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Maternal prenatal cortisol programs the infant hypothalamic–pituitary–adrenal axis

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Abstract

One of the key proposed agents of fetal programming is exposure to maternal glucocorticoids. Experimental animal studies provide evidence that prenatal exposure to elevated maternal glucocorticoids has consequences for hypothalamic–pituitary–adrenal (HPA) axis functioning in the offspring. There are very few direct tests of maternal glucocorticoids, such as cortisol, during human pregnancy and associations with infant cortisol reactivity. The current study examined the link between maternal prenatal cortisol trajectories and infant cortisol reactivity to the pain of inoculation in a sample of 152 mother-infant (47.4% girls) pairs. The results from the current study provide insight into fetal programming of the infant HPA axis, demonstrating that elevated prenatal maternal cortisol is associated with a larger infant cortisol response to challenge at both 6 and 12 months of age.

Keywords

HPA axis; Cortisol; Glucocorticoids; Pregnancy; Infant; Fetal programming

1. Introduction

Prenatal development occurs at an extremely rapid pace that far exceeds the rate of growth during every other life stage. The precise timing and sequence of events from conception to birth make the developing fetal systems particularly susceptible to organizing and disorganizing influences that shape development across the lifespan through a process known as fetal programming (Barker, 1998). One of the key proposed agents of fetal

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Appendix A. Supporting information

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programming is exposure to maternal glucocorticoids. Cortisol, a primary glucocorticoid in humans, is the end product of the hypothalamic–pituitary–adrenal (HPA) axis, an essential component of the human stress response system. During pregnancy, maternal cortisol plays a critical role in fetal development.

Maternal cortisol typically increases two- to four-fold across gestation (Mastorakos and Ilias, 2003; Sandman et al., 2006). The placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) and other regulatory molecules allow 10–20% of maternal cortisol to cross the placental barrier and enter the fetal compartment, where cortisol of maternal origin accounts for 40–50% of fetal cortisol concentrations (Gitau et al., 1998). In addition to cortisol's essential functions in maturation of fetal organs including the lungs and central nervous system (Davis et al., 2017; Glynn and Sandman, 2012; Howland et al., 2017; Ishimoto and Jaffe, 2011; Matthews, 2000; Shearer et al., 2019), variations in maternal cortisol have been found to be associated with differences in postnatal developmental trajectories, including alterations in cognitive function and greater risk of mental disorders as well as autoimmune, metabolic, and cardiovascular diseases (Braun et al., 2013; Davis and Sandman, 2010; Fowden et al., 2005; Reynolds, 2013; Sandman et al., 2016; Xiong and Zhang, 2013).

Because of the dependence of the fetal systems on maternal cortisol, fetal exposure to maternal cortisol is thought to be a critical biological mechanism involved in prenatal programming of the fetal HPA axis. Experimental studies with rodents and non-human primates suggest that prenatal exposure to maternal glucocorticoids has effects on HPA axis functioning in the offspring (Abe et al., 2007; Kapoor et al., 2008; Maccari and Morley-Fletcher, 2007; Schneider, 1992; Thayer et al., 2018). In humans, a range of prenatal influences on infant cortisol regulation have been studied, but relatively few studies have evaluated how maternal cortisol during pregnancy is associated with infant cortisol regulation (Brennan et al., 2008; Grant et al., 2009; Gutteling et al., 2004; Howland et al., 2017; O'Connor et al., 2005; Oberlander et al., 2008; Saridjan et al., 2010; Stroud et al., 2016; Tollenaar et al., 2011; Van Den Bergh et al., 2008). We previously found that elevated prenatal cortisol during the second and third trimesters was associated with a larger neonatal cortisol response to a painful stressor (a heel-stick procedure) 24 h after birth (Davis et al., 2011). Consistent with this finding, higher third trimester maternal cortisol was associated with a more pronounced infant cortisol response to inoculation at 12 months of age (Osborne et al., 2018) and higher child cortisol response to the Trier Social Stress test (Simons et al., 2019). Other studies have shown that elevated morning cortisol in early gestation was associated with higher overall cortisol levels in 4–6-year-old children on the day of a vaccination (Gutteling et al., 2004) and on school days (Gutteling et al., 2005). In contrast, there is a single study reporting no association between late gestation cortisol and child cortisol response to a stressor (Tollenaar et al., 2011) and another reporting higher amniotic fluid cortisol was associated with higher baseline cortisol and lower cortisol after a laboratory task (O'Connor et al., 2013). Other studies focusing on patterns of maternal diurnal cortisol regulation have linked circadian rhythms to infant cortisol regulation (de Weerth et al., 2013; Nazzari et al., 2019; Rash et al., 2016). Wide variability in methodologies across studies makes comparisons difficult, and there is a need for studies with longitudinal assessment of prenatal maternal cortisol throughout gestation

to more comprehensively assess the impact of timing and trajectory on infant HPA axis development (Zijlmans et al., 2015).

