The Association of Major Depression, Conduct Disorder, and Maternal Overcontrol with a Failure to Show a Cortisol Buffered Response in 4-Month-Old Infants of Teenage Mothers

Rima Azar, Daniel Paquette, Mark Zoccolillo, Franziska Baltzer, and Richard E. Tremblay

Background: Adolescent pregnancy can be associated with major depression (MD) and conduct disorder (CD). Some infants of adolescent mothers are prenatally exposed to these factors, which may result in heightened risk for perturbations of their stress systems. Between 2 and 4 months, a normal shift occurs in the adrenocortical system in which we observe a marked decrease in infant cortisol response when facing mild stressors. This study aimed to explore whether MD (lifetime, during pregnancy, postpartum), CD, and maternal overcontrol are associated with increased cortisol reactivity in 4-month-old infants of teenage mothers.

Methods: Using arm restraint as a stressor, morning salivary cortisol was taken prestressor and poststressor in 212 infants during a laboratory visit. Major depression and CD were measured with the computerized National Institute of Mental Health Diagnostic Interview Schedule (NIMH-DIS), postpartum depressive mood was measured with the Edinburgh Postnatal Depression Scale, and overcontrol was observed with the CARE-Index.

Results: Independent of the predictors, there was a dampened cortisol response. Infants of mothers with lifetime MD and of average to highly overcontrolling mothers showed increased cortisol reactivity. Conduct disorder and cortisol levels were not associated.

Conclusions: Future studies should detect whether the absence of a dampened cortisol response in infants whose mothers have lifetime MD or display overcontrolling parenting is stable over time.

Key Words: Conduct disorder, infant cortisol, major depression, maternal overcontrol

Adolescent pregnancy can be associated with major depression (MD), conduct disorder (CD), and substance abuse (Cassidy *et al.* 1996; Trad, 1995). Some infants of adolescent mothers are prenatally exposed to these risk factors. This may provide a less than optimal context for their developing stress systems. Some adolescent mothers may also have poor parenting skills like overcontrol. A promising avenue of research in early risk factors is the role of the hypothalamic-pituitary-adrenal (HPA) axis, namely cortisol reactivity. Between the ages of 2 and 4 months, a normal shift occurs in the infant adrenocortical system in which a marked decrease in cortisol response is observed when facing mild stressors (Gunnar *et al.* 1996; Gunnar 1998; Larson *et al.* 1998). Factors associated with a failure to show a cortisol buffered response may be very instructive (Larson *et al.* 1998) in clarifying processes that may endanger this mechanism. This study explored whether maternal psychopathology or overcontrol are associated with increased cortisol reactivity in 4-month-old infants of adolescent mothers.

The absence of a cortisol response is not part of normal maturation, as it is necessary and adaptive to have a physiological stress response. Nevertheless, infants reduce the magnitude of their response to a mild stressor from the exaggerated response typical of newborns. As in animals, the dampening shift in cortisol response is thought to protect the developing brain from the deleterious effects of cortisol (Meyer *et al.* 2001). Although there might be concerns when this shift does not occur, their extent is not clearly known in humans. There is currently no evidence on the threshold by which a cortisol response, when a dampened period is expected, puts the infant at greater risk. Interestingly, animal data shows that animals exposed to conditions that activated their HPA axis during infancy exhibited increased fearfulness, impaired immune system functioning, and heightened vulnerability to stressors in adulthood.

Major depression is the first prenatal factor linked to disturbances of the HPA axis. Almost 42% of adolescent mothers suffer from depressive symptoms during their third trimester of pregnancy (Barnett *et al.* 1996). This is more than double the adult rate of 20% during pregnancy (Burt and Stein 2002). Hypothalamic-pituitary-adrenal axis hormones are clearly dysregulated in adult patients with MD. Almost half of acutely depressed patients exhibit increased HPA activity, as demonstrated by high baseline cortisol levels and nonsuppression of cortisol in the dexamethasone suppression test (DST) (Parker *et al.* 2003). It has been shown that depressed adult patients without early adversity do not show high baseline cortisol levels (Heim *et al.* 2000). Hence, there might be a differential pathophysiology in the HPA axis for depressed adolescent girls. Although depression has not been consistently found to be associated with cortisol in pregnant teens (Susman *et al.* 1999), high reactivity of the HPA axis in pregnant adolescents may be responsible for adverse effects on the fetus' developing HPA axis (Ponirakis *et al.* 1998). Greater

From the University Health Network (UHN), Women's Health Program (RA), University of Toronto, Toronto, Ontario, Canada, and the Department of Psychology (RA), University of Montreal; Department of Psychology (DP), University of Montreal and Research Institute for the Social Development of Youth (RISD)-Montreal Youth Center; the Departments of Psychiatry (MZ) and Pediatrics (FB), McGill University & McGill University Health Centre-Montreal Children's Hospital; and Research Unit on Children's Psychosocial Maladjustment (RET), University of Montreal, Montreal, Quebec, Canada.

Address reprint requests to Rima Azar, Ph.D., University Health Network, Toronto General Hospital, Women's Health Program, 200 Elizabeth Street, EN-7, Room 234A, Toronto, Ontario M5G 2C4, Canada; E-mail: Rima.Azar@uhnres.utoronto.ca.

Received June 2, 2006; revised October 16, 2006; accepted November 9, 2006.

