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Higher Maternal Prenatal Cortisol and Younger Age Predict Greater Infant Reactivity to Novelty at 4 Months: An Observation-Based Study

ABSTRACT: *Distress-linked activation of the maternal hypothalamic–pituitary–adrenal (HPA)-axis is considered a pathway by which affect regulation impacts the fetal milieu and neurodevelopment. There is little direct evidence for this conceptual model. In 103 women [mean age 27.45 ($\pm$5.65) years] at 36–38 weeks gestation, salivary cortisol was measured before/after stress tasks; distress questionnaires were completed. At 18.49 ($\pm$1.83) weeks, infants underwent the Harvard Infant Behavioral Reactivity Protocol assessing cry/motor responses to novelty; women reported on infant behavior and postnatal distress. Prenatal cortisol and distress were not significantly correlated (all ps > .10). Proportional odds logistic regressions showed that neither prenatal nor postnatal distress was associated with infant responses to the Harvard Protocol yet pre-stress cortisol and maternal age were: The odds of being classified as High Reactive were 1.60 times higher [95% CI: 1.04, 2.46] for each unit of added cortisol and .90 times lower [95% CI: .82, .99] for every additional year in maternal age. No associations were found between cortisol or prenatal distress and mother-rated infant behavior; postnatal distress was positively associated with mother-rated infant negative behavior (p = .03). Observer and mother-rated infant behavior were not associated (all ps > .05). Based on independent observations of infants in contrast to maternal perceptions, these results lend support to the hypothesis that pregnant women's HPA-axis activity influences infant behavior. The impact of maternal distress was not supported, except in so far as postnatal distress may increase the likelihood of making negative judgments about infant behavior.* © 2012 Wiley Periodicals, Inc. Dev Psychobiol

Keywords: neurodevelopment; infant reactivity; prenatal; distress

INTRODUCTION

Fetal experience contributes to the determination of children's neurodevelopmental trajectories (Bale et al., 2010). Pregnancies characterized by significant maternal stress, anxiety, and depression are identified in some studies as a risk factor for psychopathology in the children (Buss, Davis, Muftuler, Head, & Sandman, 2010; Pawlby, Hay, Sharp, Waters, & O'Keane, 2009; Talge, Neal, & Glover, 2007). Distress-linked activation of the maternal hypothalamic–pituitary–adrenal axis

(HPA-axis), and, in particular, elevations in maternal glucocorticoids (GCs), are frequently described as likely pathways by which women's psychobiological affect regulation impacts the in utero environment, shaping fetal neurodevelopment and child outcomes (Charil, Laplante, Vaillancourt, & King, 2010; Glover, O'Connor, & O'Donnell, 2009; Owen, Andrews, & Matthews, 2005; Sandman, Davis, Buss, & Glynn, 2011). Direct evidence for this conceptual model is quite strong in animal studies. However, with humans, there are relatively few studies, and several factors obscure straightforward interpretation of the results.

Animal research elegantly supports the model of experience-based maternal HPA-axis activity influencing offspring development and the role of maternal GCs in this transmission (Weinstock, 2005). For example, offspring of pregnant rodents exposed daily to 45 min of one of three stressors (restraint, forced swim, or forced elevation) show heightened fear responses in the face of novelty. Yet the offspring of pregnant adrenalechtomized rodents who undergo the same stressors do not show these heightened fear responses (Salomon, Bejar, Schorer-Apelbaum, & Weinstock, 2011).

In humans, the seven studies examining both maternal prenatal cortisol and distress in relation to infant outcomes show only partial support for the hypothesis (Bergman, Sarkar, Glover, & O'Connor, 2010; Buitelaar, Huizink, Mulder, de Medina, & Visser, 2003; Davis et al., 2007; Davis & Sandman, 2010, 2012; Gutteling et al., 2005; Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2003), and some methodological issues make interpretation of the results difficult. Specifically, studies showing an impact of these prenatal maternal factors on child outcomes indicate that they are *independent* predictors. That is, elevated prenatal maternal distress and cortisol *independently* predict: less adaptive behavioral regulation in response to a stressor at birth (Davis, Glynn, Waffarn, & Sandman, 2011), difficult temperament at 2 months (Davis et al., 2007), lower development scores on the Bayley Scales of Infant Development at 12 (Davis & Sandman, 2010) and 17 months (Bergman et al., 2010), and increased anxiety at 6–9 years old (Davis & Sandman, 2012). Moreover, in each of these studies, maternal distress and cortisol were not associated (Bergman et al., 2010; Davis et al., 2007, 2011; Davis & Sandman, 2010, 2012). Other studies showing that prenatal distress and elevated cortisol are associated with lower Bayley scores at 8 and 27 months did not assess both variables in the same statistical models or report on their association (Buitelaar et al., 2003; Gutteling et al., 2005; Huizink et al., 2003). There are two other methodological issues: in the studies demonstrating prenatal maternal effects on children's

behavior, women were the source for the independent and dependent variables, describing their own pregnancy distress as well as their perceptions of infant outcomes (Davis et al., 2007; Davis & Sandman, 2012; Gutteling et al., 2005). Also, reports on older infants (Bergman et al., 2010; Davis & Sandman, 2010, 2012; Gutteling et al., 2005; Huizink et al., 2003) increase the likelihood that outcomes are heavily influenced by postnatal experience, which may not be adequately characterized by statistically controlling for self-reports of maternal postpartum mood and yet, for which, prenatal distress could be an associated "marker" variable. Two studies show aspects of maternal care to be an additive (Grant et al., 2009) or moderating influence (Bergman et al., 2010) on the effects of maternal prenatal distress on children's neurodevelopment past 6 months of age.