Early HPA axis dysregulation is hypothesized to underlie an increased risk of later vulnerability to psychopathology (Gunnar and Quevedo, 2008) and thus it is important to understand how early experiences may shape this system. This study is distinct from most prior work because it probes infant HPA axis function in response to an acute, painful stressor (i.e., inoculation). Compared to psychosocial stressors used in other studies, inoculation more effectively and reliably elicits a robust physiological stress response in infants during the first postnatal year (Davis and Granger, 2009; Gunnar et al., 1996; Lewis and Ramsay, 1995; Ramsay and Lewis, 2003). Furthermore, the current study characterizes trajectories of maternal prenatal cortisol over time, allowing for the examination of timing effects in the association between prenatal maternal cortisol secretion and infant cortisol regulation (Davis et al., 2011; Peterson et al., in press). Finally, because there is extensive evidence for sex-specific responses to the intrauterine environment (Bale, 2016; Sandman et al., 2013), the present study will evaluate whether sex moderates the association between maternal cortisol and infant HPA axis regulation (Giesbrecht et al., 2017; O'Connor et al., 2013).

Thus, the aims of the current study were to, 1) Characterize prenatal maternal cortisol trajectories from early to late gestation; 2) Examine the associations between maternal prenatal cortisol trajectories and infant cortisol reactivity to the pain of inoculation at 6 and 12 months of age, including whether there are differential associations based on timing of gestational exposure; and 3) Explore whether there are sexually dimorphic associations between maternal prenatal cortisol concentrations across gestation and infant cortisol regulation at 6 and 12 months of age. In line with the existing research described above, we hypothesized that, 1) Prenatal maternal cortisol would increase across gestation; 2) Higher prenatal maternal cortisol across gestation would be associated with a larger infant cortisol response to the pain of inoculation; and 3) The association between prenatal maternal cortisol trajectories and infant cortisol reactivity would differ by sex.

2. Materials and methods

2.1. Study overview

English-speaking, adult pregnant women with singleton pregnancies were recruited from obstetric clinics in Southern California at 15 weeks' gestation and were followed longitudinally ($N = 168$). Participants were excluded if they had (i) tobacco, alcohol or other drug use in pregnancy, (ii) use of steroid medication, or (iii) an endocrine-related medical issue. Additional criteria for inclusion in the present analyses included full term delivery (> 37 weeks' gestation; 15 (8%) participants removed for preterm delivery) and availability of data from at least three of the five prenatal visits and at least one of the postnatal visits (one participant was missing data from more than three prenatal visits and thus was excluded from analyses). Medical interviews were conducted and salivary cortisol samples were obtained five times during pregnancy: 15 ($M = 15.1$, $SD = 0.9$), 19 ($M = 19.1$, $SD = 0.9$), 25 ($M = 25.4$, $SD = 1.0$), 31 ($M = 30.8$, $SD = 0.7$), and 37 ($M = 36.6$, $SD = 0.6$) weeks' gestation. Sociodemographic information, including household income,

maternal age and education, and self-reported ethnicity, was collected using a standardized maternal interview at the first prenatal visit. At 6 (M = 6.2, SD = 0.5; N = 136) and 12 (M = 12.3, SD = 0.5; N = 107) months infant age, saliva was collected from infants before and after inoculation during routine well-baby appointments to assay for cortisol. Psychosocial interviews were conducted with the mothers at each prenatal and postnatal time point.

All study procedures were approved by the Institutional Review Board for protection of human subjects, and women provided written, informed consent for themselves and their infants.

2.2. Participants

Participants included 152 mother-infant (47.4% female) pairs (see Supplement Fig. 1 for a flow chart of sample derivation). Table 1 reports descriptive information for the study sample.