0006-3223/07/$32.00
doi:10.1016/j.biopsych.2006.11.009

maternal cortisol levels may provoke a hypersecretion of the newborn's cortisol (Field *et al.* 1995). The current study is the first to explore the link between MD in teen mothers and infants' cortisol reactivity. Our design allows us to examine three time points of depression: lifetime, during pregnancy, and postpartum. During pregnancy, maternal cortisol levels are normally tripled by the third trimester. The placenta produces a protein, the 11β-hydroxysteroid dehydrogenase (11β-OHSD-2) enzyme, which rapidly converts most of the biologically active cortisol into the inactive cortisone. Major depression during pregnancy may lead to chronically higher levels of already elevated maternal cortisol (Challis *et al.* 2001). If maternal cortisol becomes too high, a decrease in the 11β-OHSD-2 activity may occur, possibly increasing the fetus' exposure to maternal cortisol (Meyer *et al.* 2001).

Another risk factor for adolescent pregnancy is CD, which is characterized by serious aggressive and antisocial behaviors. Research in adult men has shown that antisocial behavior is associated with decreased cortisol levels (Woodman *et al.* 1978). However, the role of cortisol in teen girls with CD is less known. Susman *et al.* (1999) showed no evidence of an association between cortisol levels in pregnant adolescents with CD, whereas Pajer *et al.* (2001) found that girls with CD did have decreased cortisol levels. In a more recent study, Azar *et al.* (2004) found that cortisol levels of adolescent mothers were not associated with CD at 4 and 9 months postpartum. To our knowledge, no study has examined infant cortisol of teen mothers in relation to CD. We speculated that cortisol might be associated with CD through risky behaviors stemming from antisocial behavior in pregnant teens with or at high risk for CD. Examples of risky behaviors include nonadherence to prenatal medical visits (Susman *et al.* 1999), going to bed late, eating nonnutritional foods, or using illicit substances, which may adversely affect the fetus' developing HPA axis. Research regarding the impact of prenatal exposure to cigarette smoking on infant cortisol is underway (Azar *et al*, unpublished data).

Finally, appropriate maternal care is another mechanism that functions to protect the infant from elevations of cortisol (Watamura *et al.* 2003). Parental overcontrol is a pattern of intrusive and overstimulating behavior that can be either covertly (pseudosensitive) or overtly hostile (Crittenden 1998). For instance, covert anger can be "a cajoling sugary voice in the absence of infant responsiveness" (Crittenden 2000, p 9) or "poking the infant's body against his or her will" (Crittenden 2000, p 11). Research has demonstrated a link between maternal sensitive response (i.e., responding to the infant's needs) and infant cortisol regulation in both animals and humans (Bugental *et al.* 2003; Gunnar 1998). In contrast, Spangler *et al.* (1994) found that at 3 and 6 months of age, infants of mothers with a very low degree of sensitivity showed an increased cortisol response in comparison with infants of at least moderately sensitive mothers. In light of the Spangler *et al.* (1994) findings, overcontrol may in itself act as an acute stressor, inducing an infant cortisol response.

This study explored whether maternal depression, CD, or overcontrol are associated with increased salivary cortisol reactivity to the arm restraint procedure in 4-month-old infants of teenage mothers, despite the expected normal dampened response. We expected that arm restraint (although not all stressors) would not produce a cortisol response in the average 4-month-old. We hypothesized that there would be a significant cortisol response only in infants whose mothers: 1) had MD (lifetime, during pregnancy, or postpartum); 2) had CD; or 3) were overcontrolling. To test our hypotheses, we compared infants whose mothers displayed these factors with infants of those who did not. To further understand how maternal factors correlate with infant cortisol reactivity, we also measured mothers' cortisol levels.

Methods and Materials

Participants

The sample was comprised of 214 infants whose mothers participated in a larger 3-year longitudinal study (Paquette and Morrisson 1998) of the development of children of teen mothers. Because they are likely to have received antenatal steroids (Silver *et al.* 1993), two infants born prior to 33 weeks of gestation were excluded. The final sample was 212 infants. Pregnant subjects were recruited from a high school for pregnant teens (64%, n = 137), from foster homes located in Montreal (17%, n = 35), and from the Montreal Children's Hospital (MCH) adolescent obstetric clinic (19%, n = 40). Table 1 describes infants' and mothers' characteristics.

Measures

Cortisol. Salivary cortisol reflects the free portion of cortisol concentrations in the blood and is closely correlated to plasma free cortisol (Klimes-Dougan *et al.* 2001). We collected samples from both infants and mothers to examine the correlation between maternal and child cortisol. Saliva samples were collected at the same time to avoid circadian fluctuation. We systematically recorded milk ingestion, food intake before cortisol sampling, and quality of sleep the night before sampling and recorded when the infant slept at or on the way to the laboratory. Sixteen infants drank milk. We rinsed their mouths thoroughly with water 5 minutes prior to sample collection. Rinsing the mouth with water might influence salivary hormones in minute amounts (Whembolua *et al.* 2006). No infant or mother suffered from acute infection, severe pain, or any chronic condition known to influence cortisol levels. Among mothers who breastfed their infant, none had a lifetime diagnosis of MD or took any

