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Postnatal maternal cortisol levels predict temperament in healthy breastfed infants

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Abstract

Background: The implications of the biologically active elements in breast milk for the breastfed infant are largely unknown. Animal models suggest that ingestion of glucocorticoids during the neonatal period influences fear behavior and modifies brain development.

Aims: To determine the association between postnatal maternal cortisol levels and temperament in breastfed infants.

Study design: The relation between maternal cortisol and infant temperament was examined in breastfed and formula-fed infants. Plasma cortisol was used as a surrogate measure for breast milk cortisol levels (plasma and milk levels are correlated in the 0.6 to 0.7 range; [Patacchioli FR, Cigliana G, Cilumbriello A, Perrone G, Capri O, Alemà GS, et al. Maternal plasma and milk free cortisol during the first 3 days of breast-feeding following spontaneous delivery or elective cesarean section. *Gynecologic and Obstetric Investigations* 1992;34:159-163.]). If exposure to elevated cortisol levels during infancy influences temperament, then a relation between the two should be found among the breastfed infants, but not among the formula-fed infants.

Subjects: Two hundred fifty-three two-month-old infants and their mothers.

Outcome measures: Fearful temperament assessed with the Infant Behavior Questionnaire [Garstein MR, Rothbart MK. Studying infant temperament via the revised infant behavior questionnaire. *Infant Behavior and Development* 2003;26:64-86].

Results: Among the breastfed infants, higher maternal cortisol levels were associated with reports of increased infant fear behavior (partial $r=0.2$; $p<0.01$). This relation did not exist among the formula-fed infants. Negative maternal affect at the time of assessment did not account for the positive association in the breastfed group.

Conclusions: The findings are consistent with our proposal that exposure to cortisol in breast milk influences infant temperament. Biologically active components in breast milk may represent one avenue through which the mother shapes the development of the human infant during the postnatal period.

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1. Introduction

During the prenatal period, the large majority of environmental information the fetus receives is conveyed through biological signals from the maternal environment. In the early postnatal period, the infant is more capable of gathering information on its own, but input from the mother continues to play a critical role in determining its developmental trajectory [3–9]. One avenue through which the mother may exert biological influences on infant development during the postnatal period is through breast milk. For example, it is recognized that breast milk provides nutrition and immune protection for the infant [10]. It is somewhat less well recognized that the components of breast milk also may serve as a means of biochemical communication between mother and offspring [11–13]. Breast milk contains a wide variety of biologically active hormones – including glucocorticoids (GCs; [14,15]), hormones thought to be critical influences on development [16,17].

GCs are stress-sensitive steroid hormones that comprise the endpoint of the hypothalamic–pituitary–adrenal axis. GCs play an essential role in the normal development of the central nervous system [17]. They easily pass the blood brain barrier [18] and the limbic regions, such as the amygdala, involved in the regulation of fear, anxiety and behavioral inhibition, are particularly sensitive to their effects [19,20]. Animals exposed to increased levels of GCs early in life display increased fear and greater behavioral inhibition in the face of novelty [21–24].

A series of studies utilizing a rat model have demonstrated quite convincingly that GCs delivered via milk have lasting influences on the brain and behavior of the exposed offspring. Corticosterone (the primary GC in rodents) levels in milk were manipulated by adding the hormone to the drinking water of dams, which initiated a series of critical

events. First, it produced increased levels of corticosterone in the milk and plasma of the treated mothers – levels similar to what would be expected under conditions of mild stress [25]. Second, the labeled corticosterone was found both in the plasma and brain of the pups nursed by the exposed dams [25]. Importantly, the administration of the corticosterone to the dams did not appear to influence maternal behavior [26]. The investigators then determined the short and long-term effects of GC exposure through milk. The adrenal weights of the offspring were slightly but only temporarily reduced (by 30 days there were no differences between the groups; [26,27]). There were reduced physiological (corticosterone) and behavioral (fear) stress responses present at 15 months of age in the GC-exposed group [26–29]. In addition, learning and memory were improved in the animals exposed as infants to GCs and these effects were detectable from weaning through adulthood [26–28]. Last, the animals nursed by the exposed mothers displayed higher numbers of hippocampal GC receptors at both 30 days and at maturity [28,29].

