BRIEF REPORT

Transgenerational Effects of Posttraumatic Stress Disorder in Babies of Mothers Exposed to the World Trade Center Attacks during Pregnancy

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Context: Reduced cortisol levels have been linked with vulnerability to posttraumatic stress disorder (PTSD) and the risk factor of parental PTSD in adult offspring of Holocaust survivors.

Objective: The purpose of this study was to report on the relationship between maternal PTSD symptoms and salivary cortisol levels in infants of mothers directly exposed to the World Trade Center collapse on September 11, 2001 during pregnancy.

Design: Mothers (n = 38) collected salivary cortisol samples from themselves and their 1-yr-old babies at awakening and at bedtime.

Results: Lower cortisol levels were observed in both mothers (F = 5.15, df = 1, 34; P = 0.030) and babies of mothers (F = 8.0, df = 1, 29; P = 0.008) who developed PTSD in response to September 11 compared with 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 trimesters.

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. (*J Clin Endocrinol Metab* **90: 4115–4118, 2005**)

THAT ONLY A proportion of trauma-exposed persons develop posttraumatic stress disorder (PTSD) has prompted the search to identify factors that influence the development of this disorder after 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-h 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 live 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 pre-natal factors, is unknown. Yet, if cortisol concentrations are associated with risk for PTSD after trauma exposure, it is reasonable to suspect a contribution of early developmental factors, including *in utero* effects, because hypothalamic-pituitary-adrenal activity appears to be programed 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 hyperlipidemia) (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 September 11 during pregnancy who agreed to participate in a prospective, longitudinal epidemiologic study examining the effects of September 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 with women unexposed to September 11 during pregnancy (9).

Subjects and Methods

Subjects

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 sali-

vary samples from themselves and their babies to determine relationships among maternal PTSD symptoms and cortisol and cortisol in offspring. Mothers provided written informed consent before participation in this Institutional Review Board study, approved by the Mount Sinai School of Medicine (Bronx, NY).

Procedure

Probable PTSD and PTSD severity was derived using the PTSD Checklist (10), and severity of depression was assessed with the Beck Depression Index (11). Demographic and medical information and data regarding September 11 exposure and pregnancy outcomes were also obtained.

Salivary samples were collected at wake-up and bedtime (at least 30 min after the last evening feeding) into prelabeled Salivette tubes (Starstedt, Nuembrecht, Germany) and immediately frozen until assay. Free cortisol levels were determined by RIA as described by Goenjian *et al.* (12). The detection limit was 10 ng/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, 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 (first and second *vs.* third), and interactions were evaluated using repeated measures analysis of covariance. 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, trimester of pregnancy, or gestational age on September 11; ethnicity; level of education; body mass index; gender distribution; and birthweight or age at collection of their infants. Women with PTSD reported more depression ($t = 3.34$, df = 36; $P = 0.002$) than women without PTSD but did not differ in self-reported postpartum depression.

Repeated measures analysis of covariance revealed a significant effect of PTSD status (F = 5.15, df = 1, 34; $P = 0.030$), as well as a significant main effect for time (F = 5.67, df = 1, 34; $P = 0.023$), 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; $P = 0.015$) 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; $P = 0.008$) (Fig. 1). When data were examined including trimester of maternal exposure to September 11, maternal PTSD status remained significant (F = 11.20, df = 1, 27; $P = 0.002$), 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 September 11 (F = 10.56, df = 1, 8; $P = 0.012$), 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 ($r = 0.552$, n = 29; $P = 0.001$) and bedtime ($r = 0.681$, n = 29; $P = 0.001$) cortisol levels in offspring, respectively, con-
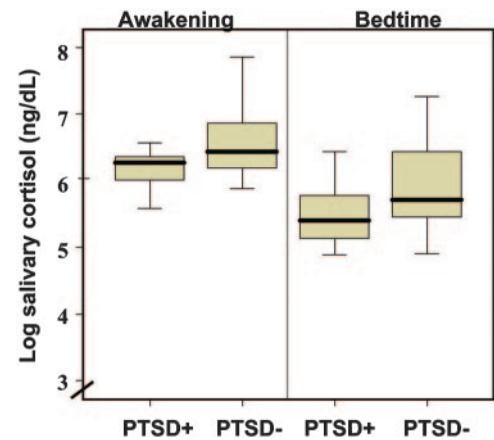