2.3. Measures

2.3.1. Salivary cortisol assessments—Maternal prenatal saliva samples were collected in the early afternoon, on average (time of day across the five assessments, M = 13:32, SD = 1.57 h), using a Salivette sampling device (Sarstedt, Numbrecht, Germany). At 6 and 12 months of age, infant saliva samples were collected upon arrival to the well-baby appointments (prior to entering the examination room), and again 20 min after a nurse administered a standard set of intramuscular injections (inoculations) in the thigh (see Gunnar et al. (2009), for a review of studies that have used this standard procedure). Infant saliva was obtained, without any stimulant, by placing a swab in the infant's mouth. The collection swab was then placed in a saliva extraction tube (Roche Diagnostics, Indianapolis, IN).

All maternal and infant saliva samples were stored at − 70 °C until assay. Thawed samples were centrifuged at 1500 rpm for 15 min before assay. Salivary cortisol levels were determined by a competitive luminescence immunoassay (LIA; IBL-America, Minneapolis, MN) with reported detection limits of 0.015 μg/ dl. The cross reactivity of the assay was < 2.5% with cortisone, prednisone, and corticosterone and < 0.1% with other naturally occurring steroids. The intra- and inter-assay coefficients of variance were 5.5% and 7.6%, respectively. Data reduction for the LIA assay was done by an automated four-parameter logistics computer program (software Mikro Win 2000; Berthold Microplate Luminometer, Berthold Detection Systems GmbH; Pforzheim, Germany). All samples were assayed in duplicate and averaged. Six infants at six months and three infants at twelve months were excluded for having cortisol concentrations more than four standard deviations above the mean.

As a measure of infant cortisol response to the inoculation, delta cortisol values at 6 and 12 months were calculated by subtracting baseline cortisol levels from response (20-min) cortisol levels.

2.3.2. Socioeconomic status (SES)—A composite variable representing SES was created by combining the standardized values of maternal years of education and household income.

2.3.3. Maternal psychological assessments—Maternal psychological assessments included measures of state anxiety (10-item state anxiety subscale of the State-Trait Anxiety Inventory; Spielberger et al., 1970) and depressive symptoms (9-item short form of the Center for Epidemiologic Studies-Depression Scale; Santor and Coyne, 1997) at 6 and 12 months infant age. Postnatal anxiety and depression scores at 6 and 12 months infant age were averaged to create an index of postnatal anxiety and postnatal depression. STAI scores at 6 and 12 months ($r = 0.59$, $p < .001$) and CES-D scores at 6 and 12 months ($r = 0.62$, $p < .001$) were statistically significantly correlated.

2.3.4. Obstetric risk and birth outcomes—The maternal medical interview and review of hospital and birth records were used to derive a well-established, binary index of obstetric risk (Hobel, 1982). This index includes known risks of preterm birth and other adverse pregnancy outcomes, including infection, pregnancy-induced hypertension, gestational diabetes, oligohydramnios, polyhydramnios, preterm labor, vaginal bleeding, placenta previa, and anemia in the index pregnancy, as well as history of preterm delivery, spontaneous abortion, stillbirth, or ectopic pregnancy (68.4% of the women in this sample had none of the obstetric risks on this index). In addition, parity, maternal age, gestational age at birth, birth weight, Apgar score at 5 min, and breastfeeding status were recorded.

2.4. Data analysis

Prior to conducting the main analyses, measures of central tendency and variance were calculated for the maternal prenatal cortisol variables and infant delta cortisol at 6 and 12 months of age. Then, bivariate correlations were examined to determine whether potential covariates (SES, postnatal anxiety and depressive symptoms, obstetric risk, primiparity, maternal age, gestational age at birth, birth weight, maternal ethnicity, infant sex, breastfeeding status, Apgar score at 5 min, whether infant was fed during well-baby appointment, number of inoculations, and times of cortisol samples) were associated with the maternal and infant cortisol variables at $p < .10$. In addition, analyses of missing values were undertaken, including a series of independent sample *t*-tests, to examine potential systematic reasons for missingness (see Supplement Table 1). These preliminary analyses were conducted using SPSS, Version 25.

Maternal cortisol values at each time point were significantly skewed and thus were log-transformed to normalize the distribution of the data. Infant delta cortisol values at 6 and 12 months were normally distributed. Of all of the potential covariates considered, only SES was associated with prenatal maternal cortisol ($r(136) = 0.20$, $p = .02$) and infant delta cortisol ($r(136) = -0.15$, $p = .09$) at only the 6-month visit. SES was included in the models at both 6 and 12 months for consistency. Although postnatal anxiety did not meet our criteria for inclusion as a covariate (it was not correlated $p < .10$ with *both* maternal prenatal cortisol and infant delta cortisol), it was correlated with 6-month delta cortisol ($r = 0.19$, $p = .03$). Because of this and the theoretical likelihood that maternal postnatal anxiety could be

influence the postnatal environment and confound the association between prenatal maternal cortisol and infant HPA, we also included postnatal STAI as a covariate in all models.