To our knowledge, only one study has considered the relation between GC levels in breast milk and human infant development. Hart et al. [30] examined this relationship in seven to eleven-day-old breastfed infants. The Neonatal Behavioral Assessment Scale was used to assess newborn neuro-behavioral functioning. Infants ingesting higher levels of cortisol (the primary GC in humans) in breast milk scored higher on the Autonomic Stability cluster of the exam, suggesting that cortisol in breast milk was positively associated with the infants ability to regulate their autonomic state and control involuntary responses such as tremors.

The purpose of the present study was to evaluate whether it is plausible that postnatal exposure to GCs in human breast milk influences fearful temperament in infants. As noted

Figure 1 Relation between maternal cortisol and infant fear behavior in breastfed infants ($n=181$).

above, the limbic regions of the brain which are involved in the regulation of fear, anxiety and behavioral inhibition, represent a primary target for GC exposure [19,20]. If GC exposure via breast milk influences fearful temperament, then we expect to find a relation between maternal cortisol and fearful temperament among breastfed infants, but not among formula-fed infants.

2. Methods

2.1. Participants

Two-hundred fifty-three mother and infant pairs who had been enrolled in a larger longitudinal study of pregnancy at the University of California, Irvine and Cedars-Sinai Medical Center, Los Angeles, participated when the infants were two-months-old (mean=8.03 weeks; sd=2.17). The study procedures were approved by the Institutional Review Boards of the participating institutions and all participants provided written informed consent. The initial prenatal enrollment criteria for the longitudinal study were: a) Over 18 years of age b) Singleton intrauterine pregnancy c) English speaking d) Absence of any condition which could affect neuroendocrine function such as endocrine, hepatic or renal disorder or the use of corticosteroid medications, e) Normal uterus and cervix and f) No nicotine, alcohol or drug use. Further, for the current study, those infants who had been admitted to the Neonatal Intensive Care Unit following delivery and those whose mothers were taking corticosteroid medications during the postpartum period were excluded. Of this final sample, 72% of the infants were being breastfed and 28% were formula-fed. Characteristics of the two groups are presented in Table 1.

2.2. Infant temperament

Infant temperament was assessed with an 8-item version of the fear subscale of the Infant Behavior Questionnaire, a widely used parent-report measure of infant temperament [2]. The fear scale assesses the extent to which infants display startle or distress in response to novel or surprising stimuli. Items include questions such as "How often during the past week did the baby startle to a loud sound or sudden noise?". Answers are given on a four-point Likert scale with the endpoints "never" to "always". The Infant Behavior Questionnaire has strong psychometric properties with a Cronbach Alpha coefficient in the current sample of 0.90. Scores on the fear subscale are stable from 2 months to 1 year [31]. Furthermore, the correlation between ratings by the primary and secondary caregiver is 0.75 [2] and maternal report of fearful temperament is correlated with observational measures of infant fear in the laboratory [32,33].

2.3. Plasma cortisol

During the afternoon (mean draw time=14:01, sd=1:38) blood samples (20 ml/draw) were obtained by antecubital venipuncture in EDTA (purple top) vacutainers and chilled on ice immediately. The time of day for the blood draw was constrained to control for the diurnal variation in cortisol. Further, an afternoon draw time was selected (as opposed to

