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# Dysmorphic and anthropometric outcomes in 6-year-old prenatally cocaine-exposed children

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**Abstract**

Dysmorphologic and anthropometric assessments were performed on 154 6-year-old children prenatally exposed to cocaine (PCE) and 131 high-risk controls (NCE) of similar race and social class. Adjusted mean height *z* scores demonstrated a dose–response with metahydroxybenzoylecgonine above a threshold of 100 ng/g of meconium and greater cocaine exposure predicted lower weight for height *z* score. Higher average alcohol exposure throughout pregnancy and 3rd trimester predicted lower head circumference and weight *z* scores, respectively. Severity of marijuana use also predicted lower height for age but greater weight for height. There was not an increased rate of minor anomalies among the PCE cohort, nor was a consistent phenotype identified. After controlling for covariates, higher average prenatal cigarette exposure predicted higher incidence of cranial facial abnormalities. First trimester alcohol exposure predicted greater rates of ear abnormalities and third trimester marijuana exposure predicted greater rates of chest and head shape abnormalities. These finding indicate that prenatal cocaine exposure has a negative effect on specific growth outcomes including standardized height and weight for height, but not a systematic pattern of structural abnormalities.


*Keywords:* Dysmorphology; Prenatal cocaine-exposure; Anthropometric; Height; Cocaine metabolite; Meconium

## 1. Introduction

Prenatal cocaine exposure (PCE) has been associated with a variety of adverse peri- and neonatal effects [32]. Included among these are prematurity, low birth weight, microcephaly, and newborn neurobehavioral abnormalities [35,37]. Vasoconstrictive effects of cocaine on the placenta [39] have raised additional concerns including increased dysmorphologic abnormalities and birth defects among exposed children. It is believed that disruptions in fetal blood flow could result in various structural abnormalities during gestation [17,32], depending on the severity and timing of cocaine exposure. However, the association between prenatal cocaine exposure and dysmorphologic abnormalities has been reported sporadically through case studies and research reports, and has not been replicated in well controlled studies at ages beyond birth. For example, Bingol et al. [7] reported an increased rate of major anomalies (exencephaly, encephalocoele) among PCE newborns compared to controls (non-drug exposed and those exposed to other drugs). They noted no difference in the occurrence of minor anomalies, such as hypertelorism, epicanthal folds, and micrognathia. In another study Hoyme et al. [18] reported on a small cohort of cocaine-exposed newborns with limb reduction defects and/or intestinal atresias, and suggested that in utero cocaine exposure may be causally related to these vascular anomalies. However, a large-scale prospective study that controlled for a large number of covariates does not support these findings. Behnke et al. [6], using 16 anthropometric measurements and a checklist of 180 physical features, in 154 prenatally cocaine-exposed infants

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and 154 non-using controls, did not identify an increased number or consistent pattern of abnormalities.

Related to fetal growth however, there are consistent findings indicating that after consideration of a large number of covariates, prenatal cocaine exposure has specific effects on infant birth parameters including head circumference, weight and length [4,5,9,11,12,31,37,41]. Growth deficits are believed to result from poor maternal nutrition, restricted placental blood flow or some other unknown mechanism. But not all studies have found a specific cocaine effect for fetal growth. Jacobson et al. [19] and Miller et al. [25] found that after control for other substances there were not weight or length differences specifically related to prenatal cocaine exposure. In later childhood (>1 year) research on cocaine effects on growth outcome is limited, and the results are contradictory. Jacobson et al. [20] reported an independent effect of prenatal cocaine exposure on weight, but not height at 13 months. Richardson [29] found an effect of prenatal cocaine exposure on head circumference, but not weight and height at 3 years of age after control for demographic and other substance exposure. In another study by Richardson et al. [30] no effect of prenatal cocaine exposure on height, weight, or head circumference was found at 6 years of age. In the only report on growth parameters at 7 years of age, after control for other exposures and demographic variables, Covington [11] found that cocaine-exposed children were up to 1 in. shorter and twice as likely to fall below the 10th percentile in height compared to controls. This relationship was mediated by maternal age, with children born to women over 30, 2 in. shorter and four times more likely to have clinical height deficits.