Multilevel modeling using hierarchical linear modeling (HLM) growth curve analyses were conducted in HLM v7 (Raudenbush et al., 2011) to assess associations between prenatal maternal cortisol and infant cortisol responsivity to stress. The level one variable (i.e. time-variant) included maternal salivary cortisol values at each prenatal visit and the level-two variables (i.e. time-invariant) included infant delta cortisol values (entered as a continuous variable), SES, and postnatal anxiety. The model intercept was centered at each prenatal time point in separate models. Sex was then tested as a moderator of the association between prenatal maternal cortisol and infant delta cortisol by adding the interaction between sex and infant delta cortisol.

3. Results

3.1. Prenatal maternal cortisol

Of the quadratic and linear models tested, model fit indices including deviance scores (−2 log likelihood; Linear: −129.72, Quadratic: −133.56) and a nonsignificant likelihood ratio test ($p = .28$) indicated that a linear model provided better fit for the prenatal cortisol trajectories. The initial model included fixed and random effects for the intercept and the linear slope. Maternal cortisol increased significantly from.27 μg/dl at 15 weeks' gestation, at a rate of.015 μg/dl per week ($p < .001$) thus, leading to average cortisol at.60 μg/dl at 37 weeks' gestation. Results were virtually identical for the sample with 12-month data. Variance for slope of maternal cortisol was not statistically significant indicating that women increased at a similar rate across pregnancy and thus, was removed from the model. Initial cortisol levels varied significantly across women for the 6 months sample (SD =0.08, $p < .01$ for the intercept at 15 weeks') and the 12-month sample (SD =0.07, $p < .01$ for the intercept at 15 weeks').

3.2. Infant baseline cortisol

Infants' baseline cortisol was not significantly associated with prenatal maternal cortisol (ps > 0.10; see Supplement Table 2).

3.3. Infant stress response

Infant cortisol levels increased from baseline in response to the inoculation at both six (Baseline: $M = 0.28$, $SD = 0.31$, Response (20-min post inoculation): $M = 0.52$, $SD = 0.54$; $t = 6.22$, $p < .001$) and twelve months (Baseline: $M = 0.24$, $SD = 0.1$; Response (20-min post inoculation): $M = 0.42$, $SD = 0.47$, $t = 4.42$, $p < .001$) (see Fig. 1). Infant delta cortisol at 6 and 12 months was modestly correlated ($r = 0.19$, $p = .07$).

3.4. Associations between prenatal maternal salivary cortisol and infant cortisol stress reactivity

Results of the multilevel modeling analyses indicated that fetal exposure to higher prenatal maternal cortisol at each gestational time point was associated with a larger infant cortisol response to inoculation at six and twelve months of age (see Fig. 2A and B for a visual

depiction of this association with the intercept centered at 15 weeks' gestation; and Table 2 for results of models centered at each gestational time point). No effects of timing were observed—maternal cortisol levels across each gestational time point were similarly associated with infant cortisol responsivity.

3.5. Sex as a moderator of the association between prenatal maternal salivary cortisol and infant cortisol stress reactivity

Sex did not moderate the association between prenatal maternal cortisol and infant cortisol responsivity to inoculations ($p's > 0.10$). See Supplement Table 3.

4. Discussion

The results from the current study provide new information about the persisting association between fetal exposure to maternal cortisol and infant HPA axis development. Fetal exposure to elevated maternal cortisol throughout gestation is associated with greater infant cortisol reactivity to a painful stressor at 6 and 12 months of age. This association remained after covarying SES and postnatal maternal distress, and further, other potentially confounding variables (i.e., obstetric risk, birth outcomes, breastfeeding status, infant sex, and maternal ethnicity) were not statistically associated with maternal cortisol or fetal cortisol. Thus, this study suggests that prenatal maternal cortisol may shape development of the offspring HPA axis, and is consistent with the hypothesis that programming of the HPA axis is a plausible mechanism by which prenatal maternal cortisol may influence offspring physical and mental health outcomes (Howland et al., 2017).