Table 1 Sample characteristics

	Breastfed (n=181)	Formula-fed (n=72)	t or χ^2
Ethnicity			10.5 *
Hispanic White	16%	25%	
Non-Hispanic White	56%	37%	
African-American	10%	17%	
Asian	13%	11%	
Other	5%	10%	
Maternal age (years)	31.9 (5.1)	28.6 (5.5)	4.3 *
Education (%>HS degree)	93%	72%	19.2 *
Annual household income	\$70,099 (31,427)	\$50,522 (29,690)	4.4 *
Marital status (% married)	80%	63%	8.2 *
Employment (% currently working)	16%	18%	0.2
Sex of infant (% male)	54%	51%	0.2
Birth order (% first born)	59%	56%	0.2
5-minute Apgar score	8.98 (0.22)	8.99 (0.21)	0.8
Birth weight (grams)	3503 (519)	3420 (535)	1.1
Gestational age at birth (weeks)	39.2 (1.46)	39.0 (1.40)	0.9
Infant age at assessment (weeks)	8.2 (2.2)	7.7 (2.1)	1.5
Maternal cortisol ($\mu\text{g/dl}$)	6.2 (3.43)	6.4 (4.82)	0.23
Fearful temperament ^a	2.1 (0.50)	2.1 (0.51)	0.1

Standard deviations presented in parenthesis when appropriate.

^a Fearful temperament was assessed with the fear subscale of the Infant Behavior Questionnaire [2]. This four-point Likert scale assesses the extent to which infants display startle or distress in response to novel or surprising stimuli.

* $p < 0.05$.

morning) because cortisol levels are more stable at this time of day being less subject to the influences of the time of awakening [34,35]. Samples were centrifuged at 2000 $\times$ g (15 min) and the plasma was decanted into polypropylene tubes containing 500 KIU/ml aprotinin (Sigma Chemical Co.; St. Louis, MO) and stored at -70°C until assayed.

Plasma cortisol levels were determined by a competitive antibody-coated tube radioimmunoassay (RIA; American Laboratory Products Company, Windham, NH). Plasma samples (25 μl) and ^{125}I -labeled cortisol (500 μl) were added to the antibody-coated tubes and incubated for 45 min in a 37°C water bath. The aspirated antibody-bound ^{125}I -radiolabeled tubes were quantified with the gamma counter. The assay has <5% cross-reactivity with 11-deoxycortisol, cortisone, prednisone, and <1% cross-reactivity with eight other naturally occurring steroids. The inter- and intra-assay CVs are less than 12% with a minimum detectable level (95% confidence) of 0.22 $\mu\text{g/dL}$.

Plasma cortisol was used as a surrogate measure for cortisol exposure in breast milk. The relation between circulating cortisol and cortisol in breast milk has been shown to be in the 0.6 to 0.7 range in women on postpartum

day 3 [1]. Although there is no published study in humans demonstrating the strength of the correlation between circulating and breast milk cortisol at any later point during the postnatal period, we believe it is likely that this relation exists beyond 3-days postpartum for the following reasons: 1) Cortisol in breast milk is of adrenal origin. There is no evidence to suggest mammary synthesis [14]. 2) Cortisol in breast milk is present and the levels are similar from 1 to 12 months postpartum [36,37]. 3) The well-documented diurnal variation in plasma cortisol is present in breast milk cortisol from the first through sixth postnatal months [36]. 4) Manipulations of plasma cortisol levels such as administration of dexamethasone, which suppresses plasma cortisol, is associated with a reduction in breast milk cortisol and has been demonstrated across the first 6 months postpartum [36]. 5) Manipulations that result in increases in circulating GCs produce concomitant changes in milk GC levels in non-human animals at various stages of lactation [25,38,39].

2.4. Additional measures

Maternal reports of ethnicity, income, educational level, marital and employment status also were collected. Information about the infants' peri- and neonatal health and Apgar scores was abstracted from the infant's medical record.

At the time of the cortisol collection, the mothers also completed Cohen's Perceived Stress Scale [40], Spielberger's State Anxiety Scale [41,42] and the Center for Epidemiological Studies Depression Scale [43]. These measures of postnatal maternal affect were included to help rule out the possibility that any association seen between cortisol and infant temperament was due to bias related to maternal dysphoria [44]. That is, to assess possibility that mothers who report more anxiety, stress or depression also report more fear behavior in their infants, and that this link might explain any relation between maternal cortisol and infant temperament.

