Transgenerational effects of posttraumatic stress disorder in babies of mothers exposed to the World Trade Center attacks during pregnancy

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Abstract

Context: Reduced cortisol levels have been linked with vulnerability to post-traumatic stress disorder (PTSD), and the risk factor of parental PTSD in adult offspring of Holocaust survivors. **Objective:** To report on the relationship between maternal PTSD symptoms and salivary cortisol levels in infants of mothers directly exposed to the World Trade Center (WTC) collapse on 9/11 during pregnancy. **Design:** Mothers (n=38) collected salivary cortisol samples from themselves and their year-old babies at awakening and at bedtime. **Results:** Lower cortisol levels were observed in both mothers (F=5.15, df=1,34, p=.030) and babies of mothers (F=8.0, df=1,29, p=.008) who developed PTSD in response to 9/11 compared to mothers who did not develop PTSD and their babies. Lower cortisol levels were most apparent in babies born to mothers with PTSD exposed in their third trimester. **Conclusions:** The data suggest that effects of maternal PTSD related to cortisol can be observed very early in the life of the offspring, and underscore the relevance of *in utero* contributors to putative biological risk for PTSD.

**Key words:** Post-traumatic stress disorder, cortisol, pregnancy, stress, 11-ß-hydroxysteroid dehydrogenase-2 (11 ß-HSD-2), transgenerational effects, glucocorticoid programming
Introduction

That only a proportion of trauma-exposed persons develop PTSD has prompted the search to identify factors that influence the development of this disorder following trauma exposure and elucidate their biological basis. Parental PTSD appears to be a salient risk factor for PTSD as evidenced by a greater prevalence of PTSD, but not trauma exposure, in adult offspring of Holocaust survivors with PTSD than in comparison subjects (1).

Reduced cortisol levels in PTSD have been reported (2). Intriguingly, significantly lower 24-hr mean urinary cortisol excretion was observed in offspring of Holocaust survivors with PTSD (3). Lower cortisol levels in the acute aftermath of trauma have also been associated with prior traumatization (4), another PTSD risk factor. Because adult Holocaust offspring also endorse more childhood adversity and subjective distress to stressful life events (5), it cannot be ruled out that cortisol levels reflect responses of offspring to their own experiences rather than parental PTSD.

On the other hand, the extent to which any risk factor for PTSD is associated with parental exposure, including prenatal factors, is unknown. Yet, if cortisol concentrations are associated with risk for PTSD following trauma exposure, it is reasonable to suspect a contribution of early developmental factors, including in utero effects, since hypothalamic-pituitary-adrenal (HPA) activity appears to be programmed by early life influences (6). Maternal exposure to glucocorticoids during pregnancy can result in lower birth weight and higher glucocorticoid levels in offspring, leading to adult disease (e.g., hypertension, insulin resistance and hyperlipidaemia) (7) and depression (8).
In the current study, we report on the relationship between maternal PTSD symptoms and salivary cortisol levels obtained at awakening and at bedtime, in mothers and infants of mothers directly exposed to the World Trade Center (WTC) collapse on 9/11 during pregnancy who agreed to participate in a prospective, longitudinal epidemiologic study examining the effects of 9/11 exposures on fetal growth and other pregnancy outcomes. We previously reported such mothers gave birth to smaller babies adjusted for gestational age at delivery, compared to women unexposed to 9/11 during pregnancy (9).

Methods

Participants: Thirty-eight participants and their infants were drawn from a larger cohort of 187 women, pregnant and present at or near the WTC, who self-referred in response to publicity of our investigation (9). At the 9-month examination of the infant, mothers were asked to collect salivary samples from themselves and their babies to determine relationships among maternal PTSD symptoms and cortisol, and cortisol in offspring. Mothers provided written informed consent prior to participation in this IRB study, approved by the Mount Sinai School of Medicine.

Procedure: Probable PTSD and PTSD severity was derived using the Post-Traumatic Stress Disorder Checklist (PCL) (10); severity of depression was assessed with the Beck Depression Index (BDI) (11). Demographic and medical information, and data regarding 9/11 exposure and pregnancy outcomes were also obtained.

Salivary samples were collected at wake-up and bedtime (at least 30 minutes following the last evening feeding) into pre-labeled Salivette tubes (Starstedt, Nuembrecht, Germany), and immediately frozen until assay. Free cortisol levels were
determined by radioimmunoassay (RIA) as described in Goenjian et al. (12). The detection limit was 10ng/dL, and intra- and interassay variability were 3.9% and 12.0% respectively.

