Title

Maternal Exposure to Childhood Trauma Is Associated During Pregnancy With Placental-Fetal Stress Physiology

Journal

Biological Psychiatry, 79(10)

ISSN

0006-3223

Authors

Moog, Nora K
Buss, Claudia
Entringer, Sonja
et al.

Publication Date

2016-05-01

DOI

10.1016/j.biopsych.2015.08.032

Peer reviewed

HHS Public Access

Author manuscript

Biol Psychiatry. Author manuscript; available in PMC 2017 May 15.

Published in final edited form as:

Biol Psychiatry. 2016 May 15; 79(10): 831–839. doi:10.1016/j.biopsych.2015.08.032.

Maternal exposure to childhood trauma is associated during pregnancy with placental-fetal stress physiology

Nora K. Moog, MSc[a,b], **Claudia Buss, PhD**[a,b,c], **Sonja Entringer, PhD**[a,b,c], **Babak Shahbaba, PhD**[d], **Daniel L. Gillen, PhD**[d], **Calvin J. Hobel, MD**[e], and **Pathik D. Wadhwa, MD, PhD**[a,c,e,f,g,h,*]

[a]University of California, Irvine, Development, Health, and Disease Research Program, 333 The City Drive West, Suite 1200, Orange, CA 92868, USA

[b]Department of Medical Psychology, Charité University Medicine Berlin, Luisenstrasse 57, 10117 Berlin, Germany

[c]Department of Pediatrics, University of California, Irvine, School of Medicine, 505 S. Main St., Suite 525, Orange, CA 92868, USA

[d]Department of Statistics, University of California, Irvine, Bren Hall 2019, Irvine, CA 92697-1250, USA

[e]Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center, 8700 Beverly Blvd, Los Angeles, CA 90048, USA

[f]Department of Psychiatry and Human Behavior, University of California, Irvine, School of Medicine, 101 The City Drive South, Building 3, Route 88, Orange, CA 92697, USA

[g]Department of Obstetrics and Gynecology, University of California, Irvine, School of Medicine, 200 S. Manchester Ave, Suite 600, Orange, CA 92868, USA

[h]Department of Epidemiology, University of California, Irvine, School of Medicine, 224 Irvine Hall, Irvine, CA 92697, USA

Abstract

Background—The effects of exposure to childhood trauma (CT) may be transmitted across generations, however the time period(s) and mechanism(s) have yet to be clarified. We address the hypothesis that intergenerational transmission may begin during intrauterine life *via* the effect of maternal CT exposure on placental-fetal stress physiology, specifically placental corticotrophin-releasing hormone (*p*CRH).

[*]Corresponding Author: Pathik D. Wadhwa, MD, PhD., Professor of Psychiatry & Human Behavior, Obstetrics & Gynecology, Pediatrics, and Epidemiology, Director, UC Irvine Development, Health and Disease Research Program, 3117 Gillespie Neuroscience Research Facility (GNRF), 837 Health Sciences Road, Irvine, CA 92697-4260, Phone: (949) 824-8238, pwadhwa@uci.edu.

FINANCIAL DISCLOSURES

The authors declare no biomedical financial interests or potential conflicts of interest.

Methods—The study was conducted in a sociodemographically-diverse cohort of 295 pregnant women. CT exposure was assessed using the Childhood Trauma Questionnaire. Placental CRH concentrations were quantified in maternal blood collected serially over the course of gestation. Linear mixed effects and Bayesian piecewise linear models were employed to test hypothesized relationships.

Results—Maternal CT exposure (CT+) was significantly associated with *p*CRH production. Compared to non-exposed women, CT+ was associated with an almost 25% increase in *p*CRH towards the end of gestation, and the *p*CRH trajectory of CT+ women exhibited an approximately two-fold steeper increase after the *p*CRH inflection point at 19 wks gestation.

Conclusions—To the best of our knowledge, this finding represents the first report linking maternal CT exposure with placental-fetal stress physiology, thus identifying a potential novel biological pathway of intergenerational transmission that may operate as early as during intrauterine life.

Keywords

childhood trauma; placental CRH; developmental programming; intergenerational transmission; preconceptional stress; pregnancy

INTRODUCTION

Traumatic events that occur *during* a woman's pregnancy likely impact the development of her as-yet-unborn child. But could traumatic exposures that may have occurred *before* the woman became pregnant, perhaps even as early as during her own childhood, also impact fetal development? As a first step towards addressing this question, we establish here an association during gestation between a woman's exposure to trauma in her own childhood and the physiology of the developing fetal-placental unit, with a focus on the production and trajectory of the major placental-fetal stress hormone - placental corticotrophin-releasing hormone (*p*CRH).

Childhood trauma (CT) represents one of the most pernicious stressors in our society. Estimates from the CDC and others suggest a majority of children are exposed to one or more traumatic events in their lifetimes (1, 2), and that 30–40% of adult women have experienced at least one, and 15–25% more than one, type of childhood trauma (3, 4). The long-term sequelae of CT exposure are well established, and include adverse psychological, biological, biophysical and behavioral states, and increased likelihood of developing mental and physical disorders such as depression, posttraumatic stress disorder (PTSD), drug addiction, obesity, cardiovascular, metabolic and autoimmune disease (5–14). Emerging evidence now suggests the long shadow cast by childhood trauma may not be restricted to only the lifespan of abused women, but also may be transmitted to another yet even more vulnerable population - their children - who have been shown to exhibit alterations in stress physiology systems (15–18), behavioral disorders such as conduct problems, internalizing and externalizing behavioral problems, and autism spectrum disorder (19–22), and obesity (23). The mechanisms and pathways underlying such intergenerational mother-to-child

transmission are not well understood, and their elucidation is an area of considerable interest and importance.

The prevailing paradigm posits such intergenerational transmission likely occurs *after* childbirth during the periods of infancy and childhood *via* the effects of CT exposure-related maternal dysfunctional states (*e.g.,* depression, low maternal sensitivity, substance use) on the quality of mother-child relationships and parenting (22, 24–26). We seek to extend this existing paradigm. We advance an interdisciplinary, translational framework to postulate that the process of intergenerational transmission may start earlier during the highly sensitive period of fetal development. We propose that the developing embryo/fetus may sense and respond to biological cues in the maternal compartment that reflect the long-term biological, biophysical, psychological or behavioral consequences that CT exposed women may bring to their pregnancy. Intergenerational transmission *in utero* is expected to be determined by, *1*) the degree to which the developing fetus can receive biological signals indicative of maternal CT-related alterations in her peripheral physiology, and *2*) the extent to which such signals participate directly or indirectly in fetal development and phenotypic specification. Based on the consideration that are no *direct* neural or vascular connections between the maternal and fetal compartments, and all communication is mediated by the placenta, an organ of fetal origin, we suggest that feto-placental stress-responsive systems, specifically the placental corticotrophin-releasing hormone (*p*CRH) system, represents an attractive candidate pathway.

In non-pregnant state CRH is secreted primarily by hypothalamic PVN neurons and plays a central role in coordinating the central and peripheral stress response (27). During pregnancy, the placenta of higher primates synthesizes and releases CRH in an exponentially increasing manner into the fetal and maternal compartments (28). *p*CRH is known to play a major, obligatory role in the initiation, maintenance, and progression of gestation, fetal development and parturition (29–32). Moreover, *p*CRH production is stress-sensitive. Its *in vitro* production is regulated in a positive, dose-dependent manner in response to all the major biological effectors of stress (33–35), and *in vivo* evidence suggests it is sensitive to suboptimal maternal physiological, clinical, social and environmental exposures (36–40). *p*CRH likely serves as a key communication signal between the mother and her as-yet-unborn child. We and others have reported that variation in *p*CRH concentration in pregnancy is associated with several key fetal and infant developmental and health outcomes (41–46). Thus, the placental CRH system appears to play a tripartite role as a sensor, transducer and effector of the consequences of intrauterine perturbations on the developing fetal brain and peripheral systems (47).