During infancy, painful stressors (i.e., inoculation) reliably produce robust increases in infant cortisol (Davis and Granger, 2009; Gunnar et al., 1996; Lewis and Ramsay, 1995; Ramsay and Lewis, 2003), and inoculation in the current study effectively elicited a cortisol response in infants at 6 and 12 months. A prior study using heelstick to elicit reactivity in neonates identified an association between elevated maternal prenatal cortisol and greater cortisol reactivity (Davis et al., 2011). The current study establishes that this association is detectable through 12 months of age. Our results also are consistent with the literature on the effects of synthetic glucocorticoids in pregnancy, which has indicated that prenatal exposure to synthetic glucocorticoids is associated with altered cortisol regulation in neonates and in children (Alexander et al., 2012; Davis et al., 2011; Edelmann et al., 2016; ter Wolbeek et al., 2015).

Although reviews of the literature have indicated that elevated prenatal maternal cortisol appears to have differential associations with infant outcomes depending on the gestational timing of exposure (Howland et al., 2017; Zijlmans et al., 2015), no timing effects were identified in the current study—there was an association between maternal prenatal cortisol concentrations at each gestational time point and greater infant cortisol reactivity to a painful stressor. The majority of prior studies either measured maternal cortisol at a single gestational timepoint or did not assess responses to a stressor that provoked reliable elevations in infant cortisol (de Weerth et al., 2013; Giesbrecht et al., 2017; Nazzari et al., 2019; O'Connor et al., 2013; Osborne et al., 2018; Tollenaar et al., 2011). Moreover, although two studies with the aforementioned differences in methodology, compared to our

study, identified sexually dimorphic associations between maternal prenatal cortisol and infant cortisol (Giesbrecht et al., 2017; O'Connor et al., 2013), our finding of a lack of sex differences in the association between maternal prenatal cortisol and infant cortisol responsivity to stress is in concordance with other work in this domain (Davis et al., 2011; Rash et al., 2016).

Exposure to elevations in prenatal maternal cortisol has the potential to influence the fetal HPA axis through several mechanisms. First, maternal prenatal cortisol may modify the offspring epigenome (Moisiadis and Matthews, 2014a, 2014b; Reynolds, 2013) through alteration in DNA methylation or methyltransferases at the glucocorticoid response elements of the genes that are either targets of or directly regulate HPA axis function (Jellyman et al., 2015). Second, elevations in prenatal maternal cortisol have been shown to alter the density of cortisol receptors and reduce glucocorticoid feedback, thereby increasing the magnitude of cortisol secretion in response to challenge (Kapoor et al., 2006). Third, excess maternal glucocorticoids in pregnancy inhibit fetal growth in the brain, heart, liver, kidney, and adrenal glands, which has been found to modify metabolic and endocrine function and affect responsivity to acute challenges in fetal sheep and foals (Fletcher et al., 2000, 2004, Jellyman et al., 2005, 2015). Additional research is needed to fully understand the precise mechanisms by which prenatal maternal cortisol influences HPA axis development and factors that may moderate these associations in humans.

A limitation of the current study is that its observational design cannot directly establish a causal relation. Thus, alternative explanations of these findings may exist, including the possible influence of maternal diet or postnatal environmental influences such as quality of caregiving (Howland et al., 2017; Kaplan et al., 2008). Another possible alternative explanation of our findings is that the association between maternal cortisol and infant cortisol reactivity may be affected by shared genes. Experimental work using a cross fostering design with rodents, however, controls for genetic influences, and our findings are consistent with studies where these experimental manipulations were possible (Abe et al., 2007; Kapoor et al., 2008; Maccari and Morley-Fletcher, 2007; Schneider, 1992; Thayer et al., 2018). Power limitations should be considered when interpreting these results, although a simulation study indicates that the sample size of the current study should yield unbiased and accurate estimates of coefficients, variance components, and standard errors (Maas and Hox, 2005).

4.1. Conclusions

In conclusion, our findings in this prospective, longitudinal cohort suggest that elevated prenatal maternal cortisol is associated with a heightened infant response to inoculation in infancy, and that this association does not appear dependent on the timing of exposure during gestation. Prenatal development is an intricately timed cascade of events, and exposure to elevations in maternal cortisol is associated with an altered developmental trajectory that influences how offspring react to challenges in infancy and, as is purported by the fetal programming hypothesis, throughout life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We confirm that this work is original and has not been published elsewhere, nor is it currently under consideration for publication elsewhere. All authors have reviewed and approved the manuscript and have no conflicts of interest to report. We thank Julia Dmitrieva for her consultation on statistical analyses.

