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

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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 corticotropin-releasing hormone (pCRH).

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 piece-wise linear models were employed to test hypothesized relationships.

RESULTS: Maternal CT exposure (CT+) was significantly associated with pCRH production. Compared with nonexposed women, CT+ was associated with an almost 25% increase in pCRH toward the end of gestation, and the pCRH trajectory of CT+ women exhibited an approximately twofold steeper increase after the pCRH inflection point at 19 weeks 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, Developmental programming, Intergenerational transmission, Placental CRH, Preconceptional stress, Pregnancy

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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 toward 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 corticotropin-releasing hormone (pCRH).

Childhood trauma (CT) represents one of the most pernicious stressors in our society. Estimates from the Centers for Disease Control and Prevention and others suggest that a majority of children are exposed to one or more traumatic events in their lifetimes (1,2) and that 30% to 40% of adult women have experienced at least one, and 15% to 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, drug addiction, obesity, and cardiovascular, metabolic, and autoimmune diseases (5–14). Emerging evidence now suggests that the long shadow cast by childhood trauma may not be restricted to only the life span 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 transmissions 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,

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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 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 there 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 fetoplacental stress-responsive systems, specifically the pCRH system, represents an attractive candidate pathway.

In the nonpregnant state, CRH is secreted primarily by hypothalamic paraventricular nucleus 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). pCRH is known to play a major, obligatory role in the initiation, maintenance, and progression of gestation, fetal development, and parturition (29–32). Moreover, pCRH 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 that it is sensitive to suboptimal maternal physiological, clinical, social, and environmental exposures (36–40). pCRH likely serves as a key communication signal between the mother and her as-yet-unborn child. We and others have reported that variation in pCRH 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 pCRH production across gestation after accounting for potential confounding factors. Because pCRH 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 pCRH 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 fetoplacental 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), unhealthy maternal behaviors (smoking), and unfavorable maternal psychological state (depression), to estimate the potential impact of maternal childhood trauma on fetoplacental 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 (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 Institutional Review Boards 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 five times over the course of their pregnancy at T1 15 ± .7 weeks (mean ± SEM) (range 13.3–17.5); T2 20.3 ± .8 weeks (range 17.0–23.2); T3 25.6 ± .8 weeks (range 24–27.3); T4 30.7 ± .6 weeks (range 29.6–32.4); and T5 36.5 ± .8 weeks (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 weeks 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 (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, physical abuse, sexual abuse, emotional neglect, and physical neglect. Details of scoring are described in the Supplement. Cutoff values for moderate or greater exposure were used to create dichotomous variables of exposure for each Childhood Trauma Questionnaire 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 analyses.

Placental CRH. pCRH 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