Table 1. Descriptive Data of 4-Month-Old Infants and Their Mothers

Characteristics of the Sample in % and Mean (SD)	
Infants	
Age	4.38 months (±SD = .4)[a]
Sex	
Girls	57% (n = 118)
Boys	44% (n = 94)
Normal and Healthy at Birth	100%
Gestational Age Range (in weeks)	39 (±SD = 1.77)[c]
Birth Weight (in kg)	3.29 (±SD = .50)
Body Mass Index (BMI)[b]	16.35 (±SD = 2.45)
Mothers	
Parity (primiparous)	100%
Age at the Time of the Study (in years)	16.9 (±SD = 1.0)
Education (in years)	8.9 (±SD = 1.4)
Ethnolinguistic Background[d]	64% French-speaking 8% English-speaking 28% other
On Welfare	27%[e]

N = 212. BMI, body mass index; SES, socioeconomic status.

[a]We consider 4 months to be an optimal age for sampling, as it ensures a good temporal proximity between cortisol measurement and the predictors.

[b]BMI was measured at the time of the study.

[c]All infants were born within the normal range (37– 42 weeks), with 200 cases born after 38 weeks of gestation.

[d]The majority of mothers were Canadians.

[e]Most mothers were of low SES.

medication while nursing. Samples were immediately stored for up to 5 months at -18°C until hormone analysis was conducted. Analysis was performed at the Department of Chemistry-Biology of the University of Quebec in Trois-Rivières (UQTR). Salivary cortisol concentrations were determined with a competitive solid-phase radioimmunoassay (RIA) designed for the quantitative measurement of cortisol (hydrocortisone, compound F). Initially applicable for plasma and urine, this design was adapted to saliva by Diagnostic Products Corporation (Los Angeles, California). The cross-reactivity was 4.7%. The intra-assay coefficient of variation of the cortisol assay was 3%. Cortisol RIA was performed twice. The repeated RIAs were highly correlated ($r = .99$, $p < .001$).

Maternal Psychopathology. We used a computerized version of the National Institute of Mental Health Diagnostic Interview Schedule (NIMH-DIS) (DSM-III-R criteria) (CDIS Group, 1991–1992) to diagnose lifetime history of MD and CD. The NIMH-DIS is a fully structured psychiatric interview for ascertaining lifetime, 1 year, 6 months, and current psychiatric diagnoses. It was chosen because: 1) it has been translated into French, the language of most of the mothers of our infant participants; 2) it assesses 12 of the 13 DSM-III-R (and 12 of the 15 DSM-IV) (American Psychiatric Association 1994) CD criterion symptoms as part of the assessment of antisocial personality disorder, which requires a childhood history of CD; and 3) it assesses lifetime, recent, and current episodes of diagnoses. Although an English version keyed to DSM-IV was released years ago, no French version existed at the time of our study. The NIMH-DIS has been used with teen mothers who had no difficulties in answering the questions (Azar *et al.* 2004). Lifetime MD was diagnosed when the mothers reported two or more episodes of major depression, regardless of age of onset. The relative frequency of the criterion symptoms of MD seems to be age-related but DSM-III-R symptom criteria are manifested by both youth and adults (Roberts *et al.* 1994). A diagnosis of CD was assigned when the mothers reported a history of three or more of the CD symptoms from criterion B (childhood history of CD) of the DSM-III-R diagnosis for antisocial personality disorder. Example of CD symptoms were often truant from school, often initiates fights, has used a weapon, has been physically cruel to people or to animals, has stolen with and without confronting a victim, has deliberately destroyed property or set fire, and has been arrested or found guilty of a crime. The DIS-III-R version is keyed toward DSM-III-R diagnoses. To measure postpartum depressive mood, we used the Edinburgh Postnatal Depression Scale (EPDS) (Cox *et al.* 1987). Validated in community samples, the EDPS shows higher sensitivity for detection of postpartum depression than consultations in primary health care (Hearn *et al.* 1998).

Maternal Overcontrol. We videotaped each infant with his or her mother during 5 minutes of unstructured play in our laboratory at the University of Montreal. Ten small toys were set out on a carpet, on which each mother was invited to play with her infant as she usually does at home. Subsequently, the first author and a research assistant (RA) blind to NIMH-DIS diagnoses and both trained by Patricia Crittenden, Ph.D. coded the videotapes using the CARE-Index (Crittenden 1998). This instrument was chosen because it assesses several dimensions (seven subscales) of maternal overcontrol: facial expression, vocal expression, position and body contact, expression of affection, turn taking, control, and choice of activity. In the CARE-Index, the observation of the mother's behavior is made in the context of the infant's behavior and vice versa. For each dimension, mothers can have a control score of 0, 1, or 2, with the most controlling score being 2. The control score ranges from 0 to 14. Interrater reliability ranged from good to excellent; the alpha coefficients varied from .84 to .95. This instrument has a high degree of stability (Crittenden and Bonvillian 1984) and was validated with families from different ethnic backgrounds (Leventhal *et al.* 2004).