One approach to honing in on the possible effects of maternal prenatal distress and cortisol on infant neurobehavioral development is to limit postnatal influences by evaluating infants closer to birth (Davis et al., 2011), and to standardize the infant evaluation by using a structured laboratory protocol, trained observers, and a standardized system for coding. The Harvard Infant Behavioral Reactivity Protocol (Kagan & Snidman, 1991a) is one such protocol, and previously has been shown to differentiate infants in relation to women's psychological functioning during pregnancy (Davis et al., 2004; Werner et al., 2007).

In this paradigm, infants are seated in a car seat on a table in the laboratory. Here, they confront a uniform series of novel stimuli (e.g., tape recorded voice, mobiles, odor). Based on their level of motor and cry/fret responses, they are judged to show high motor and cry responses ("High Reactive") or low motor and cry responses ("Low Reactive"), or to be in the Intermediate groups of high motor/low cry, or low motor/high cry reactivity (Kagan, 1994; Kagan & Snidman, 1991a). High Reactive infants are much more likely to develop an inhibited temperament style in the preschool years—characterized by shy, timid, fearful responses to unfamiliar events. Inhibited children are at greater risk of developing anxiety disorders and other problems associated with emotion regulation (Biederman et al., 2001; Hirshfeld-Becker et al., 2007; Rapee, Kennedy, Ingram, Edwards, & Sweeney, 2005; Schwartz, Snidman, & Kagan, 1999). Using the Harvard Protocol, one study found that third trimester maternal anxiety and depression were associated with High Reactive classification at 4 months (Davis et al., 2004). In our laboratory, we showed that depression and anxiety diagnosed in the third trimester predicted greater likelihood of high cry, although not high motor, reactivity. We also found that infants who were categorized as Low Reactive

were 8.4 times more likely than infants in other reactivity groups *not* to have a mother diagnosed with a mood disorder (Werner et al., 2007). Neither of these studies reported on cortisol data.

The current study aims to further the investigation of maternal prenatal distress and HPA-axis activity influencing child neurobehavioral development. Building on the prior reports, we considered women's cortisol level and self-reported distress in late pregnancy (gestational weeks 36–38) as predictors of 4-month-old behavior on the Harvard Protocol and of maternal report of infant behavior. We hypothesized that pregnant women's symptoms of distress (depression, anxiety, and elevated life stress) and higher cortisol would be associated with greater likelihood of 4-month-old infants being classified as High Reactive and as having difficult temperament according to maternal report.

METHODS

Subjects

As part of a larger study focused on maternal prenatal factors influencing fetal behavior, 334 pregnant women were recruited in the second trimester and 273 attended a third-trimester fetal assessment session. Of those women, 103 returned to our laboratory with their infants at approximately 4-month postpartum for an assessment of infant temperament. Recruitment of women carrying singleton fetuses took place between July 2001 and March 2006 via clinics affiliated with Columbia University Medical Center. Women were excluded from entering the study if they smoked during pregnancy, were taking any medications, or if there were any maternal or fetal medical complications such as hypertension, diabetes mellitus, or suspected fetal growth restriction. This study was approved by the New York State Psychiatric Institute Institutional Review Board, and all subjects gave written, informed consent.

Procedure

Between 36 and 38 weeks gestation, participants attended a laboratory session that began at 10:30 a.m. to control for diurnal variations in salivary cortisol levels. Women completed self-report questionnaires to assess their psychological distress levels. Along with the cortisol samples, heart rate (HR), blood pressure, and fetal HR were collected while women underwent stress-inducing challenge tasks [reported elsewhere (Monk et al., 2010)]. At 4-month postpartum, participants returned to the laboratory with their infants to complete the same self-report questionnaires, as well as a rating scale of infant temperament. The infants underwent the Harvard Protocol while their mothers were seated behind a one-way mirror.

Salivary Cortisol

Salivary cortisol was collected at three time points during the prenatal laboratory session: (first) after the participant arrived and consent was obtained, "Entry"; (second) just before the session started but after a brief practice of the forthcoming tasks, "Acclimate"; and (third), just after the session ended, "Recovery." There were 25 min between each sample. To obtain assays of cortisol, participants were instructed to suck and chew on a cotton roll for 1 min or until saturated.

Saturated cotton rolls enclosed in sealed tubes were stored at $-20°C$ until the time of assay. Saliva extracted from these cotton rolls was analyzed at the Analytical Psychopharmacology Laboratories at the Nathan Kline Institute. Cortisol was measured by radioimmunoassay using primary antibodies and 1,125 labeled cortisol purchased from ICN Biomedicals (Irvine, CA). The cortisol standards used were from Sigma Chemical Co (St. Louis, MO). Samples were assayed in duplicate. The intra- and inter-assay coefficients of variation were 3.0% and 6.0% at the 3.1 µg/dl level.

