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Prenatal cocaine exposures and dose-related cocaine effects on infant tone and behavior

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Abstract

Background: In experimental models, prenatal cocaine exposure has been found to perturb monoaminergic development. In humans, numerous studies have sought clinical correlates, but few have focused on dose-related effects, especially as regards neurologic function beyond the neonatal period.
Objective: To assess whether prenatal cocaine exposure has adverse effects on infant neurologic, developmental and behavioral outcomes and whether any effects are dose-dependent.
Design/Methods: Infants (398) were enrolled at birth from an urban hospital. Drug exposure was ascertained with biomarkers in hair ($n=395$), urine ($n=170$) and meconium ($n=109$). Children were followed prospectively and 286 (72%) were evaluated blind to drug exposure at 6 months of age with the Bayley scales, Fagan Scale of Infant Intelligence and a standardized neurological examination.
Results: Certain neurological findings increased significantly by the amount of cocaine detected in maternal hair, e.g. abnormality of tone, as indicated by extensor posture was detected among 28% of cocaine-unexposed infants, 43% of infants exposed to lower and 48% exposed to higher cocaine levels in maternal hair ($p<0.009$). Persistent fisting increased in a similar dose-dependent manner. These associations persisted in adjusted analyses. Prenatal cocaine exposure was not associated with developmental scores (mental, motor or novelty preference) but was associated with lower orientation scores in adjusted analyses.
Conclusions: At 6 months of age, prenatal cocaine exposure was associated with abnormalities of tone and posture and with lower orientation scores. Perturbations in monoaminergic systems by cocaine exposure during fetal development may explain the observed neurological and behavioral symptoms. Whether such findings in infancy increase the risk of later neurobehavioral problems requires further study.

Keywords: Perinatal; Cocaine exposure; Drug use; Hypertonia; Child development

1. Introduction

Although cocaine use has declined since the height of the epidemic in the 1980's, it remains a major public health problem in urban centers in the United States, where a high level of use continues. Earlier studies of *in utero* cocaine-exposed infants, which exaggerated risks to exposed offspring, were limited by lack of controlled analyses and by the lack of biological markers that quantified exposure in a cumulative manner (i.e. meconium or hair analyses). Over the last 10 years numerous controlled studies have identified developmental and behavioral differences associated with prenatal cocaine exposure. Developmental delays linked with prenatal cocaine exposure have included cognitive differences [1,52] and language delays [44,35]. Motor delays are the most consistently reported finding among cocaine exposed children [2],

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with [22,43]prenatal cocaine exposure predicting poorer fine motor development skills at age 2, particularly in hand use and eye-hand coordination [2]. Others, however, have failed to identify developmental or cognitive effects associated with prenatal cocaine exposure after controlling for confounders [41,53,25,24,51,27].

From a behavioral perspective, a convergence of experimental and clinical studies suggest that prenatal cocaine exposure disrupts the development of arousal and attention [39]. Cocaine-exposed infants exhibit a preference for higher rates of stimuli [29] excessive irritability [39] and dose-related perturbations in orientation and state regulation [17]. Exposed toddlers and grade school children show differences in task persistence and sustained attention [3,32,18,47], problems with impulse control [7], temperamental differences [50], and aggressive/hyperactive behaviors [8,19,55].

A handful of studies have prospectively assessed neurological function among cocaine-exposed children beyond the newborn period [26,36,15,6] and even fewer have quantified fetal exposure [36,16]. Lewis et al. describe higher rates of a suspect or abnormal neurological examination among cocaine exposed toddlers, but the authors did not further define the nature of neurological abnormalities [36,15]. Other have described muscle tone abnormalities, hypertonia in particular, among cocaine-exposed infants and toddlers [36,15,6,16,34]. We described hypertonia among infants at risk for HIV with cocaine exposure that resolved by 24 months [15], but were unable to control for confounding exposures, especially tobacco exposure, which has been linked to hypertonus [20].

The current study was designed to assess the effect of cocaine exposure on neurological, developmental and behavior outcome. The primary hypothesis was that children with prenatal cocaine exposure would exhibit higher rates of neurological, developmental and behavioral impairments compared to cocaine-unexposed children of comparable demographic background after controlling for confounding factors. We also hypothesized that risks would be dose dependent with higher rates of abnormalities observed with higher levels of cocaine exposure. We report on the neurologic, developmental and behavioral outcomes of infants enrolled prospectively at delivery in a longitudinal study, in whom prenatal exposure to cocaine and other drugs of abuse was determined at the time of birth with multiple biomarkers.

2. Methods

2.1. Participants

Beginning in May 2000 through November 2004 we prospectively enrolled women–infants dyads from a municipal New York City hospital at the time of delivery as part of a prenatal drug exposure study. Informed consent was obtained at the time of enrollment. The study was approved by the Columbia Institutional Review Board. Women were eligible if English speaking, non-HIV infected, and had no history of intravenous drug abuse, psychosis or bipolar disorder (as determined by chart review). Infants were eligible if >33 weeks gestational age, free of major congenital malformation and birth asphyxia (5 min Apgar >4). As we were recruiting at the time of delivery, enrollment was confined to a narrow window of opportunity that was contingent on maternal health (i.e. postpartum complications) and early discharge, as well as to staff absences due to vacation or illness. Hence, of women delivering at the hospital (n=3671), we approached 2308 : 675 were eligible and 1633 were ineligible primarily due to language constraints (non-English speaking).

Of eligible women approached for enrollment (N=675), 277 refused. We enrolled 398 women–infant dyads (59%) into the study; of these, two were excluded due to medical factors (HIV and Trisomy 21) and 16 withdrew from the study. The final cohort thus comprises 380 mother–infant pairs. We excluded 10 opiate-exposed children from the controlled analyses.

To assess whether our sample was representative of the targeted population, we compared the group that refused enrollment to our group of enrollees via chart review. Among offspring, we found no differences in gender, birth weight, birth length, or type of delivery (vaginal versus cesarean section) between groups (data not shown). Women who refused enrollment, however, were approximately a year and a half older (25.8 years±6.6) than women enrolled in the study (24.2 years±5.8, p=.007).

2.2. Procedures

Women were interviewed soon after delivery with a structured protocol that inquired about demographic information, obstetrical and medical history and drug use during and prior to the index pregnancy. The instrument, developed by Kline et al has proven sensitive in quantifying reported drug use during pregnancy [16,46,31]. Women were also administered an IQ test and a depression scale. Biological markers of drug exposure were obtained at time of delivery (hair in all, meconium and urine in a subset).

Women and their infants were invited for follow-up at 6 months of age for neurological and developmental assessment. Two hundred and eighty six infants (75% of those enrolled) were brought in for their 6-month assessment. Of these, 276 were accompanied by their biological mothers, four were accompanied by biological fathers, five by grandmothers and one by a foster mother. Comparisons between those who returned for the 6 month follow-up visit (n=286) and those who did not (n=94) revealed no significant differences in maternal age, race, education, welfare status, marital status, gravity, parity, ectopic pregnancies, stillbirths, alcohol, marijuana or cigarette use (data not shown). Women who did not return were more likely to have used cocaine during pregnancy (42% vs. 28%; p=.005) and to be unemployed (62% vs. 46%; .002) compared to women who returned for the 6 month follow-up.

2.3. Measures

2.3.1. Maternal

Caregivers were administered an IQ test that relied upon the Vocabulary and Matrix Reasoning subtests of the Wechsler