Procedure

Mothers gave informed consent at the onset of the study, which was approved by the Institutional Review Board of the Montreal Children's Hospital, by the foster homes, and by the Ethics Committee of the University of Montreal. Mothers received two home visits. The first visit aimed to conduct the NIMH-DIS interviews. The majority of the sample (71%) was visited during the seventh month of pregnancy (the remainder no more than 4 months postpartum). The second visit took place at 4 months postpartum to administer the EPDS (Cox *et al.* 1987). Each mother visited our laboratory with her 4-month-old infant. We collected salivary cortisol twice from infants and mothers. The first cortisol collection took place 5 minutes after their arrival at 10:00 AM and before the arm restraint. The second cortisol collection occurred 20 to 25 minutes after the arm restraint, because the cortisol peak response typically occurs approximately 20 minutes after the stressor (Ramsay and Lewis 2003). We used the arm-restraint procedure (Stifter and Fox 1990) to induce frustration in the infants and activate their HPA axis. During the procedure conducted by a research assistant, mothers were seated behind their infant out of their field of view. Before restraining the infant's arms, the RA explained the procedure to the mother and reassured her that it was harmless. While the RA maintained a neutral facial expression, she gently restrained both of the infant's arms on the armrests of the seat to prevent the child from moving. This position lasted 2 minutes without talking to the infant. If the infant started to cry, he or she was set free after 20 seconds of the first signs of distress. The RA kept a neutral attitude during the ensuing minute, without comforting the infant. If the infant remained distressed for 60 seconds after the end of the procedure, she tried to comfort him or her or asked the mother to do so. A free play session immediately followed the stressor. If positive enough, this experience might contribute to dampening the poststressor elevation. A stressful encounter with the mother might potentially sustain or increase the infant cortisol level.

Statistical Analyses

We used descriptive statistics to examine the distribution of cortisol data and Pearson correlations to examine the association between cortisol samples. We conducted preliminary analyses of variance (ANOVAs) to identify potential confounding variables (milk ingestion, nap in the car on the way to the laboratory, food intake, lack of sleep on the preceding night, birth weight, and body mass index [BMI]). We used a paired t test to examine cortisol response, regardless of the predictors. We tested our hypotheses using repeated measures ANOVAs. Statistical significance was defined as $p < .05$. Tests were two-tailed. Analyses were conducted with SPSS for Windows 10.0 (SPSS Inc., Chicago, Illinois).

Results

Cortisol Descriptive Statistics

Seven out of the 424 samples were extremely high (greater than 3 to 4 standard deviations of mean cortisol). Since there is no standard reference range, we consulted a clinical endocrinologist

and inquired about each extreme value. Although repeated measures ANOVA analysis is relatively insensitive to outliers, outliers were excluded from the sample because they were beyond the clinical physiological range. The distribution of cortisol data was slightly positively skewed. Since repeated measures ANOVA is insensitive to deviation from normality, there was no need to transform these data. The two cortisol samples collected from the infants correlated very highly ($r = .99$, $p < .01$).

Infants' mean cortisol levels closely correlated with mothers' cortisol ($r = .5$, $p < .01$). Infants' mean cortisol was equal to .25 μg/dL (±SD = .17) and mothers' mean cortisol was equal to .33 μg/dL (±SD = .49). Since cortisol levels did not differ by sex, we analyzed cortisol data for both sexes jointly. An ANOVA indicated that milk ingestion and washing the infant's mouth with water did not influence cortisol levels. Cortisol did not differ as a function of birth weight and of BMI. We investigated sex differences as a function of BMI and there were no significant main effects on infants' cortisol levels for either BMI or sex or the BMI and sex interaction.

Correlations Between the Adverse Factors

Depression during pregnancy correlated highly with lifetime history of MD (rho = .65, $p < .01$), an expected finding given that an episode of MD during pregnancy was calculated by subtracting the dates of NIMH-DIS interviews and the delivery to determine if the depressive episode occurred during pregnancy. Lifetime history of MD was low correlated with postpartum depressive mood (rho = .22, $p < .01$) and more moderately associated with CD diagnosis (rho = .25, $p < .01$). Maternal overcontrol did not correlate significantly with MD during pregnancy or any lifetime psychopathology.

Cortisol Response (Δ)

Cortisol response was indexed by the difference between poststressor (T2) and prestressor (T1) salivary cortisol. Consistent with our underlying hypothesis of dampened cortisol response independent of adverse factors, cortisol levels did not change from T1 to T2 [cortisol T1 - cortisol T2 = −.02, paired *t* test (190) = −1.3, ns]. Before testing our hypotheses, we examined whether poststressor cortisol may be influenced by the law of initial value (LIV) (Wilder 1956). Since the change in cortisol values was almost equal to 0 and not statistically significant, LIV correction was not indicated. A Mauchly test indicated that the assumption of sphericity was satisfied. Thus, in testing our hypotheses, we used cortisol concentrations as two levels of a within-subjects factor in repeated measures ANOVAs, which control for the effect of time.

