research on pregnancy anxiety and its role in the timing of birth and contribute to our understanding of the biological mechanisms involved.

Additionally, we identified significant differences between Latinas and non-Latina Whites in pregnancy anxiety after controlling for medical risk factors, level of education completed, adjusted household income, age at study entry, and parity. Cultural differences may in part explain these group differences. Unique cultural-based sources of anxiety in pregnancy have been identified in a few studies (Campos et al., 2007; Engle et al., 1990; Scrimshaw et al., 1997). Furthermore, qualitative research on myths about pregnancy has suggested that Mexican-American women may show heightened concerns about dying and infant death during childbirth (Scrimshaw et al., 1997). In many Latin American cultures, childbearing is a highly-valued aspect of the female role, even to the extent that men and women might believe that a woman cannot be fulfilled until she is a mother (Maldonado-Duran

et al., 2002). Other research suggests that Latino families in the United States treat pregnancy as a time of privileged social status (Fleuriet, 2009; Fleuriet and Sunil, 2014). Latina women in past research also have reported more positive attitudes toward pregnancy as compared to African-American women (Zambrana et al., 1999). However, studies have not tested whether this privileged status contributes to experiences of pregnancy anxiety in Latina women because pregnancy represents a major responsibility to the family (Fleuriet, 2009). Future research directly measuring cultural variables can help illuminate the contributors of ethnic differences in pregnancy outcomes (Betancourt and López, 1993).

4.1. Strengths and limitations

The strengths of this research include its longitudinal design, repeated measurements of psychological (e.g., pregnancy anxiety) and biological variables (placental CRH), and inclusion of key socio-demographic factors in the prediction of an objective health outcome of major public health significance. Studies with both psychosocial and biological data collected at multiple times throughout the course of pregnancy on samples of sufficient size to test these questions are rare, in part due to the difficulty of sample recruitment and retention. Such work contributes to understanding how changes in these psychological and biological factors co-occur to influence gestational length at birth.

It is important to note that the association between placental CRH and shortened gestation is based on longitudinal correlational data, and is not conclusive causal evidence of mediation. Future research is needed to test the hypothesized causal pathway between pregnancy anxiety and preterm birth as mediated by placental CRH, ideally with experimental designs. Moreover, these findings require replication in larger samples. Also, this sample of Latina women may not be representative of Latina women in the United States population because participants had to speak sufficient English to be interviewed, which skewed the sample toward more acculturated women and under-represented foreign-born women. We surmise that the effects of ethnicity would have been stronger if fewer acculturated and more foreign-born women had been included, especially given that pregnancy anxiety has been shown to be higher in less acculturated women (Fleuriet and Sunil, 2014). Furthermore, we did not examine changes in pregnancy anxiety across gestation as predictors of the mediator or outcome, which was beyond the scope of the current report. Future research on trajectories in pregnancy anxiety would be valuable. Finally, we did not examine HPA activity markers such as cortisol or ACTH as mediators, or any other biological markers such as pro-inflammatory cytokines, which are implicated in preterm birth pathways (e.g., Christian, 2012; Coussons-Read et al., 2012; Wadhwa et al., 2001).

4.2. Conclusion

In this study, we found that women who reported higher levels of anxiety regarding their pregnancies at mid and late gestation were at risk for earlier delivery. In addition, Latina women in this sample reported higher pregnancy anxiety during most of pregnancy compared to non-Latina White women, despite being more acculturated on average than a representative sample of Latinas would be. Future research can build on these findings to determine if pregnancy anxiety differs by ethnic group and can incorporate broader conceptualizations of culture. These findings highlight the HPA axis as one potential mechanism explaining the association between pregnancy anxiety and the length of gestation, as well as the role of ethnicity in moderating such effects. Why Latina ethnicity moderated the mediational pathway remains to be determined. Nonetheless, this work represents a relatively rare test of a full biopsychosocial mechanistic model and can inform future research.

Declarations of interest

None.

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