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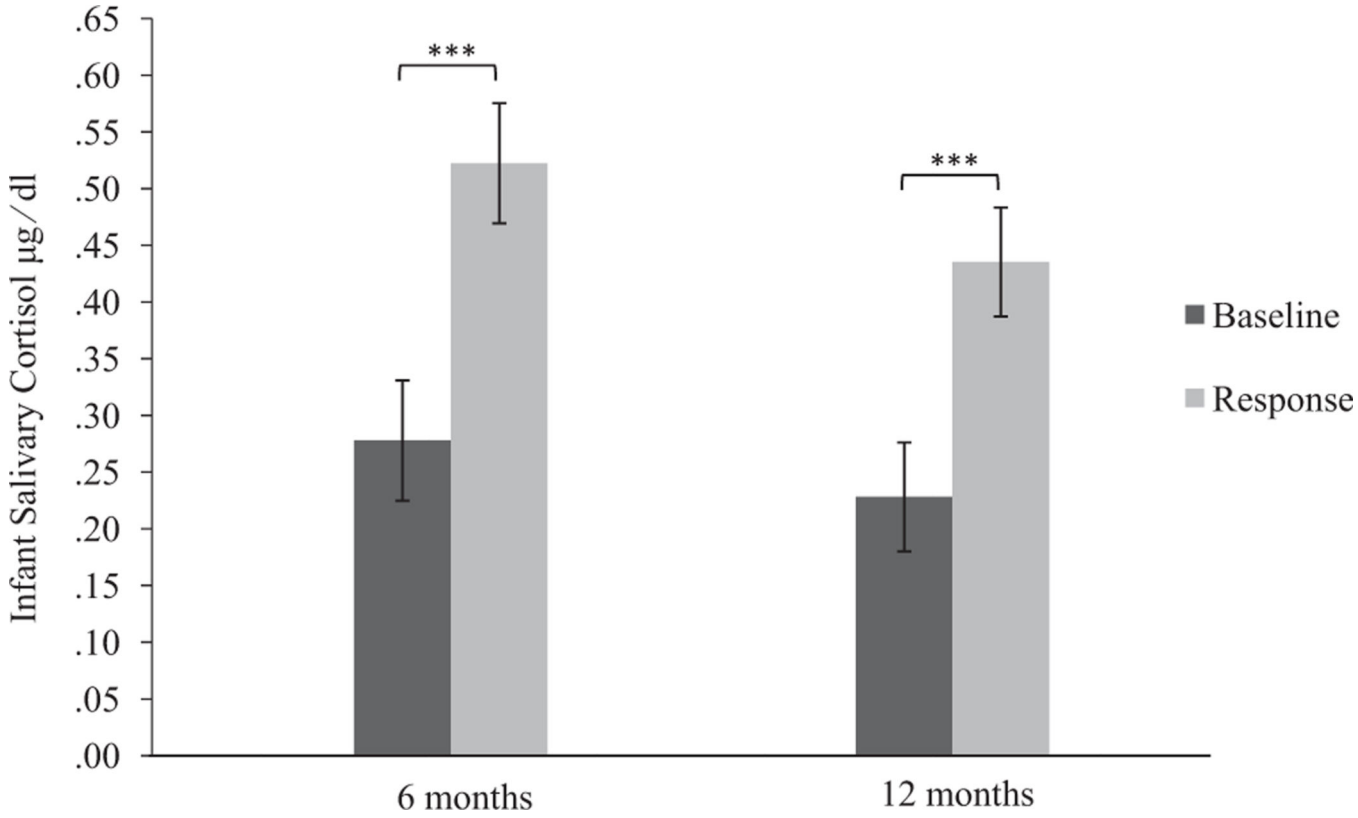

Fig. 1.

Infant cortisol responsivity to the inoculation challenge at six and twelve months. ***$p <$ .001.

