Prenatal Cocaine Exposure Related to Cortisol Stress Reactivity in 11-Year-Old Children

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Objective Determine the association between prenatal cocaine exposure and postnatal environmental adversity on salivary cortisol stress reactivity in school-aged children.

Study design Subjects included 743 11-year-old children (n = 320 cocaine-exposed; 423 comparison) followed since birth in a longitudinal prospective multisite study. Saliva samples were collected to measure cortisol at baseline and after a standardized procedure to induce psychological stress. Children were divided into those who showed an increase in cortisol from baseline to post stress and those who showed a decrease or blunted cortisol response. Covariates measured included site, birthweight, maternal pre and postnatal use of alcohol, tobacco or marijuana, social class, changes in caretakers, maternal depression and psychological symptoms, domestic and community violence, child abuse, and quality of the home.

Results With adjustment for confounding variables, cortisol reactivity to stress was more likely to be blunted in children with prenatal cocaine exposure. Children exposed to cocaine and who experienced domestic violence showed the strongest effects.

Conclusions The combination of prenatal cocaine exposure and an adverse postnatal environment could downregulate the hypothalamic-pituitary-adrenal axis resulting in the blunted cortisol response to stress possibly increasing risk for later psychopathology and adult disease. *(J Pediatr 2010;157:288-95)*.

Alterations in the reactivity of the hypothalamic-pituitary-adrenal axis (HPA) affecting cortisol levels have been related to an array of adverse outcomes ranging from medical disease to psychopathology.[1-4] In populations of at risk children, cortisol stress reactivity has been associated with low socioeconomic status (SES),[5-7] maternal depression,[8,9] maltreatment and abuse,[10-13] and exposure to community violence.[14] However, there are only 4 reports of cortisol reactivity in children with prenatal cocaine exposure. These studies have all been conducted with infants and the findings have been inconsistent.[15-18] In 2 studies, preterm neonates exposed to cocaine showed depressed cortisol responses after a standard physical examination and after a heel prick[15] and higher urinary cortisol levels compared with neonates who were not exposed to cocaine.[17] In 13-month-old infants tested before and after blood draw, prenatal cocaine exposure was associated with lower prestress cortisol.[16] Seven-month-old infants exposed to cocaine showed increased cortisol reactivity to a behavioral procedure designed to elicit arousal.[18] Cortisol reactivity in this study was also affected by instability of the infant's caregiver. Thus, among infants with higher caregiver instability those with prenatal substance exposure had higher cortisol reactivity than unexposed infants and infants with low caregiving instability. These findings suggest that postnatal environmental stress can add to the effects of prenatal cocaine exposure on cortisol reactivity.[18]

We report a study of the effects of prenatal cocaine exposure on cortisol stress reactivity in school age children. Given that children exposed to cocaine grow up in adverse environments including factors such as poverty, maltreatment, violence, parental psychopathology, and substance use,[19,20] we wanted to evaluate the possible association of prenatal cocaine exposure with cortisol reactivity in 11-year-old children, and to determine if these hypothesized associations are magnified by postnatal environmental adversity. This report is from the Maternal Lifestyle Study (MLS) multisite longitudinal cohort study on the evaluation of

BDI	Beck Depression Inventory
BSI	Brief Symptom Inventory
CD	Conduct disorder
HOME	Home Observation Measurement of the Environment
HPA	Hypothalamic-pituitary-adrenal axis
MLS	Maternal Lifestyle Study
NET	Norepinephrine transporter
ODD	Oppositional defiant disorder
SES	Socioeconomic status

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the long-term outcomes of children exposed to cocaine in utero. The 4 data collection sites are Brown University, Providence, Rhode Island; University of Miami, Miami, Florida; University of Tennessee at Memphis, Memphis, Tennessee, and Wayne State University, Detroit, Michigan.

Methods

Enrollment and exclusion criteria for the MLS have been described in detail.[21,22] The study had approval from the institutional review board at each site. Each site also had a certificate of confidentiality from the National Institute on Drug Abuse. Informed consent was obtained from all participants. Infants in the longitudinal study were selected to be in the exposed group (maternal report of cocaine or opiate use during pregnancy or gas chromatography–mass spectrometry confirmation of presumptive positive meconium screens for cocaine or opiate metabolites) or the comparison group (maternal denial of cocaine or opiate use during the pregnancy and a negative enzyme multiplied immunoassay meconium screen for cocaine and opiate metabolites). Exposed and comparison infants were group matched on race, sex, and gestational age. Mother-infant dyads (n = 1388, 658 in the exposed group and 730 in the comparison group) were enrolled in the longitudinal study at the first (1 month, age corrected for prematurity) visit.