Maternal Self-Report of Distress

At both sessions, participants completed the State Anxiety Inventory of the Speilberger State-Trait Anxiety Inventory (STAI, Spielberger, 1983), the Perceived Stress Scale (PSS, Cohen, Kamarck, & Mermelstein, 1983), and the Center for Epidemiologic Studies Depression Scale (CES-D, Radloff, 1977).

State Anxiety (STAI)

The state module of the STAI consists of 20 questions that measure the experience of anxiety at the time of testing. Anxiety scores range from 20 to 80, with high scores reflecting higher levels of anxiety. This measure has been extensively used and its reliability and validity are well-established (Spielberger, 1983). The study of the psychometric comparability of the STAI for different ethnic subpopulations indicates that this questionnaire is a reliable measure of anxiety across Caucasian, Latino, and African American populations (Novy, 1993). Coefficient alphas for these groups range from .93 to .95 (Novy, 1993).

Center for Epidemiologic Studies Depression Scale (CES-D)

The CES-D is a 20-item self-rating scale for the measurement of current depressive symptoms (Radloff, 1977). The scores range from 0 to 60. A score of 16 or more is considered an indication of depression (Knight, Williams, McGee, & Olaman, 1997). The validation and use of the CES-D in community samples has been well established (Hertzog, 1990; Radloff, 1977). It has also been shown to be highly reliable with respect to good internal consistency and test–retest reliability (Knight et al., 1997; Radloff, 1977; Roberts, 1990). In a sample of women from the community (Knight et al., 1997), Cronbach's alpha for the entire CES-D was reported to be .88.

Perceived Stress Scale (PSS)

The PSS is a 14-item instrument designed to measure the degree to which subjects appraise situations in their lives as

stressful. On the PSS, respondents rate the frequency of specific stressful experiences over the past month on a five-point scale from ''never'' to ''very often'' (e.g., ''In the last month how often have you found that you could not cope with all the things that you had to do?''). The PSS has been shown to have adequate reliability and reports an alpha of .84–.86. Moreover, the PSS was found to measure a different construct from the CES-D (Cohen et al., 1983).

Infant Neurobehavioral Development at 4 Months: The Harvard Infant Behavioral Reactivity Protocol

Following previously executed protocols (Kagan & Snidman, 1991a), infants were secured in an infant seat on the floor and administered the following five episodes while being video-taped: (1) a 60-s quiet period with the mother looking at the child with a friendly smiling expression but not speaking (she then moved behind the one-way mirror); (2) the presentation of a tape recording of eight utterances: (a) ''Hello, pretty baby. How are you today?'' (b) ''It's time to give me a great, big smile.'' (c) ''You have been a very good baby today.'' (d) ''Please won't you give us a great, big laugh?'' (e) ''Are you ready for some nice, warm milk?'' (f) ''Okay, baby. Don't you fall to sleep on us now.'' (g) ''Did you like playing these games today?'' (h) ''What a very big baby you are.''; (3) the presentation of three mobiles containing one, three, or seven moving, three-dimensional plush animal toys on three successive occasions for a total of nine 20-s trials; (4) the presentation of three olfactory stimuli (distilled water, low-concentration butanol, and high-concentration butanol) on a cotton swab. The distilled water was presented first for 10 s. Then, the low-concentration butanol was presented for 10 s on three successive trials, and the high-concentration butanol was presented for 10 s on three successive trials. Then the distilled water was presented again for 10 s; (5) a presentation of the three different mobiles containing one, three, or seven moving, three-dimensional plush shapes on three successive occasions for a total of nine 20-s trials. The protocol was videotaped using a VHS camcorder, and all tapes were viewed for coding purposes on a 13-in. television attached to a VCR.

Coding of the Harvard Infant Behavioral Reactivity Protocol

The coding of the videotaped sessions was based on the procedures used by other laboratories (Kagan & Snidman, 1991a). One of two coders (E.W. or L.E.) examined the videotapes of these sessions and assigned each infant to one of two motor activity groups based on both the frequency and the vigor of (a) limb movements (both flexing and extending); (b) arching of the back; (c) tongue protrusions; and (d) motor tension in the hands and limbs. Neither vocalization nor fretting was used in these classifications. The coder who assigned each infant to one of the two motor activity groups also assigned each infant to one of two fret-cry groups based on the frequency and intensity of fretting or crying in response to the stimuli. The infants were then classified into one of four groups: high motor/high cry (High Reactive), low motor/low cry (Low Reactive), or low motor/high cry, high motor/

low cry (Intermediate groups). Inter-rater reliability (Cohen's Kappa Coefficient) for this coding procedure has been reported to be .90 in previous research studies (Snidman, Kagan, Riordan, & Shannon, 1995). Fifty percent of the sessions were coded by two coders and inter-rater reliability (Cohen's Kappa Coefficient) for the current study was 1.00. The coders were blind to women's psychological distress status as well as to cortisol levels.

Infant Neurobehavioral Development at 4 Months: Mother-Reported Infant Behavior Questionnaire (IBQ)

The IBQ includes 94 items evaluated on a seven-point scale reflecting the relative frequency of specified infant reactions to certain situations in the last week (e.g., When put into the bath water how often did the baby wave his arm, squirm, or try to roll away?). Responses are tabulated under six subscales (activity level, distress to limitations, latency to approach novel situations (fear), duration of orienting, smiling and laughter, and soothability), which range from 1 to 7. An item-weighted sum of fear and distress to limitations subscales forms a ''Negative Reactivity'' cluster and an item-weighted sum of smiling and activity level subscales forms a ''Positive Reactivity'' cluster (Pesonen, Raikkonen, Strandberg, & Jarvenpaa, 2006). The reliability of the IBQ is good (Rothbart, 1986) ranging from .70 to .90 (Pesonen et al., 2006).