2.5. Data reduction and analysis

The primary outcome variable under examination in the larger longitudinal study from which the current study sample was drawn was preterm birth, not infant temperament. As such, no a priori sample size calculations were conducted for the detection of the associations between maternal cortisol and infant temperament. Data reduction for the RIA assay was accomplished with a computer assisted, four-parameter logistics program [45]. Group differences (breastfed vs. formula-fed) in demographic and infant characteristics first were assessed. The continuous variables were assessed with *t*-tests and for categorical variables chi-squares were employed. The relation between maternal cortisol levels and infant temperament then were assessed within each group with partial correlations adjusting for infant age at time of assessment. Because of the discrepant sample sizes in two study groups, the differences between correlation coefficients were then tested with the null hypothesis test as recommended by Cohen, et al. [46]. Last, a hierarchical regression analysis was used to assess whether maternal cortisol levels predicted variance above and beyond reports of maternal postpartum affect (depression,

anxiety and perceived stress). In this regression model maternal affect, age of infant at assessment and any maternal demographic characteristics such as race/ethnicity, maternal age or parity, that showed a relation at a significance level of less than 0.1 with infant fear were entered first and then maternal cortisol levels were entered second.

3. Results

3.1. Demographic and infant variables among breastfeeding and non-breastfeeding groups

Not surprisingly, the women who were breastfeeding differed from those who were not in that they were more likely to be non-Hispanic White and married, older, more educated and had higher incomes (See Table 1). These relations between breastfeeding status and sociodemographic factors are consistent with those documented previously [47,48].

The two groups did not differ with respect to the infant variables: birth weight, gestational age at birth, 5-minute Apgar scores, birth order, ratio of males to females, or age of infant at assessment (See Table 1). Also, the groups did not differ either in the main predictor variable or in the dependent variable (See Table 1). The groups were similar in mean maternal cortisol levels and in the distributions of cortisol levels (Levene's test for equality of variances, $F=1.12$, $p=0.29$). Further, these cortisol levels were similar to those of women from other cohorts who were assessed at 6–12 weeks postpartum [49,50]. Ratings of infant fear did not differ between the two groups and the means were consistent with ratings of fear in infants during the first year of life from other studies using this scale [2,31,51].

Three of the maternal variables listed in Table 1 reached the criterion ($p<0.1$) for entry as covariates in subsequent hierarchical regression analyses because of their association with infant fear: employment status ($t=2.5$; $p<0.05$), maternal age ($r=0.11$; $p=0.09$) and parity ($t=-1.7$; $p=0.09$). Maternal education, ethnicity, income and marital status did not reach criteria for inclusion (all $p>0.22$). In addition, because ratings of infant temperament depend in part on the age of the infant [2] and were modestly associated with temperament ratings in the current sample ($r=-0.13$; $p<0.05$), in all analyses, infant age was entered as a covariate. Ratings of infant temperament were not related to sex of the infant ($t=0.56$; $p=0.57$).

3.2. Maternal cortisol and infant temperament

Among women who were breastfeeding, there was a positive association between maternal cortisol levels and reports of infant fearfulness (partial correlation; $r=0.20$; $p<0.01$). Those mothers with higher levels of plasma cortisol and thus, higher levels in their breast milk, had infants who were exhibiting increased fearful behavior (see Fig. 1). In contrast, among those who were feeding formula, the association between maternal cortisol and temperament was not apparent (partial correlation; $r=-0.04$; $p=0.67$).