The goal of this study was to establish evidence of an association between history of maternal CT exposure and *p*CRH production across gestation after accounting for potential confounding factors. Because *p*CRH production increases in an approximately exponential manner across gestation, we sought to elucidate the precise nature of the effect by performing analyses to determine the association of maternal CT exposure with the initial production and/or the rate of change of *p*CRH production over gestation. While the present study is *not* designed to address questions related to potential mechanisms underlying any observed maternal CT-related alterations in feto-placental stress physiology, we did address

the issue of whether the effects of maternal CT exposure persist after accounting for the effects of salient gestational conditions that occur more frequently in CT+ mothers, such as clinical/obstetric complications in the index pregnancy, biophysical state (higher body-mass index; BMI), unhealthy maternal behaviors (smoking), and unfavorable maternal psychological state (depression), in order to estimate the potential impact of maternal childhood trauma on feto-placental stress physiology over and beyond that reflected in current gestational state or conditions.

METHODS AND MATERIALS

Participants

The study was conducted in a sociodemographically-diverse cohort of 295 pregnant women attending prenatal care at two university-based medical centers in southern California (see Table 1). All participants had singleton, intrauterine pregnancies with no known cord, placental, or uterine anomalies, fetal congenital malformations, or presence of any conditions known to be associated with dysregulated neuroendocrine function or corticosteroid medication use. All study procedures were approved by the IRBs of the respective institutions, and all participants provided written informed consent.

Procedures

The study employed a prospective, longitudinal design with serial assessments over the course of gestation. Participants were recruited in the first trimester of gestation. Study visits occurred up to a maximum of 5 times over the course of their pregnancy at T1 15 ± 0.7 wks (mean ± SEM) (range 13.3 – 17.5), T2 20.3 ± 0.8 wks (range 17.0 – 23.2), T3 25.6 ± 0.8 wks (range 24 – 27.3), T4 30.7 ± 0.6 wks (range 29.6 – 32.4), and T5 36.5 ± 0.8 wks (range 33.5 – 38.5) gestation. Study visit procedures included the collection of maternal venous blood, administration of structured clinical and psychosocial interviews and questionnaires, and fetal ultrasonography. Gestational age was confirmed by obstetric ultrasonographic biometry performed before 20 wks gestation using standard clinical criteria (48).

Measures

Maternal childhood trauma exposure—Maternal exposure to CT was ascertained at the T2 visit using the Childhood Trauma Questionnaire (CTQ, 49), one of the most widely-used instruments for determination of abuse and neglect experiences in childhood and adolescence (50). This 28-item measure assesses five dimensions of childhood maltreatment: emotional abuse (EA), physical abuse (PA), sexual abuse (SA), emotional neglect (EN), and physical neglect (PN). Details of scoring are described in the Supplemental Material. Cut-off values for moderate or greater exposure were used to create dichotomous variables of exposure for each CTQ subscale (emotional abuse ≥13; physical abuse ≥10; sexual abuse ≥8; emotional neglect ≥15; and physical neglect ≥10) and then summed to compute a score reflective of the total number of moderate to severe abuse and neglect categories of exposure (Total CT, with a range between 0 and 5). The Total CT score was used as the principal predictor in statistical analysis.

Placental CRH—*p*CRH concentration was determined in maternal venous blood collected at the study visits. It is important to note that the vast majority of the CRH that is detectable in maternal *peripheral* blood during pregnancy is of placental origin (51). Several extra-hypothalamic sites of CRH production do exist, including reproductive tissues and lymphocytes. However, in contrast to CRH produced by the placenta, CRH from these other tissues acts locally in an autocrine-paracrine manner (52–54). Thus, because the placenta (an organ of fetal origin) is the source of CRH measured in the plasma of pregnant women, the term *p*CRH is used.

A 20-ml blood sample was withdrawn by antecubital venipuncture into siliconized EDTA vacutainers and immediately chilled to 6°C. Samples were centrifuged at 2,000 *g* for 15 min, and the plasma was decanted into polypropylene tubes containing 500 KIU/ml aprotinin (Sigma Chemical Company, St. Louis, Mo., USA). Plasma samples were then stored at −70°C until assayed. CRH levels (pg/ml) were determined from extracted samples by radioimmunoassay (Bachem Peninsula Laboratories LLC, San Carlos, CA, USA, see Supplemental Material for assay details). Intra- and inter-assay coefficients of variance ranged from 5% to 15%, with a minimum detectable dose of 2.04 pg/ml. 9.5% of the pCRH samples were excluded due to high coefficients of variance (CV) > 15%. Specifically, of the 295 participants included in our study, 283 had a T1 visit with 82% (231) having usable CRH data based on the CV criterion; 289 had a T2 visit with 94% (272) having usable CRH data; 99 had a T3 visit with 92% (91) having usable CRH data; 89 had a T4 visit and 100% had usable CRH data; and 82 had a T5 visit with 96% (79) having usable CRH data (see Supplemental Material for further details).

Confounding—To address the possibility that any observed associations between maternal CT exposure and *p*CRH concentrations across gestation reflect residual confounding of the effects of “third” variables that may be *causally* related to both factors, we included measures of childhood socioeconomic status (SES) and race/ethnicity in the first analytic model because these factors may have *preceded* the event of maternal CT exposure (2, 39, 55). Both these variables were assessed at the T1 visit. Childhood SES was quantified using a 15-item measure that characterized distinct aspects of economic status during childhood (childhood SES mean ± SD = 10.8 ±3.1; range: 0–15).

Covariates—The second analytic model included additional covariates of sociodemographic, biophysical, obstetric, behavioral and psychological factors in the index (current) pregnancy that have been associated with *p*CRH production or childhood trauma (11, 36, 39, 40, 55–59). Sociodemographic (current SES, assessed at T1), behavioral (smoking, drug use, and alcohol consumption during pregnancy, assessed at each study visit) and psychological state (depressive symptoms, assessed at each study visit), were ascertained using standardized structured interviews and questionnaires. The 9-item short version of the Center for Epidemiological Studies Depression (CES-D, 60, 61) scale was used to quantify depressive symptomatology. To account for singular missing items the mean responses were calculated for each time point and then combined into a mean CES-D score over all assessment time points. Biological verification of self-reported smoking and illicit drug use was performed in urine using INSTANT-VIEW Multi-Test Drugs of Abuse

Panel (Alfa Scientific Designs Inc., Poway, CA, USA). Biophysical characteristics (pre-pregnancy BMI), parity, and the presence of obstetric risk conditions in the index pregnancy (hypertension, diabetes, anemia, vaginal bleeding, infection, oligohydramnios, and placental abruption) were abstracted from the antepartum and delivery medical record, as previously described (46).

Statistical Analysis

We used the likelihood-ratio test to compare a model with the main and interaction effects of CT with a simpler model that excluded these two terms. The likelihood ratio test statistic −2log(LR) indicates improvement of the model fit upon including CT as a predictor. Since the likelihood ratio test does not differentiate between the main and interaction effect of CT, and because there are multiple observations per subject, we employed linear mixed effects models to test our primary hypothesis that *p*CRH production over gestation differs as a function of maternal CT exposure (see Supplementary Material). We performed a log-transformation of *p*CRH values to linearize the approximately exponential increase in the rate of *p*CRH production over gestation (28). To estimate the rate of *p*CRH change over gestation we included an interaction effect between the total CT score and gestational age at assessment, with gestational age centered at the first study assessment time point (15 weeks gestation). Maternal race/ethnicity and childhood SES were included in this model. Secondary analyses were performed to estimate whether maternal CT exposure exerts effects over and above those of gestational conditions, including maternal socio-demographic, biophysical, obstetric, behavioral, and psychological factors. Model diagnostics were performed using the HLMdiag package (62).