The possible association of PCE with a recognizable pattern of physical findings was suggested by Fries et al. [13] and Robin and Zackai [33]. Each described similar facial and other physical findings in PCE infants that could be distinguished from those associated with prenatal exposure to alcohol or other drugs. These findings included a large anterior fontanel, prominent glabella, periorbital and eyelid edema, low nasal bridge with transverse crease, short nose with lateral buildup, and hypoplastic toenails. The authors concluded that PCE may cause a distinct phenotype. However, this assertion was challenged by a subsequent study. Little et al. [24] examined 25 prenatally cocaine-exposed newborns and 25 controls blinded to their cocaine status. They did not identify a higher rate of major or minor anomalies among the PCE children. However, they did find growth retardation and microcephaly among the PCE newborns. While this study examined both dysmorphia and growth retardation, it was limited in several ways. The study included a relatively small cohort, and was restricted to newborns. Some subtle findings may be difficult to identify in infants, or may be apparent only in older children. In an effort to explore the relationship between in-utero cocaine exposure and physical anomalies, we performed anthropometric and dysmorphologic examinations on a large sample of prenatally cocaine-exposed 6-year-old children and a high-risk control group. In addition to having a large sample size, determination of cocaine status was made through infant meconium analyses at birth, insuring correct subject grouping. It was hypothesized that children exposed to cocaine would exhibit a higher rate of dysmorphic features and maintain growth deficits identified at infant birth compared to a control group similar in race, social class and high-risk status at birth.

## 2. Methods

### 2.1. Participants

Between September 1994 and June of 1996, 415 infants (218 prenatally cocaine-exposed (PCE) and 197 non-cocaine-exposed (NCE)) were recruited from a large urban teaching hospital to participate in a longitudinal follow-up study evaluating the developmental effects of prenatal cocaine exposure from birth through 6 years of age [36]. Women determined to be at risk for prenatal substance abuse due to previous involvement with the Department of Human Services, lack of prenatal care, behavior suggesting intoxication, or self admitted drug use, were given urine drug toxicology screenings (99%). The Syva Emit method (Syva Company, Palo Alto, CA) was used for urine analyses. Positive analyses were followed up with gas chromatography. A nurse recruiter approached women screened for substance abuse. Of the women and infants identified (647), 54 were excluded (20 PCE; 34 NCE) for the following reasons: no meconium sample (15), Down Syndrome (2), maternal psychiatric history (16), primary heroin use (2), HIV positive (5), maternal low IQ (1), fetal alcohol syndrome (1), maternal age <19 years (2), infant medical illness or congenital malformation (3) maternal chronic illness (4) and other (3). One hundred and fifty five women refused to participate (49 positive, 106 negative) and 23 (9 PCE, 14 NCE) failed to come to the enrollment visit. Four hundred and fifteen women and their infants enrolled in the study. Upon agreement to participate in the study, women signed a consent form approved by the hospital's institutional review board.

For study participants, an additional biologic marker of cocaine/polydrug use, infant meconium, was collected for analyses of cocaine and its metabolites (benzoylecgonine (BZE), meta-hydroxybenzoylecgonine (m-OH-bze). Cocaethylene, a metabolite present when cocaine and alcohol are used in combination, as well as other drugs of abuse including cannabinoids (THC), opiates, phencyclidine, amphetamines, and benzodiazepines [22,28] were also assessed. Meconium sampling was completed by collecting successive diapers from the same newborn and scraping the meconium from the diaper with a wooden spatula. The sample was stirred for 5 min to insure homogeneity and kept refrigerated until analysis. Assays were completed using Abbott Diagnostic polarization immunoassay reagents (FPIA) (United States Drug Testing Laboratories, Des Plaines, IL). Cutoff levels for cocaine and metabolites were 25 ng/g. Confirmatory assays were performed on positive screening assays using gas chromatography-mass spectrometry (GC/MS) operated in electron impact, selected ion monitoring mode. Cocaine exposure status was identified by a positive response on any of the following measures: infant meconium or urine, maternal urine, or report to hospital or