Analytic Approach and Data Reduction

SAS 9.2 was used for all statistical analyses. Statistical significance was set at a p-value $<.05$. Means and standard deviations (SD) for prenatal cortisol and maternal distress variables by infant behavior rating groups (Harvard Infant Behavioral Reactivity Protocol and IBQ) were determined. Spearman's correlations between prenatal cortisol and maternal distress variables were used due to the non-normal distributions of the prenatal cortisol levels and state anxiety (STAI), based on the Kolmogorov–Smirnov test.

The main effects of maternal prenatal cortisol and prenatal and postnatal mood variables on infant behavior during the Harvard Protocol were tested using a proportional odds logistic regression. The effects of those variables on IBQ positive and negative infant behavior were tested using multiple linear regression models. Finally, parallel analyses of the associations between prenatal cortisol change (defined as cortisol difference between the Acclimate and the Recovery samples) and the two primary outcomes also were performed.

Following the protocol used in prior studies (Kagan & Snidman, 1991b), the first primary outcome, infant behavior ratings from the Harvard Protocol were categorized into groups based on their motor and cry reactivity during the protocol. Specifically, the low motor/low cry infants were defined as Low Reactive, the high motor/high cry infants were regarded as High Reactive, and the other two were classified as Intermediate, with analyses focused on the high and low groups.

The second primary outcome was infant neurobehavioral development at 4 months assessed by mother reported infant

behavior (IBQ). Following standard procedures, two summary scores were created from the questionnaire to measure infants' Negative and Positive Reactivity, respectively.

Prenatal cortisol level was estimated by the second (i.e., Acclimate) sample. Results from other studies (Davis et al., 2007, 2011; Huizink et al., 2003) indicate that the assessment of an association between maternal prenatal cortisol levels and infant outcomes should be based on the most representative cortisol sample that can be obtained in a laboratory setting. We reasoned that the Acclimate sample was most ecologically valid, and similar to the samples used in other studies given that it was collected after some period of "acclimation" to the laboratory setting and prior to the challenge tasks. For exploratory analyses, we examined the cortisol change from Acclimate to Recovery in relation to infant outcomes.

Composite scores for prenatal and postnatal mood variables were created based on studies showing a high correlation amongst maternal prenatal mood variables (Davis et al., 2011) and non-specificity of mood variables with respect to infant outcomes (Bergman et al., 2010; Davis et al., 2007, 2011; Davis & Sandman, 2010; Gutteling et al., 2005; Huizink et al., 2003). Specifically, a prenatal mood score was computed as the average of standardized prenatal STAI, CES-D, and PSS scores. Postnatal mood score was calculated similarly using postnatal data. Following other studies examining the potential influence of pregnant women's distress on child development (Davis et al., 2007; O'Connor, Heron, Glover, & The ALSPAC Study Team, 2002), we included women's postnatal mood in the models to control for this possible post-birth influence on the infant.

Finally, following other studies with similar aims (Bergman et al., 2010; Buitelaar et al., 2003; Davis et al., 2011; Gutteling et al., 2005), we included the following covariates in all analyses: sex of the newborn, maternal age, family income status (whether family's annual income is more than $26,000), and parity. We were particularly interested in maternal age as one report on prenatal influences on children's development showed an inverse association between it and children's behavioral regulation (Gutteling et al., 2005), while another indicated an assessment of maternal age that may serve to reflect other aspects of the child's postnatal context such as women's satisfaction with the caregiver role that could impact child development (Ragozin, Basham, Crnic, Greenberg, & Robinson, 1982). The $26,000 threshold is the estimated poverty level for a family of four in New York City (Paybarah, 2008). Given the impact of poverty on the social–emotional context of children's lives and their development (Shonkoff & Garner, 2012) we included this economic index in our models.

RESULTS

Description of the Sample Population

Characteristics of the women and newborns enrolled in the study are shown in Table 1, as well as of those lost to follow-up. Fully one-third of the sample who completed the study had incomes <$26,000, the estimated poverty level for a family of four in New York City; a majority of women who completed the study were

Table 1.   Demographic Characteristics of the Study Population: Maintained Versus Lost to Follow-Up

Characteristics	Mean ($\pm SD$) or % Maintained ($n = 103$)	Mean ($\pm SD$) or % Lost to Follow-Up ($n = 231$)
Maternal characteristics		
Age (years)	27.45 (± 5.65)	25.77 (± 5.74)
Education (years)	14.38 (± 3.10)	13.41 (± 2.62)
Income (% <$26,000)[a]	34.00	54.39
Ethnicity (%)		
African American	10.68	15.48
Asian	1.94	5.31
Caucasian	25.24	12.39
Latina	56.31	63.27
Other	5.83	3.54
Parity (% Nulliparous)	62.00	52.25
Prenatal Cortisol (Acclimate)	1.14 ($\pm .36$)	1.27 ($\pm .48$)
Prenatal State Anxiety (STAI)	32.12 (± 9.04)	33.68 (± 10.39)
Prenatal Perceived Stress (PSS)	22.27 (± 7.25)	24.11 (± 7.69)
Prenatal Depression (CES-D)	12.48 (± 9.09)	16.59 (± 9.90)
Infant characteristics		
Infant age at test (weeks)	18.49 (± 1.83)	—
Gestational age at birth (weeks)	39.30 (± 1.61)	39.41 (± 1.58)
Birth weight (g)	3250.97 (± 492.51)	3166.88 (± 528.37)
Sex (% female)	61.00	47.87