Main Findings

Association of Maternal Depression with Infant Cortisol. Thirty-two percent of infants ($n = 62$) had a mother with lifetime history of MD. A repeated measures ANOVA with infant cortisol levels as the within-subjects factor and NIMH-DIS lifetime history diagnosis (MD, no MD) as the between-subjects factor indicated a significant interaction between infant cortisol and lifetime history of MD diagnosis [$F(1,186) = 5.00$, $p < .05$). Thirty-seven infants of mothers with MD showed an increase of their cortisol from their pretest levels (versus 25 who showed a decrease). Thus, we examined the interaction as simple effects. Independent *t* test showed that infants of mothers with a lifetime history of MD had significantly lower cortisol levels at their arrival to the laboratory than infants whose mothers did not [.20 versus .29 μg/dL, $t(169.78) = 2.20$, $p < .05$]. Paired *t* test

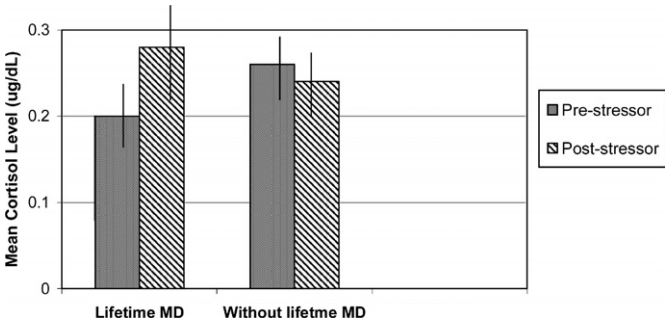

Figure 1. Mean salivary cortisol levels before and after arm restraint in 4-month-old infants of mothers with lifetime history of major depression (MD) ($n = 62$) versus infants of the control group ($n = 126$). MD, major depression.

indicated that cortisol of infants whose mother had a lifetime history of MD significantly increased from time 1 to time 2 [from .20 to .29 μg/dL, $t(61) = -2.95$, $p < .01$] (Figure 1). We examined whether MD severity was linked to infant cortisol. Severity was measured continuously (number of symptoms) and categorically: mild (0–3 symptoms), moderate (4–6 symptoms), and severe (7–9 symptoms). Neither measure was significantly associated with cortisol.

Based on the date of the NIMH-DIS interview, the date of delivery, and the mothers' self-report, we created a variable labeled "depression during pregnancy" to categorize mothers who reported an MD episode that began during pregnancy and those who did not. Results showed that for 20% ($n = 14$) of the infants born to mothers with lifetime depression, an episode of MD occurred during pregnancy. Taking cortisol levels as within-subjects factor, a repeated measures ANOVA with depression during pregnancy (MD, no MD) as the between-subjects factor showed no main effect of depression during pregnancy on cortisol [$F(1,149) = .001$, $p > .05$]. There was neither a within-subjects effect nor an interaction between depression during pregnancy and infant cortisol.

Finally, we examined whether postpartum depressive mood was associated with infant cortisol levels. There was no significant correlation between EDPS mean score and infant cortisol levels. The NIMH-DIS MD scale was administered at 4 months postpartum to 45 participants (those recruited at the MCH site). Only two of these mothers suffered from MD in the postpartum period.

Association of Maternal CD with Infant Cortisol. Eighty-nine mothers (42%) met criteria for CD diagnosis. To test the association of CD with infant cortisol, we conducted a repeated measures ANOVA with NIMH-DIS diagnosis (CD or non-CD) as the between-subjects factor and infant cortisol levels (time 1, time 2) as the within-subjects factor. Results showed that CD had no main effect on infant cortisol [$F(1,187) = 2.22$, ns]. There was no significant within-group effect and no interaction between maternal CD and infant cortisol.

Association of Maternal Overcontrol with Infant Cortisol. The mean score for maternal overcontrol was 5.7 (±SD = 3.4, range 0–14). A repeated measures ANOVA with cortisol as the within-subjects factor and overcontrol scores as the between-subjects factor indicated a significant interaction between maternal overcontrol and infant cortisol [$F(14,175) = 2.03$, $p < .05$]. Hence, we examined the interaction as simple effects. We used an *F* test at each level of cortisol. Results showed that the second cortisol level differed as a function of maternal overcontrol

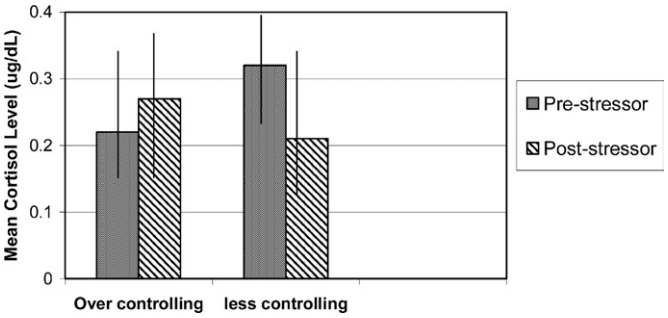

Figure 2. Mean salivary cortisol levels before and after arm restraint in 4-month-old infants of overcontrolling mothers ($n = 146$) versus infants of the comparison group of less controlling mothers ($n = 66$).

[$F(14,187) = 1.84$, $p < .05$]. Because there was no research-based or clinical cutoff for this scale, we used a cutoff criterion of 25% percentile rank and performed a paired t test to compare cortisol levels in infants of "low controlling" mothers (lower 25% percentile rank) versus "average to high overcontrolling" mothers (upper 25% percentile rank). Results showed that in comparison with infants of low controlling mothers ($n = 66$), infants of average to high overcontrolling mothers ($n = 146$) showed a significant increase in cortisol levels from time 1 to time 2 [from .21 to .26 μg/dL, $t(142) = -2.33$, $p < .05$] (Figure 2).

