Published in final edited form as:
Neurotoxicol Teratol. 2008 ; 30(2): 96–106.

The Effects of Prenatal Cocaine Use on Infant Development

Gale A. Richardson, Ph.D.[a], **Lidush Goldschmidt, Ph.D.**[b], and **Jennifer Willford, Ph.D.**[a]
Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 15213

Abstract

This study examined the effect of prenatal cocaine use on infant physical, cognitive, and motor development, and temperamental characteristics, controlling for other factors that affect infant development. Women were, on average, 26.8 years old, had 12 years of education, and 46% were African American. During the first trimester, 18% were frequent users of cocaine (≥ 1 line/day). The infants were, on average, 14.6 months old at this follow-up phase. Women who used cocaine during pregnancy rated their infants as more fussy/difficult and unadaptable than did women who did not use cocaine. Cocaine use in the second trimester was associated with significantly lower motor scores on the Bayley Scales of Infant Development (BSID) [9]. There was no effect of prenatal cocaine use on BSID mental performance or on growth. These findings are consistent with other reports in the literature and with the hypothesis that prenatal cocaine exposure affects development through changes in neurotransmitter systems.

Keywords

prenatal cocaine exposure; infant development; growth; cognitive development; motor development; temperament

1. Introduction

In the 2003 National Household Survey on Drug Abuse, 12.4% of 18- to 25-year-old women reported they had ever used cocaine and 5% reported use during the past year [87]. Rates of prenatal cocaine use have varied from 1% in the National Pregnancy and Health Survey [64] to 2.6% in a partially rural sample from Florida [33] to 18% in an inner-city sample from Boston [96]. In our longitudinal study of prenatal cocaine exposure (PCE), 8% of women attending a prenatal clinic reported first trimester cocaine/crack use [70]. Thus, the effects of prenatal cocaine use on infant development are an important public health issue.

While the majority of the research on PCE has focused on neonatal effects, some investigations have explored the effects of PCE during the infancy period. One outcome of interest has been the growth of offspring exposed to cocaine. Chasnoff et al. [20] compared the offspring of three groups of women at 3, 6, 12, 18, and 24 months: (1) cocaine, alcohol, and marijuana users, (2) alcohol and marijuana users, and (3) non-drug-users. In the two drug-exposed groups, the average head circumferences were smaller compared with the non-drug-exposed infants at

Correspondence should be sent to: Gale A. Richardson, Ph.D., Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213: telephone: 412-681-3482; fax: 412-246-6875; e-mail: gar@pitt.edu.
[a]University of Pittsburgh School of Medicine
[b]University of Pittsburgh Medical Center

each follow-up point, although the two drug groups did not differ from each other. Hurt et al. [41] reported that cocaine-exposed infants had reduced weight and head circumference at 6, 12, 18, and 24 months, but there was no control for factors such as prenatal care, or prenatal alcohol and tobacco use. By contrast, Jacobson, Jacobson, and Sokol [42] found no effects of PCE on weight, length, or head circumference at 6½ months, and in the same study at 13 months, PCE was associated with increased weight. Brown et al. [13], Chiriboga, Kuhn, and Wasserman [21], Fetters and Tronick [34], and Kilbride et al. [48] also reported that there were no effects of PCE on growth during infancy.

Researchers have also investigated the effects of PCE on infant cognitive and motor development. There have been consistent reports of no detrimental effects of PCE on global cognitive development during infancy, as measured by the Mental Development Index (MDI) of the Bayley Scales of Infant Development (BSID [9] and BSID-II [10]) [4,12,13,20,21,32, 36,41,43,48,58–60,65]. Only a few studies have reported detrimental effects on MDI scores. Alessandri, Bendersky, and Lewis [2] found an effect of PCE on the MDI at 18 months of age, but not at 8 months. Singer et al. [82], in a sample recruited from a high-risk follow-up clinic, reported that prenatal exposure to cocaine was associated with lower MDI scores at approximately 17 months of age. In a different sample, Singer et al. [83] also found decreased MDI scores at 12 and 24 months of age, after controlling for covariates of PCE. Behnke et al. [11] found that PCE predicted 6-month development, defined as a latent construct including MDI and PDI.

Most investigators have also not found detrimental effects of PCE on infant motor development, as measured by the Psychomotor Development Index (PDI) of the BSID or by the Peabody Developmental Motor Scales [2–4,12,13,21,34,36,41,43,58–60,65,83]. By contrast, Singer et al. [82] found that PCE was associated with lower PDI scores at about 17 months. Fetters and Tronick [34] found that infants who were prenatally exposed to cocaine had poorer motor performance on the Movement Assessment of Infants at 7 months of age. Miller-Loncar et al. [62] reported that PCE was associated with poorer motor skills: The exposed group showed gross motor deficits early in infancy, but by 18 months were not different from the comparison group.

Only a few investigators have studied the effects of prenatal cocaine use on infant temperament. Mayes et al. [58] reported that 3-month-old infants who were exposed to cocaine prenatally were more fussy and irritable during an information processing task than were non-exposed infants. Edmondson and Smith [32] found that 6-month-old infants who were prenatally exposed to cocaine were reported by their mothers to be more difficult (defined as uncooperative and arrhythmic) than non-exposed infants. However, in that study, there was no statistical control for other factors that differed between the exposed and non-exposed groups. By contrast, Arendt et al. [4], Frank et al. [36], and Messinger et al. [60] did not find an effect of PCE on trained assessors' ratings of the infant's behavior, such as activity level, task orientation, or emotion regulation, as assessed during the BSID administration.