[a]Estimated poverty level for a family of four in New York City.

ethnic minorities, all infants were considered full term, and more than half the infants were female. Women who returned for the 4-month postpartum session were not significantly different from those who did not with respect to all demographic variables. However, there were significant differences on all cortisol and mood variables except STAI. Those lost to follow-up had higher cortisol values and were more distressed. Clearly, we experienced significant attrition due to insufficient resources allocated to efforts to maintain the sample.

Maternal Self-Reported Distress and Prenatal Cortisol

To investigate relations among maternal indicators of distress (both self-report distress variables and cortisol) prior to modeling these variables in relation to the outcomes of interest, as well as making composite maternal mood variables, a correlation matrix was produced. Pairwise Spearman's correlation coefficients between prenatal cortisol and maternal self-reported distress are presented in Table 2. By Spearman's rank test, there were no significant correlations between prenatal cortisol and any of the maternal self-reported distress variables. Prenatal cortisol and the two composite mood variables were not significantly correlated (all $ps > .10$). Of interest, there were relatively strong correlations amongst the three mood variables within time periods, that is, prenatal or postnatal, as well as across these time periods. These results support our analytic plan in generating a composite score for maternal

mood and considering prenatal and postnatal maternal moods, and cortisol, as independent factors in potentially contributing to infant outcomes.

Infant Behavior Ratings: Harvard Infant Behavioral Reactivity Protocol and the IBQ

Based on the Harvard Protocol, infants were rated as High ($n = 25$, 24.27%), Intermediate ($n = 29$, 28.16%), and Low ($n = 49$, 47.57%) Reactive, respectively. The proportion of infants rated as High Reactive was comparable to those in other studies, that is, approximately 20% (Kagan, 1997; Kagan, Reznick, & Snidman, 1988; Kagan & Snidman, 1991a). The mean ($\pm SD$) Positive and Negative Reactivity ratings on the IBQ were 4.53 ($\pm.74$) and 2.94 ($\pm.58$), respectively. These averages for Positive and Negative Reactivity are comparable to those found in other studies (Davis et al., 2007; Hane & Fox, 2006). There were no significant relations between infants' classification on the Harvard Protocol and maternal report of Positive or Negative Reactivity on the IBQ (all $ps > .05$).

Descriptive Data on Maternal Prenatal Factors by Infant Group

Descriptive statistics (mean, *SD*, and ranges) for maternal cortisol and mood variables for each reactivity group based on the Harvard Protocol (Low, Intermediate, High) are provided in Table 3. Maternal cortisol was significantly higher for infants in the High Reactivity group compared to the Low Reactivity group (see

Table 2. Prenatal Cortisol and Maternal Self-Reported Distress Correlations[a]

	Cortisol Change (Recovery– Acclimate)	Prenatal State Anxiety (STAI)	Postnatal State Anxiety (STAI)	Prenatal Depression (CES-D)	Postnatal Depression (CES-D)	Prenatal Perceived Stress (PSS)	Postnatal Perceived Stress (PSS)
Prenatal Cortisol (Acclimate)	$-.31$**	.04	$-.03$	.13	.12	.12	.11
Cortisol change (Recovery–Acclimate)		.05	.14	.11	.11	.20	.09
Prenatal State Anxiety (STAI)			.57**	.45**	.33**	.48**	.47**
Postnatal State Anxiety (STAI)				.32**	.52**	.51**	.52**
Prenatal Depression (CES-D)					.49**	.65**	.50**
Postnatal Depression (CES-D)						.40**	.73**
Prenatal Perceived Stress (PSS)							.55**

[a]The value is expressed as *r*, where *r* is Spearman correlation.
**$p < .01$.

Table 3.   Maternal Cortisol and Distress Variables by Infant Groups on the Harvard Protocol[a]

Variable	Low Reactive ($n = 49$)	Intermediate ($n = 29$)	High Reactive ($n = 25$)
Prenatal cortisol (Acclimate)[b]	$3.14 \pm .95$*	$3.09 \pm .83$*	3.78 ± 1.51
Cortisol reactivity (Recovery–Acclimate)	$.21 \pm 1.06$	$.31 \pm 1.03$	$-.19 \pm .50$
Prenatal mood	$-.06 \pm .81$	$.16 \pm .88$	$-.03 \pm .89$
Postnatal mood	$-.10 \pm .77$	$.32 \pm 1.02$	$.00 \pm 1.05$

[a]All values are expressed as $\bar{x} \pm SD$.
[b]The unit for cortisol measure is μg/dl.
*Group mean is significantly different from the mean of High Reactive group with *p*-value $< .05$.