Statistical analyses were conducted on log-transformed data. Potential confounds such as maternal age, ethnicity, body mass index (BMI), hours of sleep and wakefulness, and breastfeeding were tested for associations with cortisol. Only mother’s age was correlated with maternal and baby cortisol levels and was used as a covariate.

The primary questions concerned the relationship between maternal PTSD and cortisol and infant cortisol levels and the impact of pregnancy trimester of exposure on these relationships. Effects of diagnostic status of the mother (group), time of day (awakening vs. bedtime), trimester (1st and 2nd vs. 3rd), and interactions were evaluated using repeated measures analysis of covariance (ANCOVA). Pearson’s correlational analyses determined relationships among cortisol levels in mothers and infants and cortisol levels in infants and maternal symptom severity.

Results

Mothers with and without PTSD were well-matched in that no significant differences were detected in maternal age at 9/11, ethnicity, level of education, trimester of pregnancy on 9/11, or BMI, or in gender distribution, gestational age on 9/11, birthweight, or age at collection of their infants. Women with PTSD reported more depression (t=3.34, df=36, p=.002) than women without PTSD, but did not differ in self-reported post-partum depression.

Repeated measures ANCOVA revealed a significant effect of PTSD status (F=5.15, df=1,34, p=.030), as well as a significant main effect for time (F=5.67, df=1,34,
p=.023), supporting the well-documented diurnal rhythm of cortisol with morning higher than evening levels. The covariate of maternal age (F=6.56, df=1,34, p=.015) was significant. There were no effects of trimester on maternal cortisol.

Salivary cortisol was also significantly lower in the offspring of women with PTSD (F=8.0, df=1,29, p=.008) (Figure 1). When data were examined including trimester of maternal exposure to 9/11, maternal PTSD status remained significant (F=11.20, df=1,27, p=.002), with no effect of trimester. However, examination of PTSD effects in each trimester separately, revealed a significant effect of maternal PTSD in infants born to mothers pregnant in the third trimester on 9/11 (F=10.56, df=1,8, p=.012), but not in infants born to mothers in the first or second trimesters.

Maternal log-transformed awakening and bedtime cortisol levels were correlated with log-transformed awakening (r=.552, n=29, p=.001) and bedtime (r=.681, n=29, p=.001) cortisol levels in offspring, respectively, controlling for maternal age. Figure 2 shows the correlation between severity of maternal PTSD symptoms and awakening cortisol levels in infants, highlighting individual data based on trimester of exposure. A similar, though not significant, association was observed with maternal PTSD symptoms and infant bedtime cortisol (r=-.323, df=29, p=.076). There were no correlations with awakening (r=-.067, df=29, p=.719), or bedtime (r=-.150, df=29, p=.422), infant cortisol levels and depression severity.
Discussion

Our findings demonstrate lower cortisol levels in mothers who developed PTSD following exposure to the WTC attacks on 9/11 compared to similarly-exposed mothers who did not develop PTSD, consistent with previous literature (2). Strikingly, babies of mothers who developed PTSD also showed lower salivary cortisol levels in the first year of life. Lower cortisol levels were most apparent in babies born to mothers with PTSD in their third trimester on 9/11, yet PTSD symptom severity in the entire sample was correlated with infant cortisol levels regardless of trimester. In contrast, cortisol levels in babies were unrelated to maternal depression. The data suggest that effects of maternal PTSD on cortisol can be observed very early in the life of the offspring, and underscore the relevance of in utero effects as contributors to putative biological risk factor for PTSD.

Transgenerational effects of trauma have often been attributed to non-genetic, largely postnatal influences such as vicarious traumatization of the offspring by the parents’ communication of their trauma to the child or other consequences of parental symptoms (e.g., poor parenting) (1,3). Because offspring were only a year old at the time of endocrine testing, other potential hypothesized mechanisms, related to early social regulation (13), glucocorticoid programming in utero (6), and/or shared underlying genetic susceptibility (14), are more relevant to the cortisol alterations observed.

With respect to social regulation, babies being raised under conditions of neglect or abusive care have low ambient cortisol levels (15). Offspring of Macaque monkeys exposed to maternal stress resulting from unpredictable foraging demands during a critical, early post-partum developmental window, show lasting corticotrophin-releasing
factor elevations and low cortisol levels (16), a profile observed in PTSD (3). Marmoset monkeys exposed to early maternal separations (17), and monkeys exposed to stressful peer-rearing (18), also show reduced basal cortisol (17). Even in rodents, results of cross-fostering studies demonstrate that even brief exposures in postnatal maternal care during a critical period can have permanent neuroendocrine effects in offspring (19). Thus, mothers with PTSD post-partum may display different or inconsistent behavior towards their offspring, affecting glucocorticoid regulation.