Next, to test our hypothesis that there is no initial difference in *p*CRH production between CT+ and CT− women but that the difference would emerge later and become progressively larger with advancing gestation, Bayesian piecewise linear modeling was employed to determine whether there is a constant multiplicative shift in the non-linear growth rate of pCRH concentrations across gestation, or whether one or more points of time in gestation exist when significant changes in the rate of pCRH increase across gestation occur (i.e. knot points). Our model was trained on 70% of the data, and its predictive performance (measured in terms of mean squared error, MSE) was evaluated on the remaining 30% of the data (63). The procedure was stratified by CT status. All models were adjusted for the covariates described above.

RESULTS

Approximately one half (57.3%) of the study participants reported no or low exposure childhood trauma; 19.3% reported exposure to a single category of abuse or neglect; and 23.4% reported exposure to multiple types of maltreatment (see Table S1 in Supplemental Material). The mean number of traumas (total CT) in the exposed population was 2.06 (± 1.22 SD). The percentage of participants scoring above the cut-off for depression ranged between 7.8% and 11.1% at the different time points during pregnancy.

Compared to CT− women, CT+ women had a lower childhood SES, lower current income, were younger at their first delivery, had marginally higher parity, higher depressive symptomatology, and were less likely to be of non-Hispanic White race/ethnicity (Table 1).

The likelihood-ratio test comparing the models with and without total CT revealed a significant effect of CT exposure on *p*CRH production across gestation (−2log(LR) = 7.56, $p = 0.02$). Thus, the total CT score significantly contributed to the model's explanation of the *p*CRH variation. The results of the mixed effects model revealed that the strength of the association between CT exposure and *p*CRH production increased over the course of gestation, as indicated by the significant interaction between total CT and gestational age at assessment (Table 2). To interpret the results, the logarithmized *p*CRH values were retransformed by exponentiation, which provides an estimate of the change in median CRH as a function of CT and GA. Specifically, at 15 weeks gestation (the first assessment time point), exposure to one additional trauma category corresponded to less than 1% increase in median CRH value, but at 36 weeks gestation (the last assessment time point) each additional trauma category corresponded to a 12.1% increase in median *p*CRH (see Figure 1). Given that women in the CT+ group were exposed to a mean of 2.06 categories of trauma, their average CT exposure corresponded to a 24.9% higher concentration in median *p*CRH towards the end of gestation compared to CT− women (Figures 1 and 2).

The results of the second linear mixed effects model (to ascertain whether the effects of maternal CT exposure on *p*CRH persist after accounting for the effects of salient gestational conditions that may be associated with both childhood trauma and placental physiology) remained altogether unchanged, indicating that childhood trauma appears to exert an effect on *p*CRH over and above these potential covariates ((−2log(LR) = 7.21, $p = 0.02$; see Table 3)). The analyses were repeated including only subjects with at least two *p*CRH measures, which did not appreciably change the results. The significance of the likelihood ratio test comparing the model with and without CT as a predictor improved slightly (−2log(LR) = 8.85, p = 0.01). The parameter estimates of the mixed effects model are shown in Table S2.

The Bayesian piecewise linear models of CRH trajectory analysis trained three models - a simple linear regression (with 0 knots), and two piece-wise linear models with 1 and 2 knots, respectively. Based on the resulting MSEs (0.375, 0.328, 0.329 respectively), the model with 1 knot was selected as the best-fitting model (lowest MSE term). The estimate for the location of the knot point was at 19 weeks gestation. There were no substantial differences between the CT+ and CT− groups in terms of the knot's location, however, their *p*CRH trajectories were different in terms of the intercept and slopes before and after the knot (see Table 4). The change in the second slope (i.e. rate of change after 19 weeks gestation) differed significantly between subjects with and without CT. In the CT− group, the median of *p*CRH increased *multiplicatively* by 1.09 (i.e., 9%) per week from 19 wks gestation onwards, whereas in the CT+ group the median of *p*CRH increased *multiplicatively* by 1.20 (i.e., 20%) per week from 19 wks gestation onwards. Thus, the exponential increase in *p*CRH production over the latter part of gestation among CT+ women is approximately *double* that of CT− women.

DISCUSSION

To the best of our knowledge, this is the first study to establish an association between a woman's exposure to trauma in her own childhood and placental-fetal stress physiology during pregnancy. Consistent with our hypothesis, *p*CRH production over gestation was significantly greater in women exposed to childhood trauma, with a graded effect such that exposure to two types of trauma (the mean number in the exposed group) corresponded to an almost 25% increase in *p*CRH concentrations towards the end of gestation. Maternal CT exposure was not associated with the initial production or a shift in the gestational time point of a change in the non-linear rate of *p*CRH increase (which occurred at 19 weeks gestation), but with an approximately *two-fold* greater increase in the rate of *p*CRH production over the second half of gestation. These effects remained statistically significant after accounting for the effects of potential confounding variables and other gestational conditions related to either *p*CRH production or exposure to childhood trauma.

Previous studies have established an association between a woman's history of CT exposure and the subsequent course and outcome of her pregnancy (56, 64, 65), maternal psychological states and conditions in pregnancy (depression, anxiety, PTSD (57, 66)), and *maternal* gestational physiology (endocrine, immune/inflammatory state) (56, 67–69). The current findings extend this research to the physiological function of the placental-fetal unit, which is a critical link in making the case for the biological plausibility of intergenerational transmission during the intrauterine period of life.

The clinical significance in terms of intergenerational transmission of the observed maternal CT exposure-related differences in *p*CRH production across gestation is presently unknown. However, we note that the pattern of differences in the *p*CRH trajectory by CT status in our study is of similar nature and magnitude to what has previously been reported in pregnancies complicated by preeclampsia and preterm birth (70, 71). Additional support for the biological plausibility of our hypothesis that *p*CRH physiology may act as a mediator of intergenerational transmission of the effects of maternal CT exposure derives from the observation that many of the adverse pregnancy, fetal, birth and postnatal outcomes associated with *p*CRH dysregulation in pregnancy (such as intra-amniotic infection (72), growth and size at birth (46), preterm delivery (46, 71), difficult infant temperament (42), and obesity (44),) are *antecedents* of the same alterations in stress physiology systems and neurodevelopmental disorders that are manifest in children of CT+ mothers (15–21).

In terms of generalizability, we note the prevalence of CT in our study population was similar to that reported in previous large, population-based samples (4, 73). When stratified by CT exposure, our study population differed with respect to their childhood SES and race/ethnicity, which is consistent with previous reports in non-pregnant populations of a higher CT prevalence among individuals with a lower childhood SES and among African Americans and Hispanics compared to non-Hispanic Whites (1, 2). Moreover, our finding of an association of CT exposure with higher parity and younger age at first pregnancy also is consistent with previous reports (64, 74) and with the tenets of life history theory (75).