Fig. 1, $F_{1,85} = 4.93$, $p < .05$). In contrast, there were no significant differences between these groups of infants in the maternal prenatal and postnatal mood variables.

Regression Analyses: Relation of Prenatal Cortisol and Distress Variables to Infant Outcomes

Proportional odds logistic regression was used to assess the relation of prenatal cortisol and the distress variables to infant reactivity ratings on the Harvard Protocol with adjustment for covariates. We tested the proportional odds assumption, and no violation of this assumption was found. The results are shown in Table 4. Prenatal cortisol and maternal age were significantly related to infant reactivity ratings. The odds of being classified as High Reactive were 1.60 times greater [95% CI: 1.04, 2.46] for every 1-unit increase in prenatal cortisol. The odds of being classified as High Reactive were .90 times lower [95% CI: .82, .99] for every 1-year increase in maternal age. Neither prenatal nor

FIGURE 1 Mean and standard error of maternal prenatal cortisol across the laboratory session by 4-month-old infant High or Low Reactive Behavior based on the Harvard Protocol. **$p < .01$ based on ANOVA test.

postnatal mood was significantly associated with infant reactivity ratings.
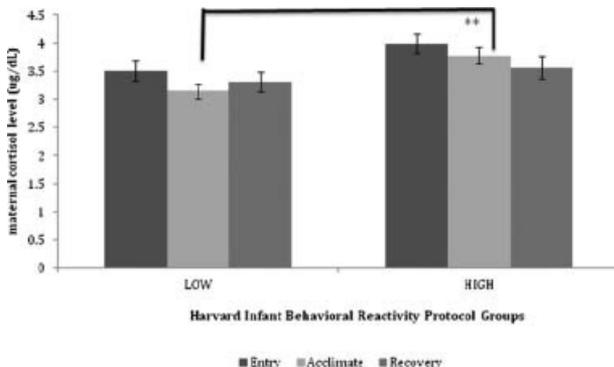
When cortisol reactivity (Recovery–Acclimate) was added to the model, replacing the Acclimate sample, there was only a marginal relation with infant group ($p = .09$) and maternal age remained the only significant predictor of infant behavior.

The relations of prenatal and postnatal predictors to maternal report on the IBQ with adjustment for covariates were tested by multiple linear regression models. No significant associations between cortisol and infant behavior described by maternal report, or between maternal prenatal distress and infant behavior, according to results on the IBQ, were observed (see Tab. 4). Postnatal distress was significantly associated with infant Negative Reactivity, but not with Positive Reactivity. Based on the model, 1-unit increase in maternal postnatal distress was related to a .24-unit increase in mother-rated infant Negative Reactivity ($p = .03$).

Replacing the Acclimate cortisol sample with cortisol reactivity in the model examining Negative Reactivity produced very similar findings. Maternal postnatal distress remained a significant predictor of infant Negative Reactivity, while no significant effect of cortisol reactivity was found. There were no significant results for the infant Positive Reactivity model.

Post Hoc Exploration of Maternal Age

To explore the role of maternal age in infant behavioral outcomes, we considered its association with other variables: older age was associated with lower cortisol levels, higher incomes, as well as less distress prepartum and postpartum (all $ps < .05$).

DISCUSSION

In this longitudinal study spanning pregnancy to early infancy, higher maternal cortisol in the third trimester was associated with observer ratings of infants'

Table 4.   Regression Models Testing the Effects of Prenatal Cortisol, Prenatal Mood, and Postnatal Mood on Infant Behavior

	Infant Reactivity Ratings[a] (Harvard Protocol)			Negative Reactivity[b] (IBQ)			Positive Reactivity[b] (IBQ)		
	Odds Ratio	95% CI	*p*-Value	β	95% CI	*p*-Value	β	95% CI	*p*-Value
Prenatal Cortisol (Acclimate)	1.60	(1.04, 2.46)	**.03**[*]	.09	(−.03, .20)	.15	−.03	(−.18, .13)	.72
Prenatal mood[c]	.72	(.34, 1.50)	.38	.00	(−023, .23)	.99	−.14	(−.44, .16)	.35
Postnatal mood[c]	.96	(.49, 1.88)	.91	.24	(.03, .44)	**.03**[*]	.24	(−.04, .51)	.09
Infant sex[d]	1.45	(.60, 3.50)	.41	.03	(−.22, .28)	.80	−.25	(−.58, .07)	.13
Family income[e]	1.13	(.39, 3.27)	.82	−.14	(−.45, .16)	.35	−.32	(−.72, .07)	.10
Parity[f]	.47	(.18, 1.22)	.12	−.07	(−.34, .19)	.58	−.04	(−.38, .31)	.83
Maternal age	.90	(.82, .99)	**.03**[*]	.01	(−.02, .03)	.51	−.01	(−.04, .02)	.52

[a]Analysis by proportional odds logistic regression model adjusted for covariates listed in the table: infant sex, family income, parity, and maternal age.

[b]Analysis by multiple linear regression models adjusted for covariates listed in the table.

[c]Prenatal and postnatal mood scores were the average of standardized STAI, CES-D, and PSS scores measured at prenatal and postnatal time points, respectively.

[d]Male infant was the reference group in all models.

[e]Family income is 1 if it is >$26,000 and 0 otherwise. Odd ratio indicates the odds of 0 versus 1.