On the other hand, the particularly strong effects of PTSD on cortisol in mothers exposed in the 3rd trimester of pregnancy implicates the involvement of prenatal factors. Stress-induced increases in glucocorticoids during pregnancy influences fetal brain development, producing permanent changes in glucocorticoid programming in offspring in both human and animals, that are, in part, dependent on the gestational age of the fetus (6).

Both stress exposure during pregnancy, and reduced activity of placental 11ß hydroxycortisteroid dehydrogenase type 2 (11ß-HSD-2), the enzyme that catalyses rapid conversion of maternal cortisol to inert cortisone, result in an increased exposure of the fetus to glucocorticoids, resulting in low birth weight, and the subsequent development of metabolic syndrome and other diseases (7). Although prenatal stress and glucocorticoid exposure have been associated with elevated glucocorticoid levels in the offspring in rodents and, less certainly (6,8), in humans, maternal PTSD with its attendant chronic reductions in maternal cortisol, and perhaps induction of placental 11ß-HSD2, might conceivably associate with programming of reduced HPA activity in the offspring despite the transient stress of 9/11 exposure. Indeed, though 9/11 exposure overall was related to
reduced birth weight, adjusted for gestational age, this finding did not appear to be related to the presence of PTSD in mothers (9).

The contribution of pre-pregnancy or pre-traumatic risk factors, including genetic, cannot be excluded as a mechanism of cortisol transmission to offspring, since maternal PTSD may in part reflect genetic, or genetic-environmental interactions regulating individual differences in cortisol or cortisol responses to stress that may, in turn, be transmitted (14). Such factors may explain heterogeneity in the sample regarding psychological or hormonal responses to the events of 9/11, and mediating coping strategies that facilitate quicker recovery. The correlation between maternal PTSD and cortisol levels in infants was remarkably similar to that reported between parental PTSD and urinary cortisol levels in adult offspring of Holocaust survivors ($r= -.46$) (3). The current findings extend those observations by suggesting that extrinsic environmental conditions occurring in offspring later in life cannot fully account for transgenerational transmission of cortisol related to parental PTSD. On the other hand, the similarity between correlations observed in the current study of one-year old offspring and adult offspring of Holocaust survivors should not preclude longitudinal investigation of these effects since even effects related to *in utero* programming, and/or early stress can change over time. For example, elevated salivary cortisol levels in offspring were observed at three years but not seven years (20). Thus, there are likely to be contributions to cortisol levels based on the offspring’s own development history. The current cohort provides an opportunity to examine the longitudinal development in cortisol over time in relation to both remitted or ongoing maternal symptoms and factors related to child development, and accordingly, to disentangle the contributions of genetic, pre-pregnancy, *in utero*, and
post-partum influences on offspring cortisol levels in a sample where the intensity, frequency and duration of the stressor is clearly defined and the symptoms, clearly quantified in a prospective manner.
References:


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Figure 1. Infant cortisol levels at awakening and bedtime, divided on the basis of presence or absence of maternal PTSD.

Figure Legend. The darkened vertical lines in each box represent the median values for the data, with the boxes representing data points within the upper and lower hinges (75\textsuperscript{th} percentile and 25\textsuperscript{th} percentile). No data points were farther than 1.5 times the interquartile range from the median (i.e., outliers). The log-transformed mean awakening cortisol levels in infants with and without maternal PTSD, respectively, was 6.39 ± 0.51 (176.30 pmol/L) and 7.14 ± 1.14 (196.99 pmol/L), and for bedtime 4.90 ± 0.79 (135.19 pmol/L) and 7.14 ± 1.14 (196.99 pmol/L).
Figure 2. Correlation between maternal PTSD symptom severity and infant log-transformed salivary cortisol levels at awakening.

**Figure Legend.** Circles represent data from mothers exposed in their first trimester ($r = -.029$, $n=8$, $p = .945$), triangles represent data from mothers exposed in their second trimester ($r = -.293$, $n=13$, $p = .331$), and squares represent mothers exposed in their third trimester ($r = -.605$, $n=12$, $p = .037$). Mean salivary cortisol levels of infants of mothers with and without PTSD, exposed at first trimester were (6.70±0.29 (184.85 pmol/L) and 7.29 ±1.69 (201.13 pmol/L) respectively), second trimester (6.46±0.25 (178.23 pmol/L) and 6.84±0.97 (188.72 pmol/L) respectively), and third trimester (6.16 ±0.66 (169.95 pmol/L) and 7.51 ±1.00 (207.20 pmol/L) respectively).
Log salivary cortisol (ng/dL)

PTSD Total Score

$r = -.371, n=33, p=.034$