Overlapping Maternal Risk Factors and Infant Cortisol. Forty-eight mothers (21% of the total sample) who displayed average to highly overcontrolling behavior had a lifetime history of MD. Forty-four mothers (19.3%) had CD while also having a lifetime history of MD. However, there was no significant interaction between MD and overcontrol. The cortisol levels of infants in both groups of mothers did not differ significantly from cortisol levels of infants of mothers from the discrete nonoverlapping groups, respectively.

Discussion

Consistent with longitudinal data (Gunnar *et al.* 1996) or reviews of the literature (Graham *et al.* 1999) and independent of the predictors, there was no cortisol response to arm restraint in 4-month-old infants. As predicted, there was a difference in infants of mothers with MD and overcontrolling mothers on this measure, despite the dampened cortisol response period. However, there was no association between CD and infant cortisol reactivity. This study found a high correlation between infants' and mothers' cortisol levels. In line with animal studies showing a high positive correlation in rhesus monkeys (Fleming *et al.* 1999), this result may reflect a nature (genes) and nurture (early environmental influences) interaction.

Our study showed that lifetime MD is associated with increased infant cortisol reactivity. Three explanations of this finding are possible. First, lower baseline levels of cortisol (T1) in infants of mothers with history of MD may partly explain their increased poststressor cortisol measure. Perhaps this latter is the most significant finding of the study, which appears to concur with the Susman *et al.* (1999) hypothesis that lower levels of cortisol may be a physiological marker of depression in teens. Second, our finding on lifetime MD may indicate a biological risk for stress reactivity. A possible underlying mechanism between lifetime MD and infant cortisol may be the genetic effect (Bartels *et al.* 2003) or, rather, the interaction between genotype and early life experience. The increased infant cortisol reactivity may be due to propensity for depression, as found in a study with older children (Lupien *et al.* 2000). Third, it remains possible that it is not history of MD that is linked to stress reactivity but rather other associated factors like prenatal stress or anxiety. Interestingly, we did not find an association between infant cortisol and MD during pregnancy. This last finding appears in line with the Susman *et al.* (1999) result indicating an absence of association between depression and plasma cortisol concentrations in pregnant adolescents but contradicts other findings (Field *et al.* 1995). The nonsignificant finding concerning MD during pregnancy must be considered with caution due to the small number of infants born to mothers depressed during pregnancy. Our finding raises the question of whether the correlation between lifetime history of MD, which corresponds to two or more depressive episodes, and infant cortisol response is cumulative. It is possible that, for a handful of mothers, depression during pregnancy corresponded to the first episode. A single first depressive episode (even during pregnancy) may be insufficient to alter the mother's cortisol levels and consequently the cortisol levels of their fetus/infant. Our finding of a link between lifetime MD and infant cortisol, with no correlation between postpartum depression and cortisol, gives more weight to a biochemical transmission of MD. However, our data did not show that severity of MD was associated with infant cortisol.

Infants of average to highly overcontrolling mothers did not display a dampened cortisol response. Overcontrol, which may represent a lack of parental sensitivity, might induce stress in the offspring. This may have contributed to the increase in cortisol ascending curve (in cases where an increase occurred) or slowed down the decrease (in other cases). Our finding corroborates the results of Spangler *et al.* (1994) of an increase in cortisol in 3-month-old and 6-month-old infants whose mothers had a high degree of lack of sensitivity. Our result also confirms findings from a study with infants of mothers with depressive symptoms (Diego *et al.* 2002): 3-month-old infants of intrusive mothers showed increased salivary cortisol following interactions with their mothers compared with infants of withdrawn mothers. In contrast to the Diego *et al.* (2002) study, ours included a large sample of depressed/controlling mothers and used a diagnostic instrument (NIMH-DIS versus Center for Epidemiologic Studies Depression Scale [CES-D]). Futhermore, in our study, mothers' overcontrol was not correlated with any psychopathology, which indicates that the association of overcontrol with cortisol does not seem to be an artifact of relations between cortisol and comorbid depression.

Nevertheless, stressors and social support have been shown to be strong predictors of depression in low-income adolescent mothers (McKenry *et al.* 1990). In turn, depression in teen mothers might be associated with difficulties in sensitive parenting, namely in the form of overcontrol (Cassidy *et al.* 1996). Hence, it remains possible that our groups of depressed and overcontrolling mothers might have differed from the nondepressed and noncontrolling mothers on their levels of perceived stress and low social support. It seems potentially important that overcontrol might act as a proximal factor amenable to intervention.

A final finding was that CD was not associated with infant cortisol reactivity. Hence, our data did not support our speculation about prenatal risky behaviors and the fetus/infant HPA axis. The noncorrelation of CD and infant cortisol, despite the significant (although low) correlation between CD and history of MD, gives more power to the association observed between history of MD and infant cortisol. However, the risky behaviors we specu-

lated about to explain how CD can be linked to infant cortisol might have been shared with depression (self-medication).

The strengths of this study are a large sample size and comparison groups for each predictor. However, the data should be interpreted cautiously given the following limitations: first, arm restraint has not been used with 4-month-old infants to study their HPA axis. Thus, and because of possible error of measurement, caution should be exercised in interpreting the decreased responsivity of the axis. Second, saliva samples were taken between 10:00 AM and 11:00 AM, a period during which the normative awakening peak in cortisol levels is not fully captured. This limitation is mitigated because the cortisol circadian rhythm may not yet be stable in all the infants (de Weerth *et al.* 2003). Third, we have a single morning and one poststressor measure instead of multiple samples (Ramsay and Lewis 2003). The prestressor level may have been, at least partly, a response to an earlier stressor. Treating cortisol as two-point time measures may mitigate this limitation. Our data also point to the need for standard reference ranges for normal cortisol values, to better interpret cortisol patterns in infants facing adverse factors. Fourth, we measured overcontrol in a single artificial setting, which limits the generalizability of the findings.