[f]Parity is 1 if the woman had no child and 0 otherwise. Odd ratio indicates the odds of 0 versus 1.

[*]$p < .05$; significant results appear in bold.

increased motor and cry behavior to novelty at 4 months old. These results extend those of most prior studies in showing a relation between prenatal maternal HPA-axis activity and infant development by (1) basing results on a standardized protocol and observer-rated coding system in contrast to mothers' perceptions of their children and, (2), assessing infants closer to birth to decrease the influence of postnatal experiences not included in the study's analyses. However, other results do not support the conceptual model that maternal prenatal distress-activated HPA axis activity influences infant development. There were no associations between maternal distress and cortisol or maternal distress and either objectively observed or mother-reported infant behavior. However, maternal postnatal distress was positively associated with mother-rated infant negative behavior.

Our results extend those of other groups (Davis et al., 2007) in showing a relation between maternal prenatal cortisol level and infant reactivity. In her study, higher cortisol at 30–32 weeks gestation was associated with maternal reports of greater distress to novelty at 2 months, as judged by maternal report. Here, we show a similar association based on maternal cortisol level at 36–38 weeks gestation and trained observer ratings of infant cry and motor responses to a standardized protocol of novel stimuli (the Harvard Infant Behavioral Reactivity Protocol). In a sample of 17 infants (which did not include maternal distress in the design) late-term

maternal cortisol levels predicted observer-rated infant behavior; research has shown that women with higher versus lower late third trimester cortisol (based on a median split) had infants who cried, fussed, and made more negative expressions during at-home video tapings of bath time throughout the first 5 months of life (de Weerth, van Hees, & Buitelaar, 2003). Taken together, these results suggest a relation, albeit modest, between pregnant women's cortisol levels and infant neurobehavioral development. These findings are significant because they show a potentially modifiable factor (maternal HPA axis activity) influencing an aspect of infant temperament (reactivity), and because this characteristic of child neurobehavioral development, greater reactivity assessed by the Harvard Protocol, is a risk factor for future anxiety disorders in childhood and adolescence (Biederman et al., 1993, 2001; Hirshfeld et al., 1992; Schwartz et al., 1999).

There are several hypothesized mechanisms by which variation in pregnant women's HPA-axis activity may impact infant neurobehavioral development, particularly with respect to amplified fear responses and/or anxiety ("context fear"; Davis, 2006). As cortisol passes the blood brain barrier (Zarrow, Philpott, & Denenberg, 1970), exposure to elevated maternal GCs could directly influence fetal brain development, in particular in limbic regions such as the amygdala, a structure centrally involved in the expression of fear and anxiety. Animal studies show that prenatal GC

exposure increases corticotropin releasing hormone (CRH) levels in the central nucleus of the amygdala and that GC exposure stimulates CRH mRNA expression in the amygdala. Intra-amygdala administration of CRH is anxiogenic (summarized in Seckl, 2004). Prenatal stress leads to increased CRH in the offspring's amygdala, similar to GC exposure, and a CRH antagonist can diminish fear behavior associated with prenatal stress exposure (Ward, Johnson, Salm, & Birkle, 2000). It also is possible that higher maternal cortisol may indicate higher maternal HPA-axis functioning, including CRH (of placental origin), which may act directly on the fetal brain. Alternatively, fetal exposure to excessive CRH may influence the fetal HPA-axis system, including cortisol production and the feed-back regulation of this stress-response system, and, specifically, GC receptor development in the limbic system, with implications for the neurobehavioral regulation of responses to novelty (Maccari et al., 2003; Owen et al., 2005), and neurobiological patterns that may contribute to the development of anxiety disorders.

Following the popular conceptual model suggesting that maternal prenatal distress affects infant behavior via activation of the maternal HPA axis (Charil et al., 2010; Glover et al., 2009; Owen et al., 2005; Sandman et al., 2011), we predicted that pregnant women's self-reported distress would be associated with observer ratings of infants' High Reactive behavior to novelty as well as with maternal reports of more negative temperament. However, the results did not support this prediction. To date, many of the studies on the relation between pregnant women's self-reported distress and infant functioning have yielded inconsistent results. For example, Davis et al. (2007) found that maternal prenatal depression but not stress and anxiety, predicted Negative Reactivity when including prenatal cortisol and postnatal mood in the model. In another study (Davis et al., 2004), both maternal depression and anxiety were significant predictors of infant reactivity. Conversely, another study (DiPietro, Novak, Costigan, Atella, & Reusing, 2006) showed that prenatal distress was associated with positive effects in infant development (i.e., advanced motor and mental development).

These inconsistent findings may be, in part, a result of the variability in the methods used to assess maternal and infant functioning. In a prior study, we found that pregnant women with diagnosed depression and/or anxiety (as judged by an observer using a structured clinical interview) are more likely to have 4-month-old infants who cry in response to novelty (based on the Harvard Protocol, Werner et al., 2007). Observer-based ratings of women's psychological functioning may lead to a more valid measurement and/or set a higher threshold for affect dysregulation, both of which may improve the reliability of the prenatal maternal mood assessment.