Because the sample sizes of the two groups were discrepant and thus might account for the different associations between cortisol and temperament, we used the null hypothesis test for the difference between two correlations

Table 2 Hierarchical regression model examining whether maternal cortisol levels account for unique variance in infant fear beyond postnatal maternal affect among breastfed infants ($n=181$)

	R^2	ΔR^2	β	Partial r
Model 1	0.09 *			
Infant age			-0.07	-0.07
Parity (birth order)			0.12	0.13
Maternal age			-0.06	-0.06
Employment status			-0.08	-0.08
Perceived stress			0.04	0.03
State anxiety			0.20	0.14
Depression			0.01	0.01
Model 2	0.13 *	0.04 *		
Infant age			-0.11	-0.10
Parity (birth order)			0.15	0.16
Maternal age			-0.08	-0.09
Employment status			-0.06	-0.06
Perceived stress			0.02	0.01
State anxiety			0.20	0.14
Depression			0.03	0.02
Maternal cortisol			0.21 **	0.21 **

Note: Parity coded 0=primiparous and 1=multiparous. Employment status coded 0=not employed outside the home or on leave from work and 1=working outside the home.

* $p<0.05$.

** $p<0.01$.

and confirmed that they were in fact statistically significantly different ($z=1.74$; $p<0.5$).

3.3. Potential confounding of negative maternal affect

A statistically reliable relation has been reported between maternal affect and maternal reports of infant temperament [52–54]. It also has been shown that psychological states are related to parenting behaviors [52–58] and cortisol levels [59,60]. Thus, it is conceivable that our findings could be spurious (although the fact that the relation was not found among non-breastfeeding pairs already argues strongly against this possibility). In order to address this, a hierarchical regression analysis was conducted in which the measures perceived stress, state anxiety and depression were entered first and then maternal cortisol. Even when maternal affect and maternal demographic characteristics predictive of infant fear, were taken into account statistically, the relation between cortisol and infant fear remained statistically significant with a similar effect size (See Table 2).

4. Discussion

Based on our data, it seems plausible that GC levels in breast milk influence fearful temperament in infants. Specifically, our data suggest that higher levels of postnatal maternal cortisol are associated with reports of increased fearful behavior among breastfed infants. Of course, this study did not directly assess cortisol levels in breast milk – instead, plasma cortisol levels were used as a marker of breast milk

levels. We believe the findings support our proposal that exposure to cortisol in breast milk influences human infant development for the following reasons: 1) the relation between plasma cortisol levels and breast milk levels is fairly high [1] 2) the relation between fear and cortisol only was found to exist among those infants who were breastfed and not among those who were not and 3) adjusting statistically for maternal demographic characteristics, perceived stress, state anxiety and depression did not alter the relation found between cortisol and temperament among the breastfeeding women. Our study was limited by the fact that we relied on maternal reports of infant temperament which are potentially subject to bias [44,61] and by the fact that we did not have measures of mother–infant interaction and so could not evaluate this as a possible contributor to our effects.

Our findings are consistent with the expanding literature documenting lasting influences of prenatal exposure to GCs on emotion regulation. Animal models demonstrate that prenatal exposure to GCs is associated with increased fear and anxiety behavior in offspring [21,22]. Similarly, human fetuses exposed to higher levels of maternal cortisol late in pregnancy have been shown to exhibit more fussing, crying and negative facial expressions as infants [62] and those exposed to synthetic GCs exhibit increased shyness and emotionality during the first 5 years of life [23] and increased aggressive behavior at 6 years of age [63].

In the rodent models, exposure to heightened levels of GCs ingested in milk is associated with decreased fear behavior, whereas we found the opposite patterns in humans [26–28]. It is impossible to determine from the present study whether these differences are due simply to interspecies differences, to differences in timing of exposure (the early post-partum period in rats is more similar to the late prenatal period in humans than to the postnatal period; [64]), to timing of measurement of outcomes, to the degree of GC exposure (the rodent models employed experimental manipulations of GCs while our study examined naturally occurring levels) or to some other factor.

The importance of very early experience in shaping health and behavior across the lifespan has become increasingly well documented [65,66]. It appears that breast milk may provide one additional avenue through which the mother may influence the development of her offspring. The biochemical messages that characterize maternal–fetal communication during the prenatal period may extend into the postnatal period through messages contained in breast milk.

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