The two major biological pathways by which maternal CT exposure could influence *p*CRH physiology are *via* maternal endocrine and immune/inflammatory stress biology. Exposure to CT is associated in non-pregnant individuals with changes in HPA axis baseline activity as well as reactivity in response to stressors or pharmacological challenges (76), and, in pregnant women, with alterations in baseline cortisol and in the cortisol awakening response (68, 69). In contrast to their inhibitory effect on *hypothalamic* CRH, glucocorticoids stimulate *placental* CRH production (77). In turn, *p*CRH can stimulate the production of cortisol from the maternal and fetal adrenals (78). Maternal cortisol may, therefore, partially mediate the effect of CT exposure on *p*CRH. In this context, it is interesting to note that the observed inflection point in the non-linear trajectory of pCRH at 19 weeks gestation in our study coincides with the time period when the fetal adrenals start producing appreciable amounts of cortisol (79), suggesting the feto-placental unit of CT+ pregnant women may be more sensitive to the positive feedback of cortisol. Maternal stress, anxiety or depression (i.e. conditions that are among the most prevalent psychological sequelae of CT) have been associated during gestation with several adverse neurodevelopmental outcomes in the children of affected mothers (80). Alterations in the functioning or regulation of the maternal and fetal hypothalamic pituitary adrenal (HPA) axes are commonly discussed as mechanisms that may mediate these associations (81–83). It is conceivable that the psychological consequences of CT are associated with an increased secretion of cortisol from the maternal adrenal, which may stimulate *p*CRH production, and which, in turn, could stimulate the release of cortisol from the fetal adrenals. The second biological pathway relates to the interaction of the maternal immune/inflammatory system with *p*CRH. Secretion of *p*CRH is directly stimulated by pro-inflammatory cytokines such as *IL*-1 and microbial antigens (84). CRH, in turn, has been shown to have a pro-inflammatory effect in the periphery (85, 86), and increased levels of *p*CRH have been associated with intra-amniotic infection (72, 87). Moreover, previous studies of non-pregnant CT+ women have reported they exhibit an increased inflammatory status (88–90). Thus, the maternal environment also may modulate *p*CRH production via changes in the inflammatory milieu.

It has previously been suggested that the intergenerational transmission of the effects of maternal CT exposure may occur in postnatal life *via* the detrimental effects of maternal CT-related psychological states on maternal-child relationships and suboptimal parenting behaviors (91, 92). Prenatal and postnatal periods of intergenerational transmission are not mutually exclusive. However, it is important to ascertain whether this effect starts during intrauterine life for at least two reasons. First, the elucidation of the time windows and mechanisms underlying intergenerational transmission is necessary to develop efficacious strategies for primary prevention. Second, the characteristics of the offspring at birth (e.g., newborn temperament) may, in part, influence the nature of postnatal mother-child dyadic interactions to moderate the effects of postnatal maternal CT-related characteristics. If such offspring characteristics at birth have already been adversely impacted by maternal CT-related gestational effects, they would be expected to further accentuate the consequences of dysregulated mother-child relationships. Indeed, *p*CRH has been previously demonstrated to be a predictor of child temperament (42).

In summary, childhood abuse and neglect represent one of the most pervasive, persistent and pernicious stressors in our society. Emerging evidence now suggests its adverse

consequences may not be restricted to the exposed women alone, but may also be transmitted to their children. It is critical to arrive at a better understanding of this process for elucidating biological pathways and developing interventions in order to ultimately break the vicious cycle of the enduring consequences of early life stress passed down from a vulnerable population of abused women to the even more vulnerable population of their unborn children. The present study represents the first step towards addressing the hypothesis that the inter-generational transmission of these adverse effects may start as early as during the child's intrauterine period of life by establishing an association between a woman's exposure to abuse or neglect in her own childhood and the physiology of the placental-fetal unit of her as-yet-unborn child.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported, in part, by US PHS (NIH) grants RO1 HD-060628, PO1 HD-047609, R01 HD-041696, R29 HD-33506 (all to PDW), RO1 MH-105538 (to CB, PDW and Damien Fair), and R01 NS-41298 (to Curt Sandman).

References

1. (CDC) CfDCaP . Adverse childhood experiences reported by adults --- five states, 2009. MMWR Morb Mortal Wkly Rep. 2010; 59:1609–1613. [PubMed: 21160456]
2. Hussey JM, Chang JJ, Kotch JB. Child maltreatment in the United States: prevalence, risk factors, and adolescent health consequences. Pediatrics. 2006; 118:933–942. [PubMed: 16950983]
3. Scher CD, Forde DR, McQuaid JR, Stein MB. Prevalence and demographic correlates of childhood maltreatment in an adult community sample. Child Abuse Negl. 2004; 28:167–180. [PubMed: 15003400]
4. Walker EA, Unutzer J, Rutter C, Gelfand A, Saunders K, VonKorff M, et al. Costs of health care use by women HMO members with a history of childhood abuse and neglect. Arch Gen Psychiatry. 1999; 56:609–613. [PubMed: 10401506]
5. Anda RF, Felitti VJ, Bremner JD, Walker JD, Whitfield C, Perry BD, et al. The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. Eur Arch Psychiatry Clin Neurosci. 2006; 256:174–186. [PubMed: 16311898]
6. MacMillan HL, Fleming JE, Streiner DL, Lin E, Boyle MH, Jamieson E, et al. Childhood abuse and lifetime psychopathology in a community sample. Am J Psychiatry. 2001; 158:1878–1883. [PubMed: 11691695]
7. Springer KW, Sheridan J, Kuo D, Carnes M. Long-term physical and mental health consequences of childhood physical abuse: results from a large population-based sample of men and women. Child Abuse Negl. 2007; 31:517–530. [PubMed: 17532465]
8. Widom CS. Posttraumatic stress disorder in abused and neglected children grown up. Am J Psychiatry. 1999; 156:1223–1229. [PubMed: 10450264]
9. Thomas C, Hypponen E, Power C. Obesity and type 2 diabetes risk in midadult life: the role of childhood adversity. Pediatrics. 2008; 121:e1240–1249. [PubMed: 18450866]
10. Dong M, Giles WH, Felitti VJ, Dube SR, Williams JE, Chapman DP, et al. Insights into causal pathways for ischemic heart disease: adverse childhood experiences study. Circulation. 2004; 110:1761–1766. [PubMed: 15381652]
11. Danese A, Moffitt TE, Harrington H, Milne BJ, Polanczyk G, Pariante CM, et al. Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. Arch Pediatr Adolesc Med. 2009; 163:1135–1143. [PubMed: 19996051]