Although some measures were retrospective and based on a correlational design, they provided tentative evidence that, in this sample, lifetime MD and overcontrol are associated with a nondampened cortisol response. Dampening of cortisol reactivity at 4 months of age is probably a sign of healthy functioning (Gunnar and Cheatham 2003). Future longitudinal studies should detect whether the absence of a dampened cortisol response in infants whose mothers have a history of MD or are overcontrolling is stable over time. A related question that warrants investigation is whether these infants are at increased risk for later stress-related psychopathology. Could the observed increases be extreme normal variations in cortisol reactivity? Based on one single study, we cannot rule out this possibility. Are the increases in cortisol large enough to affect the developing brain and warrant the concern of clinicians? Without replication, this question remains open. Future studies should explore protective factors that promote resilience of the infants' plastic HPA system when stressed. Such early resilience research can help tease out the relationship between maternal lifetime MD and infant cortisol in preparation for clinical interventions or policy efforts.

This study was supported by grants from the Fonds de la Recherche en Santé du Québec (FRSQ), the Medical Research Council of Canada, and the Montreal Children's Hospital Research Foundation. The first author's work was supported by postdoctoral fellowship awards from the Canadian Institutes of Health Research (CIHR) and Ontario Women's Health Council (OWHC), doctoral training awards from the Social Sciences & Humanities Research Council of Canada (SSHRC), and from the Fonds pour la Formation des Chercheurs et l'Aide à la Recherche (FCAR).

We thank the research assistants for contributing to data collection, Donald Morrisson for support in data processing, Miguel Chagnon for statistical advice, Celia Rodd for clinical endocrinological advice, Mirella De Civita for her comments on the earlier draft of this paper, University Health Network (UHN) Quality of Life Manuscript-Review Seminar members for their feedback on versions of this article, and Donna E. Stewart for revising the last version. We are deeply indebted to the teenage mothers and their infants.

American Psychiatric Association (1994): *Diagnostic and Statistical Manual of Mental Disorders, 4th ed.* Washington, DC: American Psychiatric Association.

Azar R, Paquette D, Zoccolillo M, Quiros E, Baltzer F, Tremblay RE (2004): Cortisol levels and conduct disorder in adolescent mothers. *J Am Acad Child Adolesc Psychiatry* 43(4):461–468.

Barnett B, Joffe A, Duggan AK, Wilson MD, Repke JT (1996): Depressive symptoms, stress, and social support in pregnant and post-partum adolescents. *Arch Pediatr Adolesc Med* 150(1):64–69.

Bartels M, de Geus EJC, Kirschbaum C, Sluyter F, Boomsma DI (2003): Heritability of daytime cortisol levels in children. *Behav Genet* 33(4):421–433.

Bugental DB, Martorell GA, Barraza V (2003): The hormonal costs of subtle forms of infant maltreatment. *Horm Behav* 43:237–244.

Burt VK, Stein K (2002): Epidemiology of depression throughout the female life cycle (2002). *J Clin Psychiatry* 63(7):9–15.

Cassidy B, Zoccolillo M, Hughes S (1996): Psychopathology in adolescent mothers and its effects on mother-infant interactions: A pilot study. *Can J Psychiatry* 4:379–384.

CDIS Group (1991–1992): *Computerized French Version of DIS III-R.* Ottawa: University of Ottawa & Ottawa Civic Hospital.

Challis JRG, Sloboda S, Matthews S, Holloway N, Alfaidy D, Patel FA, *et al.* (2001): The fetal placental hypothalamic-pituitary-adrenal (HPA) axis, parturition and post natal health. *Mol Cell Endocrin* 185:135–144.

Cox JL, Molden JM, Sagovsky R (1987): Detection of postnatal depression: Development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry* 150:782–786.

Crittenden P (1998): *CARE-Index Manual*. Miami: Family Relations Institute.

Crittenden P (2000): *CARE-Index Coding Manual*. Miami: Family Relations Institute.

Crittenden P, Bonvillian JD (1984): The relationship between maternal risk status and maternal sensitivity. *Am J Orthopsychiatry* 54(2):250–262.

de Weerth C, Zijl RH, Buitelaar JK (2003): Development of cortisol circadian rhythm in infancy. *Early Hum Dev* 73(1–2):39–52.

Diego MA, Field T, Hart S, Hernandez-Reif M, Jones N, Cullen C, *et al.* (2002): Facial expressions and EEG in infants of intrusive and withdrawn mothers with depressive symptoms. *Depress Anxiety* 15:10–17.

Field T, Fox NA, Pickens J, Nawrocki T (1995): Right frontal EEG activation in 3- to 6-month-old infants of depressed mothers. *Dev Psychol* 31:358–363.

Fleming AS, O'Day DH, Kramer GW (1999): Neurobiology of mother-infant interactions: Experience and central nervous system plasticity across development and generations. *Neurosci Biobehav Rev* 23:673–685.