FIG. 1. Infant cortisol levels at awakening and bedtime, divided on the basis of presence or absence of maternal PTSD. The *darkened vertical lines* in each *box* represent the median values for the data, with the *boxes* representing data points within the upper and lower hinges (75th and 25th percentiles). No data points were more 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, were 6.39 ± 0.51 (176.30) and 7.14 ± 1.14 (196.99) pmol/liter, and bedtime levels were 4.90 ± 0.79 (135.19) and 7.14 ± 1.14 (196.99) pmol/liter.

trolling 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, although not significant, association was observed with maternal PTSD symptoms and infant bedtime cortisol ($r = -0.323$, df = 29; $P = 0.076$). There were no correlations with awakening ($r = -0.067$, df = 29; $P = 0.719$), bedtime ($r = -0.150$, df = 29; $P = 0.422$), infant cortisol levels, and depression severity.
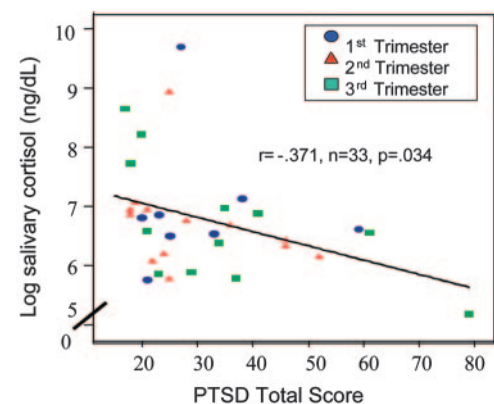

FIG. 2. Correlation between maternal PTSD symptom severity and infant log-transformed salivary cortisol levels at awakening. *Circles*, Data from mothers exposed in their first trimester ($r = -0.029$, n = 8; $P = 0.945$); *triangles*, data from mothers exposed in their second trimester ($r = -0.293$, n = 13; $P = 0.331$); *squares*, mothers exposed in their third trimester ($r = -0.605$, n = 12; $P = 0.037$). Mean salivary cortisol levels of infants of mothers with and without PTSD exposed at first trimester were 6.70 ± 0.29 (184.85) and 7.29 ± 1.69 (201.13) pmol/liter, respectively; second trimester, 6.46 ± 0.25 (178.23) and 6.84 ± 0.97 (188.72) pmol/liter, respectively; and third trimester, 6.16 ± 0.66 (169.95) and 7.51 ± 1.00 (207.20) pmol/liter, respectively.

Discussion

Our findings demonstrate lower cortisol levels in mothers who developed PTSD after exposure to the WTC attacks on September 11 compared with 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 trimesters on September 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 nongenetic, 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 1 yr old at the time of endocrine testing, other potential hypothesized mechanisms, related to early social regulation (13), glucocorticoid programing *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 postpartum 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 postpartum may display different or inconsistent behavior toward their offspring, affecting glucocorticoid regulation.

On the other hand, the particularly strong effects of PTSD on cortisol in mothers exposed in the third 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 programing 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 11β hydroxycorticosteroid dehydrogenase type 2, the enzyme that catalyzes 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 11β hydroxycorticosteroid dehydrogenase type 2 might conceivably associate with programing of reduced hypothalamic-pituitary-adrenal activity in the offspring despite the transient stress of September 11 exposure. Indeed, although September 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 prepregnancy or pretraumatic risk factors, including genetic, cannot be excluded as a mechanism of cortisol transmission to offspring because 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 September 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 = −0.46) (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 1-yr-old offspring and adult offspring of Holocaust survivors should not preclude longitudinal investigation of these effects because even effects related to *in utero* programing and/or early stress can change over time. For example, elevated salivary cortisol levels in offspring were observed at 3 yr but not 7 yr (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, prepregnancy, *in utero*, and postpartum influences on offspring cortisol levels in a sample where the intensity, frequency, and duration of the stressor is clearly defined, and the symptoms are clearly quantified in a prospective manner.

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Erratum

In the article "CLINICAL REVIEW: Osteoporosis after Solid Organ Transplantation" by N. M. Maalouf and E. Shane (*The Journal of Clinical Endocrinology & Metabolism* **90:**2456–2465, 2005), the statements on bone histomorphometry after lung transplantation were incorrectly referenced (*page 2459, first 2 sentences of last paragraph*). The correct citation should be Ref. 25 (Haworth CS, Webb AK, Egan JJ, Selby PL, Hasleton PS, Bishop PW, Freemont TJ 2000 Bone histomorphometry in adult patients with cystic fibrosis. Chest 118: 434–439). *The authors regret the error.*