12. Heim C, Newport DJ, Heit S, Graham YP, Wilcox M, Bonsall R, et al. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. JAMA. 2000; 284:592–597. [PubMed: 10918705]
13. Heim C, Shugart M, Craighead WE, Nemeroff CB. Neurobiological and psychiatric consequences of child abuse and neglect. Dev Psychobiol. 2010; 52:671–690. [PubMed: 20882586]
14. Heim C, Binder EB. Current research trends in early life stress and depression: Review of human studies on sensitive periods, gene–environment interactions, and epigenetics. Experimental Neurology. 2012; 233:102–111. [PubMed: 22101006]
15. Jovanovic T, Smith A, Kamkwalala A, Poole J, Samples T, Norrholm SD, et al. Physiological markers of anxiety are increased in children of abused mothers. J Child Psychol Psychiatry. 2011; 52:844–852. [PubMed: 21501167]
16. Brand SR, Brennan PA, Newport DJ, Smith AK, Weiss T, Stowe ZN. The impact of maternal childhood abuse on maternal and infant HPA axis function in the postpartum period. Psychoneuroendocrinology. 2010; 35:686–693. [PubMed: 19931984]
17. Bierer LM, Bader HN, Daskalakis NP, Lehrner AL, Makotkine I, Seckl JR, et al. Elevation of 11β-hydroxysteroid dehydrogenase type 2 activity in Holocaust survivor offspring: Evidence for an intergenerational effect of maternal trauma exposure. Psychoneuroendocrinology. 2014; 48:1–10. [PubMed: 24971590]
18. Lehrner A, Bierer LM, Passarelli V, Pratchett LC, Flory JD, Bader HN, et al. Maternal PTSD associates with greater glucocorticoid sensitivity in offspring of Holocaust survivors. Psychoneuroendocrinology. 2014; 40:213–220. [PubMed: 24485493]
19. Collishaw S, Dunn J, O'Connor TG, Golding J. Maternal childhood abuse and offspring adjustment over time. Development and psychopathology. 2007; 19:367–383. [PubMed: 17459175]
20. Thompson R. Mothers' violence victimization and child behavior problems: examining the link. Am J Orthopsychiatry. 2007; 77:306–315. [PubMed: 17535128]
21. Roberts AL, Lyall K, Rich-Edwards JW, Ascherio A, Weisskopf MG. Association of maternal exposure to childhood abuse with elevated risk for autism in offspring. JAMA Psychiatry. 2013; 70:508–515. [PubMed: 23553149]
22. Plant DT, Barker ED, Waters CS, Pawlby S, Pariante CM. Intergenerational transmission of maltreatment and psychopathology: the role of antenatal depression. Psychol Med. 2013; 43:519–528. [PubMed: 22694795]
23. Roberts AL, Galea S, Austin SB, Corliss HL, Williams MA, Koenen KC. Women's experience of abuse in childhood and their children's smoking and overweight. American journal of preventive medicine. 2014; 46:249–258. [PubMed: 24512863]
24. Berlin LJ, Appleyard K, Dodge KA. Intergenerational continuity in child maltreatment: mediating mechanisms and implications for prevention. Child development. 2011; 82:162–176. [PubMed: 21291435]
25. Dixon L, Hamilton-Giachritsis C, Browne K. Attributions and behaviours of parents abused as children: a mediational analysis of the intergenerational continuity of child maltreatment (Part II). J Child Psychol Psychiatry. 2005; 46:58–68. [PubMed: 15660644]
26. Appleyard K, Berlin LJ, Rosanbalm KD, Dodge KA. Preventing early child maltreatment: implications from a longitudinal study of maternal abuse history, substance use problems, and offspring victimization. Prev Sci. 2011; 12:139–149. [PubMed: 21240556]
27. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. JAMA. 1992; 267:1244–1252. [PubMed: 1538563]
28. Sorem KA, Smikle CB, Spencer DK, Yoder BA, Graveson MA, Siler-Khodr TM. Circulating maternal corticotropin-releasing hormone and gonadotropin-releasing hormone in normal and abnormal pregnancies. Am J Obstet Gynecol. 1996; 175:912–916. [PubMed: 8885747]
29. Smith R. Parturition. N Engl J Med. 2007; 356:271–283. [PubMed: 17229954]
30. Makrigiannakis A, Zoumakis E, Kalantaridou S, Coutifaris C, Margioris AN, Coukos G, et al. Corticotropin-releasing hormone promotes blastocyst implantation and early maternal tolerance. Nat Immunol. 2001; 2:1018–1024. [PubMed: 11590404]

31. Giovannelli A, Greenwood SL, Desforges M, Sibley CP, Petraglia F. Corticotrophin-releasing factor and urocortin inhibit system A activity in term human placental villous explants. Placenta. 2011; 32:99–101. [PubMed: 21093910]
32. Smith R, Mesiano S, Chan EC, Brown S, Jaffe RB. Corticotropin-releasing hormone directly and preferentially stimulates dehydroepiandrosterone sulfate secretion by human fetal adrenal cortical cells. J Clin Endocrinol Metab. 1998; 83:2916–2920. [PubMed: 9709969]
33. Korebrits C, Yu DH, Ramirez MM, Marinoni E, Bocking AD, Challis JR. Antenatal glucocorticoid administration increases corticotrophin-releasing hormone in maternal plasma. Br J Obstet Gynaecol. 1998; 105:556–561. [PubMed: 9637127]
34. Petraglia F, Sutton S, Vale W. Neurotransmitters and peptides modulate the release of immunoreactive corticotropin-releasing factor from cultured human placental cells. Am J Obstet Gynecol. 1989; 160:247–251. [PubMed: 2563197]
35. Donoghue JF, Leitch IM, Boura AL, Walters WA, Giles WB, Smith R, et al. Fetal placental vascular responses to corticotropin-releasing hormone in vitro. Effects of variation in oxygen tension. Placenta. 2000; 21:711–717. [PubMed: 10985975]
36. Herrmann TS, Siega-Riz AM, Hobel CJ, Aurora C, Dunkel-Schetter C. Prolonged periods without food intake during pregnancy increase risk for elevated maternal corticotropin-releasing hormone concentrations. Am J Obstet Gynecol. 2001; 185:403–412. [PubMed: 11518900]
37. Hobel CJ, Dunkel-Schetter C, Roesch SC, Castro LC, Arora CP. Maternal plasma corticotropin-releasing hormone associated with stress at 20 weeks' gestation in pregnancies ending in preterm delivery. Am J Obstet Gynecol. 1999; 180:S257–263. [PubMed: 9914629]
38. Tse AC, Rich-Edwards JW, Koenen K, Wright RJ. Cumulative stress and maternal prenatal corticotropin-releasing hormone in an urban U.S. cohort. Psychoneuroendocrinology. 2012; 37:970–979. [PubMed: 22154479]
39. Kramer MS, Lydon J, Seguin L, Goulet L, Kahn SR, McNamara H, et al. Non-stress-related factors associated with maternal corticotrophin-releasing hormone (CRH) concentration. Paediatr Perinat Epidemiol. 2010; 24:390–397. [PubMed: 20618729]
40. O'Keane V, Lightman S, Marsh M, Pawlby S, Papadopoulos AS, Taylor A, et al. Increased pituitary-adrenal activation and shortened gestation in a sample of depressed pregnant women: a pilot study. J Affect Disord. 2011; 130:300–305. [PubMed: 21093926]
41. Ellman LM, Schetter CD, Hobel CJ, Chicz-Demet A, Glynn LM, Sandman CA. Timing of fetal exposure to stress hormones: effects on newborn physical and neuromuscular maturation. Dev Psychobiol. 2008; 50:232–241. [PubMed: 18335490]
42. Davis EP, Glynn LM, Dunkel Schetter C, Hobel C, Chicz-Demet A, Sandman CA. Corticotropin-releasing hormone during pregnancy is associated with infant temperament. Developmental neuroscience. 2005; 27:299–305. [PubMed: 16137987]
43. Sandman CA, Wadhwa PD, Chicz-DeMet A, Porto M, Garite TJ. Maternal corticotropin-releasing hormone and habituation in the human fetus. Dev Psychobiol. 1999; 34:163–173. [PubMed: 10204092]
44. Gillman MW, Rich-Edwards JW, Huh S, Majzoub JA, Oken E, Taveras EM, et al. Maternal corticotropin-releasing hormone levels during pregnancy and offspring adiposity. Obesity (Silver Spring). 2006; 14:1647–1653. [PubMed: 17030976]
45. Fasting MH, Oken E, Mantzoros CS, Rich-Edwards JW, Majzoub JA, Kleinman K, et al. Maternal levels of corticotropin-releasing hormone during pregnancy in relation to adiponectin and leptin in early childhood. J Clin Endocrinol Metab. 2009; 94:1409–1415. [PubMed: 19190112]
46. Wadhwa PD, Garite TJ, Porto M, Glynn L, Chicz-DeMet A, Dunkel-Schetter C, et al. Placental corticotropin-releasing hormone (CRH), spontaneous preterm birth, and fetal growth restriction: a prospective investigation. Am J Obstet Gynecol. 2004; 191:1063–1069. [PubMed: 15507922]
47. Buss C, Entringer S, Wadhwa PD. Fetal programming of brain development: intrauterine stress and susceptibility to psychopathology. Science signaling. 2012; 5:pt7. [PubMed: 23047922]
48. O'Brien GD, Queenan JT, Campbell S. Assessment of gestational age in the second trimester by real-time ultrasound measurement of the femur length. Am J Obstet Gynecol. 1981; 139:540–545. [PubMed: 7193418]