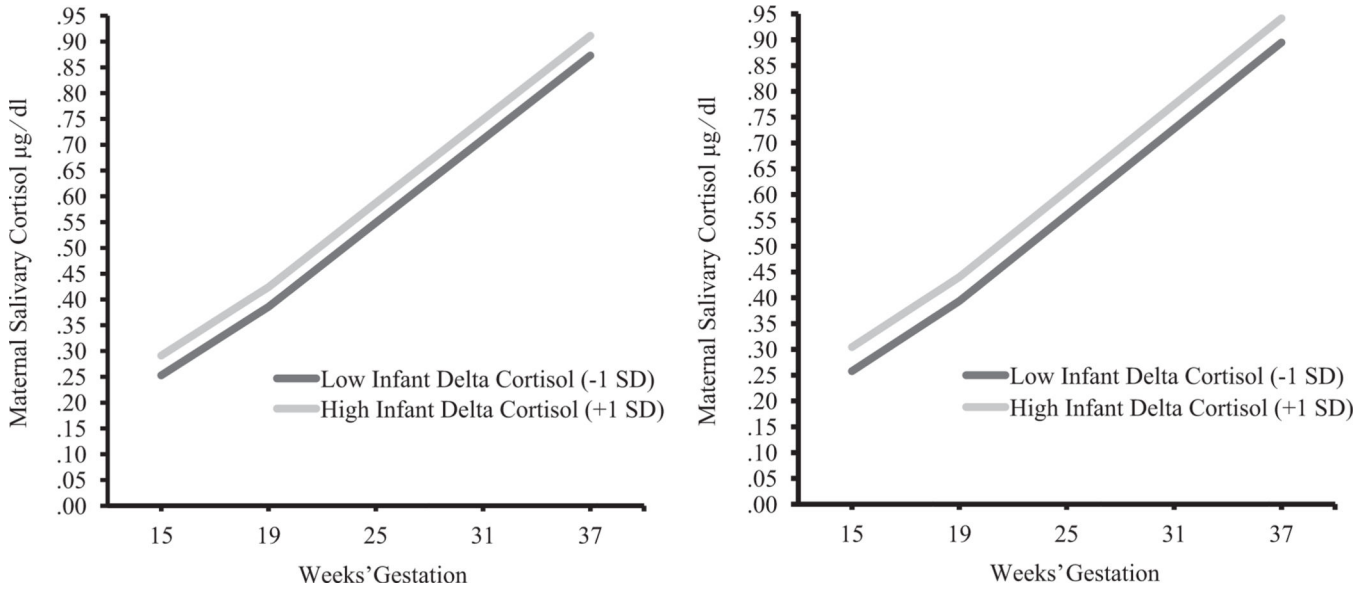

Fig. 2.

A, 2B. The association between maternal salivary cortisol across gestation and infant delta cortisol at 6 months (left) and 12 months (right) when the intercept was centered at 15 weeks' gestation, the first gestational time point. Infants that were exposed to higher overall maternal salivary cortisol levels across pregnancy had a higher delta cortisol in response to stress (green). Note: Top and bottom SD displayed for visualization purposes only. Both maternal and infant salivary cortisol were analyzed as continuous variables.

Table 1

Descriptive statistics for study variables and demographic characteristics (N = 152).

Maternal Characteristics	**M (SD) or n (%)**
Maternal age at delivery (years)	30.3 (5.2)
Parity (% primiparous)	72 (47.4%)
Maternal education	
High school or less	29 (23.0%)
Some college	27 (21.4%)
College degree	47 (37.3%)
Post-graduate degree	23 (18.3%)
Household income	
$0 to $30,000	27 (18.0%)
$30,001 to $60,000	41 (27.3%)
$60,001 to $100,000	48 (31.9%)
Over $100,000	34 (22.7%)
Race/ethnicity	
Non-Latina White	77 (50.7%)
Latina	36 (23.7%)
Asian	17 (11.2%)
African American	5 (3.3%)
Multi-Ethnic	17 (23.7%)
Cortisol at 15 weeks' gestation (μg/dl)	0.3 (0.2)
Cortisol at 19 weeks' gestation (μg/dl)	0.4 (0.2)
Cortisol at 25 weeks' gestation (μg/dl)	0.5 (0.3)
Cortisol at 31 weeks' gestation (μg/dl)	0.5 (0.2)
Cortisol at 37 weeks' gestation (μg/dl)	0.6 (0.2)
Infant Characteristics	
Gestational age at birth (weeks)	39.5 (1.1)
Birth weight (grams)	3415.2 (438.7)
Apgar score (5 min)	9.0 (0.3)
Sex at birth (% female)	72 (47.4%)
Baseline cortisol at 6 months (μg/dl)	0.3 (0.3)
Response (20-min) cortisol at 6 months (μg/dl)	0.5 (0.5)
Delta cortisol at 6 months (μg/dl)	0.2 (0.5)
Baseline cortisol at 12 months (μg/dl)	0.2 (0.2)
Response (20-min) cortisol at 12 months (μg/dl)	0.4 (0.3)
Delta cortisol at 12 months (μg/dl)	0.2 (0.3)

Note. Descriptive statistics for raw cortisol values are presented.