Graham YP, Heim C, Goodman SH, Miller AH, Nemeroff CB (1999): The effects of neonatal stress on brain development: Implications for psychopathology. *Dev Psychopathol* 11:545–565.

Gunnar MR (1998): Quality of early care and buffering of neuroendocrine stress reactions: Potential effects on the developing human brain. *Prev Med* 27:208–211.

Gunnar MR, Brodersen L, Krueger K, Rigatuso J (1996): Dampening of adrenocortical responses during infancy: Normative changes and individual differences. *Child Dev* 67:877–889.

Gunnar MR, Cheatham CL (2003): Brain and behaviour interface: Stress and the developing brain. *Infant Ment Health J* 24(3):195–211.

Hearn G, Iliff A, Jones I, Kirby A, Ormiston P, Parr P, *et al.* (1998): Postnatal depression in the community. *Br J Gen Pract* 48:1064–1066.

Heim C, Newport DJ, Heit S, Graham YP, Wilcox M, Bonsall R, *et al.* (2000): Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *JAMA* 284(5):592–597.

Klimes-Dougan B, Hastings PD, Granger D, Usher BA, Zahn-Waxler C (2001): Adrenocortical activity in at-risk and normally developing adolescents: Individual differences in salivary cortisol basal levels, diurnal variation, and responses to social challenges. *Dev Psychopathol* 13:695–719.

Larson MC, Gunnar MR, Hertsgaard L (1998): The effects of morning naps, car trips, and maternal separation on adrenocortical activity in human infants. *Child Dev* 62:362–372.

Leventhal A, Jacobsen T, Miller L, Quintana E (2004): Caregiving attitudes and at-risk maternal behavior among mothers with major mental illness. *Psychiatr Serv* 55(12):1431–1433.

Lupien SJ, King S, Meaney M, McEwen BS (2000): Child's stress hormone levels correlate with mother's socioeconomic status and depressive state. *Biol Psychiatry* 48:976–980.

McKenry PC, Browne DH, Kotch JB, Symons MJ (1990): Mediators of depression among low-income, adolescent mothers of infants: A longitudinal perspective. *J Youth Adolesc* 19(4):327–347.

Meyer SE, Chrousos GP, Gold PW (2001): Major depression and the stress system: A life span perspective. *Dev Psychopathol* 13:565–580.

Pajer K, Gardner W, Rubin RT, Perel J, Neal S (2001): Decreased cortisol levels in adolescent girls with conduct disorder. *Arch Gen Psychiatry* 58:297–302.

Paquette D, Morrisson D (1998): *Projet La Mère Veille: un profil descriptif de100 mères adolescentes*. Montreal: IRDS.

Parker KJ, Schatzberg AF, Lyons DM (2003): Neuroendocrine aspects of hypercortisolism in major depression. *Horm Behav* 43:60–66.

Ponirakis A, Susman EJ, Stifter CA (1998): Negative emotionality and cortisol during adolescent pregnancy and its effects on infant health and autonomic nervous system reactivity. *Dev Psychobiol* 33(2):163–174.

Ramsay D, Lewis M (2003): Reactivity and regulation in cortisol and behavioural responses to stress. *Child Dev* 74(2):456–464.

Roberts RE, Lewinsohn PM, Seeley JR (1994): Symptoms of DSM-III-R major depression in adolescence: Evidence from an epidemiological survey. *J Am Acad Child Adolesc Psychiatry* 34(12):1608–1617.

Silver RK, MacGregor SN, Farell EE, Sholl JS, Hobart ED (1993): Antenatal steroid therapy before 33 weeks' gestation. *Int J Gynaecol Obstet* 41(1):23–26.

Spangler G, Schieche lU, Maier U, Ackermann C (1994): Maternal sensitivity as an external organizer for biobehavioural regulation in infancy. *Dev Psychobiol* 27(7):425–437.

Stifter CA, Fox N (1990): Infant reactivity: Physiological correlates of newborn and 5-month temperament. *Dev Psychol* 26(4):582–588.

Susman EJ, Schmeelk KH, Worall BS, Granger DA, Ponirakis A, Chrousos GP (1999): Corticotropin-releasing hormone and cortisol: Longitudinal associations with depression and antisocial behaviour in pregnant adolescents. *J Am Acad Child Adolesc Psychiatry* 38:460–467.

Trad PV (1995): Mental health of adolescent mothers. *J Am Acad Child Adolesc Psychiatry* 34(2):130–142.

Watamura SE, Donzella B, Alwin J, Gunnar MR (2003): Morning-to-afternoon increases in cortisol concentrations for infants and toddlers at child care: Age differences and behavioral correlates. *Child Dev* 74(4): 1006–1020.

Whembolua GL, Granger DA, Singer S, Kivlighan KT, Marguin JA (2006): Bacteria in the oral mucosa and its effects on the measurement of cortisol, dehydroepiandrosterone, and testosterone in saliva. *Horm Behav* 49:478–483.

Wilder J (1956): The law of initial value in neurology and psychiatry. *J Nerv Ment Dis* 125:73–86.

Woodman DD, Hinton JW, O'Neil MT (1978): Cortisol secretion and stress in maximum security hospital patients. *J Psychosom Res* 22:133–136.