49. Bernstein, DP.; Fink, L. Childhood Trauma Questionnaire: a retrospective self-report manual. San Antonio, TX: The Psychological Corp; 1998.
50. Baker AJL. Adult recall of childhood psychological maltreatment: Definitional strategies and challenges. Children and Youth Services Review. 2009; 31:703–714.
51. Goland RS, Wardlaw SL, Stark RI, Brown LS Jr, Frantz AG. High levels of corticotropin-releasing hormone immunoactivity in maternal and fetal plasma during pregnancy. J Clin Endocrinol Metab. 1986; 63:1199–1203. [PubMed: 3020078]
52. Di Blasio AM, Pecori Giraldi F, Vigano P, Petraglia F, Vignali M, Cavagnini F. Expression of corticotropin-releasing hormone and its R1 receptor in human endometrial stromal cells. J Clin Endocrinol Metab. 1997; 82:1594–1597. [PubMed: 9141555]
53. Karalis K, Sano H, Redwine J, Listwak S, Wilder RL, Chrousos GP. Autocrine or paracrine inflammatory actions of corticotropin-releasing hormone in vivo. Science (New York, NY). 1991; 254:421–423.
54. Kalantaridou SN, Zoumakis E, Makrigiannakis A, Lavasidis LG, Vrekoussis T, Chrousos GP. Corticotropin-releasing hormone, stress and human reproduction: an update. Journal of reproductive immunology. 2010; 85:33–39. [PubMed: 20412987]
55. Chen Y, Holzman C, Chung H, Senagore P, Talge NM, Siler-Khodr T. Levels of maternal serum corticotropin-releasing hormone (CRH) at midpregnancy in relation to maternal characteristics. Psychoneuroendocrinology. 2010; 35:820–832. [PubMed: 20006448]
56. Leeners B, Stiller R, Block E, Gorres G, Rath W. Pregnancy complications in women with childhood sexual abuse experiences. Journal of psychosomatic research. 2010; 69:503–510. [PubMed: 20955870]
57. Seng JS, Sperlich M, Low LK. Mental health, demographic, and risk behavior profiles of pregnant survivors of childhood and adult abuse. J Midwifery Womens Health. 2008; 53:511–521. [PubMed: 18984507]
58. Alvarez J, Pavao J, Baumrind N, Kimerling R. The relationship between child abuse and adult obesity among california women. American journal of preventive medicine. 2007; 33:28–33. [PubMed: 17572308]
59. Currie J, Widom CS. Long-term consequences of child abuse and neglect on adult economic well-being. Child maltreatment. 2010; 15:111–120. [PubMed: 20425881]
60. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Applied Psychological Measurement. 1977; 1:385–401.
61. Santor DA, Coyne JC. Shortening the CES–D to improve its ability to detect cases of depression. Psychological Assessment. 1997; 9:233.
62. Loy A, Hofmann H. HLMdiag: A Suite of Diagnostics for Hierarchical Linear Models in R. Journal of Statistical Software. 2014; 56:1–28.
63. Hastie, T.; Tibshirani, R.; Friedman, J. Data Mining, Inference, and Prediction. 2. New York: Springer; 2009. The Elements of Statistical Learning; p. 763
64. Lukasse M, Schei B, Vangen S, Oian P. Childhood abuse and common complaints in pregnancy. Birth. 2009; 36:190–199. [PubMed: 19747265]
65. Stevens-Simon C, McAnarney ER. Childhood victimization: relationship to adolescent pregnancy outcome. Child Abuse Negl. 1994; 18:569–575. [PubMed: 7922731]
66. Lang AJ, Rodgers CS, Lebeck MM. Associations between maternal childhood maltreatment and psychopathology and aggression during pregnancy and postpartum. Child Abuse Negl. 2006; 30:17–25. [PubMed: 16406025]
67. Cammack AL, Buss C, Entringer S, Hogue CJ, Hobel CJ, Wadhwa PD. The association between early life adversity and bacterial vaginosis during pregnancy. Am J Obstet Gynecol. 2011; 204:431 e431–438. [PubMed: 21419384]
68. Bublitz MH, Stroud LR. Childhood sexual abuse is associated with cortisol awakening response over pregnancy: Preliminary findings. Psychoneuroendocrinology. 2012
69. Shea AK, Streiner DL, Fleming A, Kamath MV, Broad K, Steiner M. The effect of depression, anxiety and early life trauma on the cortisol awakening response during pregnancy: preliminary results. Psychoneuroendocrinology. 2007; 32:1013–1020. [PubMed: 17855000]

70. Ellis MJ, Livesey JH, Inder WJ, Prickett TC, Reid R. Plasma corticotropin-releasing hormone and unconjugated estriol in human pregnancy: gestational patterns and ability to predict preterm delivery. Am J Obstet Gynecol. 2002; 186:94–99. [PubMed: 11810092]
71. Warren WB, Gurewitsch ED, Goland RS. Corticotropin-releasing hormone and pituitary-adrenal hormones in pregnancies complicated by chronic hypertension. Am J Obstet Gynecol. 1995; 172:661–666. [PubMed: 7856702]
72. Florio P, Romero R, Chaiworapongsa T, Kusanovic JP, Torricelli M, Lowry PJ, et al. Amniotic fluid and umbilical cord plasma corticotropin-releasing factor (CRF), CRF-binding protein, adrenocorticotropin, and cortisol concentrations in intraamniotic infection and inflammation at term. J Clin Endocrinol Metab. 2008; 93:3604–3609. [PubMed: 18559919]
73. Gerdner A, Allgulander C. Psychometric properties of the Swedish version of the Childhood Trauma Questionnaire-Short Form (CTQ-SF). Nord J Psychiatry. 2009; 63:160–170. [PubMed: 19021077]
74. Chisholm JS, Quinlivan JA, Petersen RW, Coall DA. Early Stress Predicts Age at Menarche and First Birth, Adult Attachment, and Expected Lifespan. Human Nature. 2005; 16:233–265. [PubMed: 26189749]
75. Belsky J. Childhood experience and the development of reproductive strategies. Psicothema. 2010; 22:28–34. [PubMed: 20100424]
76. Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. The link between childhood trauma and depression: insights from HPA axis studies in humans. Psychoneuroendocrinology. 2008; 33:693–710. [PubMed: 18602762]
77. Cheng YH, Nicholson RC, King B, Chan EC, Fitter JT, Smith R. Glucocorticoid stimulation of corticotropin-releasing hormone gene expression requires a cyclic adenosine 3′,5′-monophosphate regulatory element in human primary placental cytotrophoblast cells. J Clin Endocrinol Metab. 2000; 85:1937–1945. [PubMed: 10843178]
78. McLean M, Bisits A, Davies J, Woods R, Lowry P, Smith R. A placental clock controlling the length of human pregnancy. Nat Med. 1995; 1:460–463. [PubMed: 7585095]
79. Ishimoto H, Jaffe RB. Development and Function of the Human Fetal Adrenal Cortex: A Key Component in the Feto-Placental Unit. Endocrine Reviews. 2011; 32:317–355. [PubMed: 21051591]
80. O'Donnell K, O'Connor TG, Glover V. Prenatal stress and neurodevelopment of the child: focus on the HPA axis and role of the placenta. Developmental neuroscience. 2009; 31:285–292. [PubMed: 19546565]
81. Coe CL, Lubach GR. Fetal Programming: Prenatal Origins of Health and Illness. Current Directions in Psychological Science. 2008; 17:36–41.
82. Huizink AC, Robles de Medina PG, Mulder EJH, Visser GHA, Buitelaar JK. Stress during pregnancy is associated with developmental outcome in infancy. Journal of Child Psychology and Psychiatry. 2003; 44:810–818. [PubMed: 12959490]
83. O'Connor TG, Ben-Shlomo Y, Heron J, Golding J, Adams D, Glover V. Prenatal anxiety predicts individual differences in cortisol in pre-adolescent children. Biological psychiatry. 2005; 58:211–217. [PubMed: 16084841]
84. Uh A, Nicholson RC, Gonzalez GV, Simmons CF, Gombart A, Smith R, et al. Lipopolysaccharide stimulation of trophoblasts induces corticotropin-releasing hormone expression through MyD88. Am J Obstet Gynecol. 2008; 199:317 e311–316. [PubMed: 18771998]
85. Wang W, Nan X, Ji P, Dow KE. Corticotropin releasing hormone modulates endotoxin-induced inflammatory cytokine expression in human trophoblast cells. Placenta. 2007; 28:1032–1038. [PubMed: 17568667]
86. Theoharides TC, Singh LK, Boucher W, Pang X, Letoumeau R, Webster E, et al. Corticotropin-releasing hormone induces skin mast cell degranulation and increased vascular permeability, a possible explanation for its proinflammatory effects. Endocrinology. 1998; 139:403–413. [PubMed: 9421440]
87. Torricelli M, Novembri R, Bloise E, De Bonis M, Challis JR, Petraglia F. Changes in placental CRH, urocortins, and CRH-receptor mRNA expression associated with preterm delivery and chorioamnionitis. J Clin Endocrinol Metab. 2011; 96:534–540. [PubMed: 21106714]