At the one month visit, each mother was interviewed for a detailed inventory of her legal and illegal drug use during pregnancy. Prenatal cocaine use was categorized into high, some, and no use. High cocaine use referred to ≥3 times/wk use in the first trimester. Any other use was referred to as some cocaine use. Prenatal tobacco use was categorized into high (≥10 cigarettes/d), some (<10 cigarettes/d), and no use. Prenatal alcohol use was categorized into high (≥0.5 oz absolute alcohol/d), some (<0.5 oz/d), and no use. Prenatal marijuana was categorized into high (≥0.5 joints/d), some (<0.5 joint/d), and no use. For tobacco, alcohol and marijuana the per day values were calculated for the entire pregnancy. These cutoffs have been used in our previous work.[21,23] Postnatal substance use of cocaine (number days/week), cigarettes (number/day), alcohol (number drinks/day), and marijuana (number joints/day) was based on caretaker interview visits from 4 months to 11 years averaged across visits for each substance. The number of changes in primary caretaker was computed from 1 month to 11 years. Socioeconomic status (SES) was measured with the Hollingshead Index of Social Position[24,25] based on education and occupation averaged over annual visits. Child abuse was ascertained by caregiver report and defined as "Yes" if a Child Protective Services case was opened for evidence of physical and/or sexual abuse at any age from 1 month to 11 years. Domestic violence was defined as "Yes" if any physical or sexual abuse was reported by the caregiver at any annual visit. Community violence was based on the averaged scores of 2 questionnaires; child-report Things I've Seen and Heard at age 8[26] and caregiver-report Survey of Exposure to Community Violence at age 9.[27] Caretaker psychological distress was the averaged number of psychological symptoms above clinical cutoff on the Brief Symptom Inventory (BSI)[28] at 4 and 30 months and 4½ -, 9-, and 11-year visits. Depression was the averaged scores on the caregiver report Beck Depression Inventory (BDI) at 4 and 30 months and 4½ -, 7-, 9-, and 11-year visits. The quality of the home environment was based on averaged scores on the Home Observation Measurement of the Environment (HOME Scale)[29] during home visits at the 10 months and 5½ ,- and 9-year visits.

Cortisol stress reactivity was measured based on an expanded version of the Trier Social Stress Test[30] administered at age 11. The Trier task is a standardized protocol for the induction of moderate psychosocial stress in laboratory settings and has been widely used in children and adults as well as in clinical populations.[31,32] The Trier is a motivated performance task consisting of a preparation period (5 minutes) followed by a test period in which the subject has to deliver a free speech (5 minutes) and perform mental arithmetic (5 minutes) in front of an audience. With this, the total exposure time adds up to 15 minutes. We added a mirror tracing task[33,34] to provide a challenging nonverbal performance task. In this 5 minute task, the child used a mirror that reversed directionality as they traced the figure of a 6-sided star. The apparatus beeped for each error and the child was instructed to begin again.

Four saliva samples were collected. The prebaseline sample was collected 20 minutes before the start of the Trier task. The prebaseline task was a computerized task of executive function that was familiar to the children. The baseline sample was collected just before the start of the Trier test. The baseline task (between the first two samples) was an interview conducted by a research assistant on topics that were innocuous and familiar to the child from previous visits (eg, Extracurricular Activities). The first reactivity sample was collected at the end of the mirror tracing task (20 minutes from the onset of the Trier) and the second reactivity sample was collected 20 minutes after the end of the mirror tracing task. During this period, we conducted a debriefing interview with the child, where the research assistants explained the purpose of the tasks and reassured the child that they performed well. Previous research is inconsistent as to whether cortisol levels peaked at 20 minutes post stress onset then recover to baseline levels at 40 minutes or are maintained at the same level 20 to 40 minutes after stress onset.[35,36] Thus we collected cortisol samples at both 20 and 40 minutes after stress.

To collect the samples, the child deposited saliva through a straw directly into a 2-mL vial for each of the four specimens. Ideally, the samples were ≥1.0 mL, but 0.5 mL was accepted if collection time was over 3 minutes. The vials were all pre-labeled with study site, ID and sample type with unique barcodes (provided by Salimetrics, LLC, State College, Pennsylvania). Samples were immediately placed in a −20°C freezer until shipped on dry ice to Salimetrics Laboratory (Salimetrics, LLC) for assay. All samples were assayed in duplicate for salivary cortisol using a highly sensitivity cortisol enzyme immunoassay kit. Each test uses 25 μL of saliva,