In addition, as previously indicated, other reports showing a significant association between maternal report of prenatal distress and infant behavior use maternal reports for her self-assessment of prenatal distress as well as for infant neurobehavioral activity (Davis et al., 2007; Davis & Sandman, 2012; Gutteling et al., 2005), that is, for both the independent and dependent variables. Although some researchers argue that parents are the best source of description of their children (Rettew & McKee, 2005), others have questioned whether maternal reports of infant temperament are sufficiently unbiased, or instead, reflective of, and thus highly correlated with, maternal distress, which often is maintained from the pregnancy to the postnatal period (DiPietro, Hodgson, Costigan, & Johnson, 1996; Pesonen, Raikkonen, Strandberg, & Jarvenpaa, 2005; Zeanah, Keener, Stewart, & Anders, 1985). Importantly, we found no relation between observer-based and maternal ratings of the infant, yet a positive association between maternal postpartum distress and maternal assessment of infant negative behavior, both of which suggest a potential for women's psychological functioning to be influencing their perceptions of their children. Basing studies on observer ratings of *both* maternal distress and infant behavior would provide a more rigorous test of the role of prenatal maternal distress in infant neurobehavioral outcomes.

Our results also contradict the prenatal distress-HPA-axis activation hypothesis with respect to the data on distress and cortisol: there were no associations between pregnant women's distress and their cortisol level, a finding similar to that in other reports (Davis et al., 2007; Davis & Sandman, 2010; Kivlighan, DiPietro, Costigan, & Laudenslager, 2008; Petraglia et al., 2001; Davis & Sandman, 2010). Two of the few papers that have found an association used a specific standard for psychological distress—that which meets criteria for psychopathology (Brand, Engel, Canfield, & Yehuda, 2006; Evans, Myers, & Monk, 2008). Possibly, during pregnancy, the association between psychological functioning and cortisol is more reliably detected when the level of distress is more significant and the HPA-axis is thus equally altered. Other methods, such as collecting cortisol samples throughout pregnancy, and at multiple time points within a 24-hr period, also are likely to provide more valid and reliable data, which can help determine the role of women's mood-based variation in cortisol and infant development.

There was an association between older maternal age and decreased likelihood for infant High Reactive behavior. One study on maternal prenatal factors on

infant outcomes also found an inverse association between maternal age and negative/more reactive infant behavior (Gutteling et al., 2005; Orlebeke, Knol, Boomsma, & Verhulst, 1998); other studies of maternal prenatal factors and infant outcomes note that maternal age was reported, but do not specify whether it was examined as a covariate in analyses (Davis et al., 2007; Davis & Sandman, 2010; Huizink et al., 2003). There are data suggesting that older parental age is associated with greater satisfaction with parenting, more optimal parent–infant interaction, and less problem behavior in infants (Orlebeke et al., 1998; Ragozin et al., 1982). As shown in our post hoc analyses, older maternal age was associated with higher income, less distress, and lower cortisol, indicating that it likely represents several aspects of the infant's environment that can influence parenting, parenting resources, and child behavioral development.

To adequately control for postnatal factors, maternal age, as well as other parenting factors with which it may be associated, should be considered in research on the maternal prenatal influences on infant development. Three studies, one from our laboratory (Kaplan, Evans, & Monk, 2007), have shown that care giving quality can modify the influence of maternal prenatal cortisol (Bergman et al., 2010) and psychiatric symptoms (Grant et al., 2009; Kaplan et al., 2007) on infant neurobehavioral development. That maternal age was strongly related to observer ratings of infant reactivity to novelty, yet is only inconsistently considered in other reports on maternal prenatal factors and infant outcomes, underscores the challenges of fetal origins research: How to adequately consider additional variables that impact child development, directly or indirectly, without overshadowing the prenatal influence of maternal factors, given that the reported effect sizes for the prenatal factors range from 3% to 22% of the variance (Talge et al., 2007)?

This study has limitations related specifically to the cortisol protocol. First, maternal cortisol was collected only once in the third trimester. Recent studies based on maternal cortisol collection throughout pregnancy have shown that assays from the first trimester may be most strongly predictive of infant neurobehavioral development (e.g., Davis et al., 2011). However, our aim was not to determine the timing of the potential maternal cortisol influence on infant development, but simply to detect an association between prenatal maternal cortisol level and an objective measure of infant behavior. Although the daily timing of cortisol collection was tightly controlled, multiple cortisol assays would have improved reliability and validity of this variable, and the robustness of the study's results. In addition, because there was significant attrition in our sample, and

those who did not return for the follow-up session at 4 months had higher levels of prenatal distress and cortisol, our results may not generalize to women who are experiencing greater psychobiological affect dysregulation during pregnancy. It seems the more distressed women were, the harder it was for us to keep them engaged in our study. Alternatively, it is possible that inclusion of these participants might have strengthened our findings.

To summarize, the data here show that maternal GCs, specifically higher maternal cortisol in the third trimester of pregnancy, are associated with increased likelihood of showing fret or cry behavior and motor activity in response to stimuli (High Reactive) at 4 months of age, a finding that is in line with results of rodent and primate studies of prenatal stress exposure (Weinstock, 2005). This report extends results of other studies by demonstrating this association based on observer, versus maternal, ratings of infant behavior. Whether maternal prenatal cortisol is a strong enough signal to be detected in multivariate, ecologically valid, methodologically rigorous studies of prenatal and postnatal factors influencing fetal-infant behavioral development is a key area for future research.

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