88. Danese A, Pariante CM, Caspi A, Taylor A, Poulton R. Childhood maltreatment predicts adult inflammation in a life-course study. Proc Natl Acad Sci U S A. 2007; 104:1319–1324. [PubMed: 17229839]

89. Dube SR, Fairweather D, Pearson WS, Felitti VJ, Anda RF, Croft JB. Cumulative childhood stress and autoimmune diseases in adults. Psychosom Med. 2009; 71:243–250. [PubMed: 19188532]

90. Rooks C, Veledar E, Goldberg J, Bremner JD, Vaccarino V. Early trauma and inflammation: role of familial factors in a study of twins. Psychosom Med. 2012; 74:146–152. [PubMed: 22286843]

91. Pereira J, Vickers K, Atkinson L, Gonzalez A, Wekerle C, Levitan R. Parenting stress mediates between maternal maltreatment history and maternal sensitivity in a community sample. Child Abuse Negl. 2012; 36:433–437. [PubMed: 22633056]

92. Roberts R, O'Connor T, Dunn J, Golding J, Team AS. The effects of child sexual abuse in later family life; mental health, parenting and adjustment of offspring. Child Abuse Negl. 2004; 28:525–545. [PubMed: 15159068]

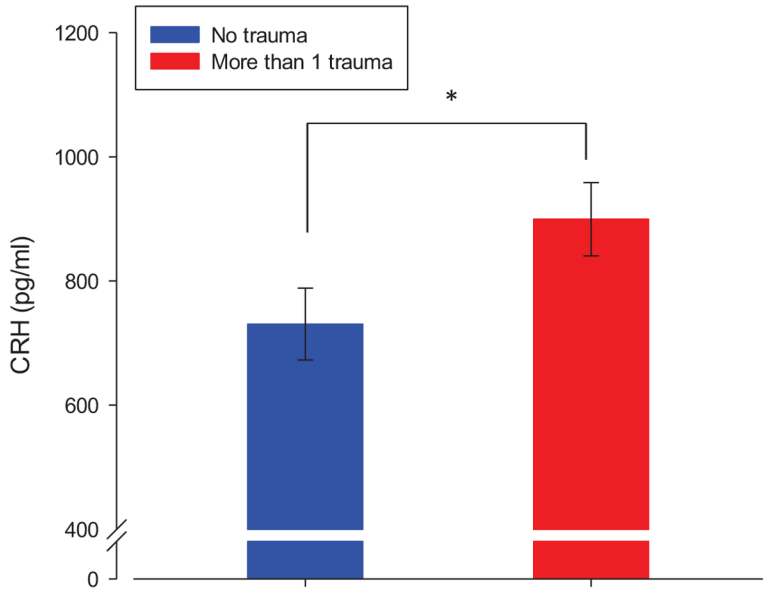

Figure 1.

Scatterplot depicting the relationship between maternal childhood trauma and placental CRH over the course of gestation. The black square represents the point of inflection at 19 weeks of gestation. Analyses were performed using the continuous total CT variable as predictor and logCRH as outcome and including all covariates. For illustration purposes the difference in non-logarithmized CRH values between the two groups representing no trauma exposure and exposure to more than one trauma are presented in the figure.