Table 2

Multilevel models of the association between prenatal maternal cortisol and infant cortisol response to inoculation (delta cortisol) with postnatal maternal anxiety and socioeconomic status entered as covariates.

	Infant Delta Cortisol Reactivity					
	6 months (*N* = 136)			**12 months (*N* = 107)**		
Fixed Effects	***Estimate***	***SE***	***T***	***Estimate***	***SE***	***T***
Intercept centered at 15 weeks						
Model 1						
Maternal cortisol intercept, β_{00}	0.272***	0.015	17.85	0.282***	0.016	18.06
Model 2						
Maternal cortisol intercept, β_{00}	0.272***	0.015	18.06	0.281***	0.015	18.42
Infant delta salivary cortisol, β_{01}	0.042*	0.020	2.08	0.054*	0.022	2.51
Postnatal maternal anxiety, β_{02}	−0.040*	0.019	−2.15	−0.028	0.018	−1.52
Socioeconomic status, β_{03}	0.013*	0.006	2.31	0.002	0.006	0.40
Intercept centered at 19 weeks						
Model 1						
Maternal cortisol intercept, β_{00}	0.331***	0.013	26.33	0.343***	0.013	27.01
Model 2						
Maternal cortisol intercept, β_{00}	0.330***	0.012	26.85	0.342***	0.012	27.79
Infant delta salivary cortisol, β_{01}	0.042*	0.020	2.08	0.054*	0.022	2.51
Postnatal maternal anxiety, β_{02}	−0.040*	0.019	−2.15	−0.028	0.018	−1.52
Socioeconomic status, β_{03}	0.013*	0.006	2.31	0.002	0.006	0.40
Intercept centered at 25 weeks						
Model 1						
Maternal cortisol intercept, β_{00}	0.418***	0.011	38.50	0.434***	0.011	38.31
Model 2						
Maternal cortisol intercept, β_{00}	0.418***	0.010	39.87	0.434***	0.011	39.93
Infant delta salivary cortisol, β_{01}	0.042*	0.020	2.08	0.054*	0.022	2.51
Postnatal maternal anxiety, β_{02}	−0.040*	0.019	−2.15	−0.028	0.018	−1.52
Socioeconomic status, β_{03}	0.013*	0.006	2.31	0.002	0.006	0.40
Intercept centered at 31 weeks						
Model 1						
Maternal cortisol intercept, β_{00}	0.505***	0.013	39.22	0.525***	0.014	36.65
Model 2						
Maternal cortisol intercept, β_{00}	0.505***	0.012	40.63	0.526***	0.014	38.10
Infant delta salivary cortisol, β_{01}	0.042*	0.020	2.08	0.054*	0.022	2.51
Postnatal maternal anxiety, β_{02}	−0.040*	0.019	−2.15	-0.028	0.018	−1.52

	Infant Delta Cortisol Reactivity					
	6 months (*N* = 136)			12 months (*N* = 107)		
Fixed Effects	***Estimate***	***SE***	***T***	***Estimate***	***SE***	***T***
Socioeconomic status, β_{03}	0.013 *	0.006	2.31	0.002	0.006	0.40
Intercept centered at 37 weeks						
Model 1						
Maternal cortisol intercept, β_{00}	0.592 ***	0.017	34.10	0.616 ***	0.020	31.12
Model 2						
Maternal cortisol intercept, β_{00}	0.592 ***	0.017	35.04	0.618 ***	0.019	32.17
Infant delta salivary cortisol, β_{01}	0.042 *	0.020	2.08	0.054 *	0.022	2.51
Postnatal maternal anxiety, β_{02}	−0.040 *	0.019	−2.15	−0.028	0.018	−1.52
Socioeconomic status, β_{03}	0.013 *	0.006	2.31	0.002	0.006	0.40

Note. Model 1 is the growth curve model of maternal cortisol across gestation. Model 2 assesses prenatal maternal cortisol associations with infant delta cortisol, with postnatal maternal anxiety and socioeconomic status entered as covariates. Fixed effect estimates with robust standard errors are presented.

* $p < .05$.

*** $p < .001$.