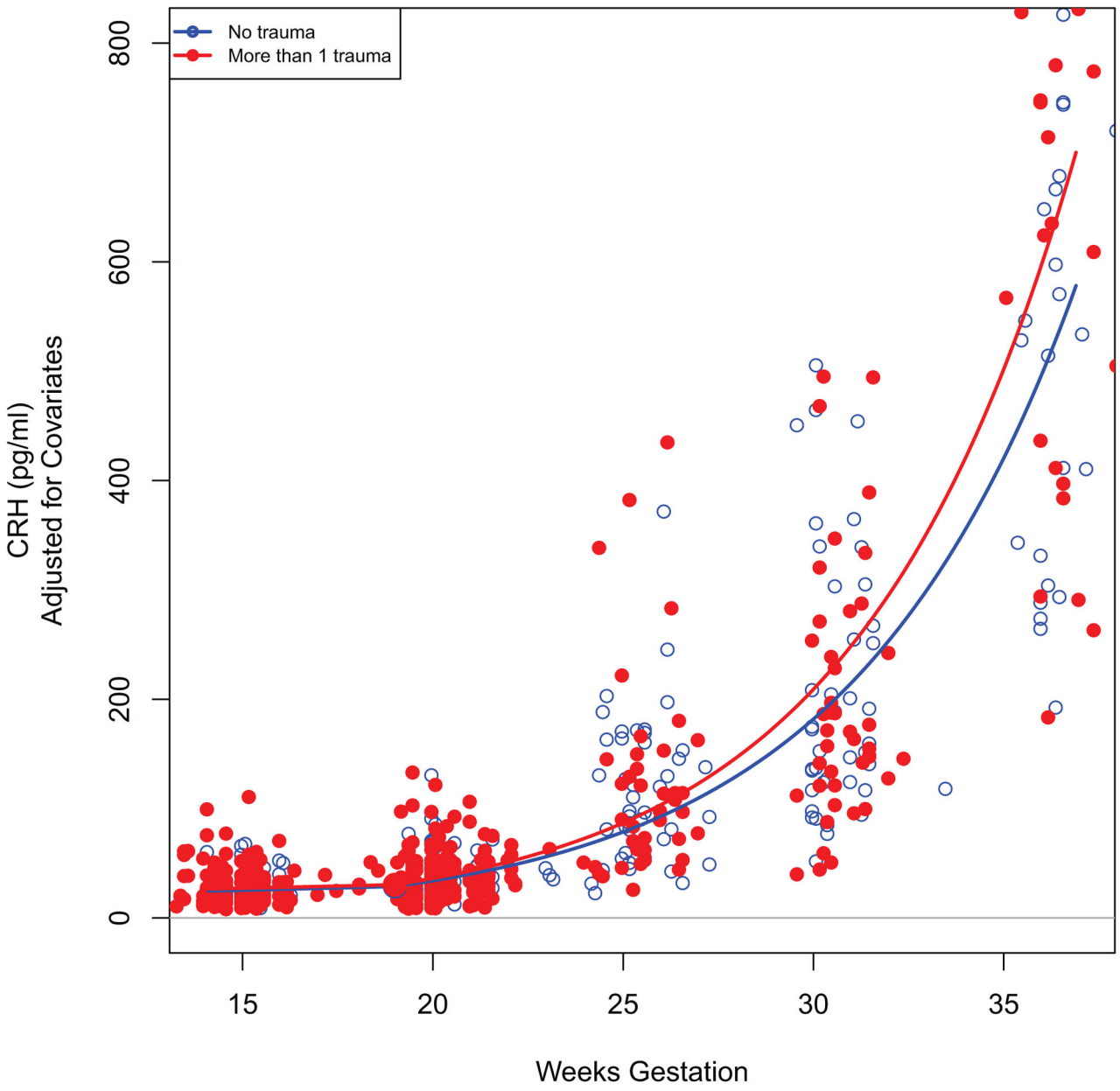

Figure 2.

Association between maternal childhood trauma and placental CRH concentrations at 36 weeks gestation. Error bars represent standard error of the mean (SEM). Analyses were performed using the continuous total CT variable as predictor and logCRH as outcome and including all covariates. For illustration purposes the difference in non-logarithmized CRH values between the two groups representing no trauma exposure and exposure to more than one trauma are presented in the figure.

Table 1

Frequencies and means (SD) of maternal characteristics in the whole sample and in women meeting criteria for any type of childhood trauma vs. women without childhood trauma.

Characteristic	Complete sample N = 295	CT-group (no childhood trauma) N=169 (57.3%)	CT+ group (≥ 1 type of childhood trauma) N=126 (42.7%)
Race/ethnicity, n (%)			
Non-Hispanic White	96 (32.5%)	67 (39.6%)	29 (23.0%) **
Hispanic	100 (33.9%)	54 (32.0%)	46 (36.5%)
African American	58 (19.7%)	31 (18.3%)	27 (21.4%)
Childhood SES, mean ± SD	10.92 ± 3.12	11.51 ± 2.75	10.08 ± 13.42 ***
Presence of any obstetric risk condition, n (%)	78 (26.4%)	41 (24.3%)	37 (29.4%)
Smoking in pregnancy = 1, n (%)	26 (8.8%)	11 (6.5%)	15 (11.9%)
Drug use in pregnancy = 1, n (%)	14 (4.7%)	5 (3.0%)	9 (7.1%)
Alcohol in pregnancy = 1, n (%)	48 (16.3%)	24 (14.2%)	24 (19.0%)
Family income index, mean ± SD	6.36 ± 3.28	6.79 ± 3.39	5.79 ± 3.04 *
Age at delivery, yrs, mean ± SD	28.92 ± 5.90	29.12 ± 6.08	28.64 ± 5.66
Age at first delivery, yrs, mean ± SD	24.72 ± 6.04	25.33 ± 6.28	23.89 ± 5.63 *
Parity, mean ± SD	1.07 ± 1.07	0.97 ± 1.00	1.21 ± 1.14 †
Pre-pregnancy BMI, mean ± SD	26.26 ± 6.24	25.87 ± 6.10	26.80 ± 6.40
Depression (CES-D), mean ± SD	0.70 ± 0.46	0.57 ± 0.37	0.87 ± 0.51 ***

Note. CT = childhood trauma; SES = socioeconomic status; BMI = Body-Mass Index; CES-D = Center for Epidemiological Studies - Depression

† $p < .10$;

* $p < .05$;

** $p < .01$;

*** $p < .001$ compared to CT−

Table 2

Model 1: Effect estimates of the linear mixed effects model with log-*p*CRH as the outcome and Total CT and potentially confounding covariates as predictors.

Likelihood ratio test (comparing null with full model) = 7.56, p=0.02					
	Estimate	**SE**	**df**	**t-value**	***p*-value**
GA	0.136	0.004	415	38.351	<0.001*
Total CT	0.005	0.029	264	0.185	0.85
Total CT*GA	0.005	0.002	415	2.356	0.02*
White	0.091	0.098	264	0.237	0.36
Hispanic	0.024	0.103	264	0.237	0.81
African-American	−0.083	0.114	264	−0.726	0.47
Childhood SES	0.010	0.012	264	0.790	0.43

Note. GA = gestational age at assessment; CT = childhood trauma; SES = socioeconomic status

* $p < .05$

Table 3

Model 2: Effect estimates of the linear mixed effects model with logCRH as the outcome and CT Total and full list of covariates as predictors.

Likelihood ratio test (comparing null with full model) = 7.21, p=0.02					
	Estimate	**SE**	**df**	**t-value**	***p*-value**
GA	0.135	0.004	384	35.556	<0.001*
Total CT	0.004	0.032	236	0.132	0.90
Total CT*GA	0.005	0.002	384	2.322	0.02*
White	0.082	0.103	236	0.794	0.43
Hispanic	0.031	0.108	236	0.282	0.78
African-American	−0.019	0.125	236	−0.150	0.88
Childhood SES	0.006	0.013	236	0.460	0.65
Parity	−0.062	0.033	236	−1.863	0.06
Family Income	0.008	0.012	236	0.686	0.49
Pre-preg BMI	−0.008	0.006	236	−1.362	0.18
Obstetric risk	0.091	0.077	236	1.176	0.24
Smoking	−0.147	0.121	236	−1.219	0.22
Drugs	0.062	0.172	236	0.364	0.72
Alcohol	−0.091	0.091	236	−1.008	0.32
Depression	0.042	0.080	236	0.530	0.60

Note. GA = gestational age at assessment; CT = childhood trauma; SES = socioeconomic status; Pre-preg BMI = pre-pregnancy body mass index

* $p < .05$

Table 4

Point estimates and 95% probability intervals for the regression parameters of the piecewise linear models for subjects with complete trajectories.

	Point Estimate	95% Probability Interval
Intercept for CT−	3.36	3.18–3.54
Intercept for CT+	3.27	3.06–3.47
Difference in the intercept between CT+ and CT−	−0.09	−0.36–0.17
First slope[a] for CT−	0.06	0.00–0.12*
First slope[a] for CT+	0.00	−0.07–0.06
Difference in the first slope[a] between CT+ and CT−	−0.06	−0.15–0.02
Second slope[b] for CT−	0.09	0.02–0.15*
Second slope[b] for CT+	0.18	0.11–0.26*
Difference in the second slope[b] between CT+ and CT−	0.09	0.00–0.20*

Note. Included are all subjects with at least one observation in each trimester; CT = childhood trauma.

[a]The term ‘first slope’ refers to the slope of the log CRH trajectory *before* the inflection point of 19 wks gestation.

[b]The term ‘second slope’ refers to the slope of the log CRH trajectory *after* the inflection point of 19 wks gestation.

*$p < .05$