The inconsistencies in this literature could be due to a number of methodologic limitations, including: 1) failure to control for differences in the demographic composition, health and nutritional status, amount of prenatal care, and prenatal alcohol, marijuana, and tobacco use between exposed and non-exposed groups [70]; 2) the methods used to ascertain drug use [74]; 3) recall bias in studies that use retrospective reporting at delivery or in the postpartum period of drug use over the entire pregnancy; and 4) high rates of subject loss and differential rates of attrition between exposure groups. These factors limit the conclusions that can be drawn from these studies and may seriously bias the interpretation of the findings.

The present research is a longitudinal, prospective study of cocaine use during each trimester of pregnancy. This study overcame the methodologic problems of some previous studies in the following ways: 1) the sample, drawn from a group of women attending a large prenatal clinic, represented a general population rather than a sample of women in drug treatment; 2) recall bias was minimized by interviewing the women regarding their substance use at the end of each trimester, and all women were interviewed at the same time points; 3) the quantity, frequency, mode, and pattern of cocaine, crack, alcohol, marijuana, tobacco, and other drug use were assessed for each trimester of pregnancy; and 4) data were collected on demographic factors, home environment, and lifestyle of the mothers, allowing for control of potential confounding variables. The purpose of this report is to evaluate the effects of prenatal exposure to cocaine on infant physical, cognitive, and motor development, and temperamental characteristics.

2. Methods

2.1. Study Design

The study sample consisted of women and infants participating in a longitudinal investigation of the effects of prenatal cocaine/crack use. Written consent was obtained for both mothers and infants according to guidelines established by the University's Institutional Review Board and by the Research Review and Human Experimentation Committee of Magee-Womens Hospital. A Confidentiality Certificate, obtained from the Department of Health and Human Services, assured participants that their responses could not be subpoenaed.

Women who were at least 18 years of age were initially interviewed when they came for prenatal care during their fourth or fifth prenatal month. During this interview, information was obtained about the use of cocaine and crack in the year prior to pregnancy and during the first trimester, as well as the use of tobacco, alcohol, marijuana, and other illicit substances during the same time periods. All women who reported any cocaine or crack use during the first trimester were enrolled. The next woman interviewed who reported no cocaine or crack use both during the year prior to pregnancy and during the first trimester was also enrolled.

Women selected into the study were interviewed at 7 months and at 24 hours postdelivery about their substance use during the second and third trimesters, respectively. Demographic, life-style, and psychological characteristics were also assessed at each phase. All infants underwent comprehensive physical examination, generally within 24 to 48 hours of delivery, by study nurse clinicians who were unaware of prenatal exposure status. The infant's length and head circumference were measured and gestational age was assessed with a modification of the Dubowitz assessment [5]. Birth weight was transcribed from the medical records.

At approximately 1 year postpartum, mothers brought their babies to our project offices for assessment. Infants who had been born prematurely were scheduled according to their adjusted chronological age. A physical exam was conducted, the infant's growth was measured, and the infant's medical history, including injuries, illnesses, and hospitalizations, was obtained from the mother. Mental and motor development were assessed with the BSID MDI and PDI, respectively [9], by the nurse clinician or a psychology graduate student trained to administer the BSID. (The BSID-II was not available at the initiation of the 1-year follow-up.) The examiners also completed the Infant Behavior Record (IBR) of the BSID, after the administration of the BSID. The IBR is a rating of the examiner's perception of the infant's cooperativeness, fearfulness, responsiveness to people and objects, attention span, activity, and reactivity. On the IBR, examiners also rated the adequacy of the BSID as an indicator of the child's characteristics. Examiners were blind to prenatal and current substance use status.

Mothers were interviewed about their substance use during the last year, and about their demographic, social support, household composition, and psychological characteristics. Maternal depression was assessed using the Center for Epidemiological Studies - Depression Scale [68] and hostility was measured by the Spielberger State-Trait Anxiety Inventory [84].

The mother's view of the infant's temperament was measured using the Infant Characteristics Questionnaire (ICQ) [7]. This scale consists of 32 items rated on 7-point scales describing four dimensions of temperament: fussy/difficult, unadaptable, persistent, and unsociable. The scale has been used extensively in research and has been demonstrated to have adequate reliability. Cronbach's alphas for the current sample were 0.73, 0.71, 0.72, and 0.41 for the fussy/difficult, unadaptable, persistent, and unsociable scales, respectively. The unsociable scale was eliminated from the analyses because of the low alpha.

Information on the home environment was obtained from the PROCESS scale [18]. The developmental stimulation subscale includes items such as the amount of time spent talking with the child and helping the child to learn new skills. The organization subscale includes items that reflect the regularity of the child's eating and sleeping habits. Cronbach's alphas for the current sample were 0.60 and 0.46 for the developmental stimulation and organization scales, respectively. The organization scale was eliminated from the analyses because of the low alpha.

2.2. Sample Characteristics

Women were recruited for the study between March 1988 and December 1992. Ninety percent of those approached agreed to participate. Medical chart reviews of a random sample of women who refused to participate indicated that only 5% had a history of drug use during the current pregnancy. Of the women initially interviewed, 320 (18%) met the inclusion criteria and were enrolled into the study. Between enrollment and delivery, subjects were eliminated for the following reasons: home delivery (N = 1), miscarriage/abortion/fetal death (N = 5), moved (N = 11), lost to follow-up (N = 1), and refused (N = 2). Thus, delivery assessments were completed on 300 women. Four pairs of twins and 1 child with Trisomy 21 were excluded from additional follow-up, resulting in a birth cohort of 295 mothers and infants. Births occurred from 1988 to 1993.

From birth to the 1-year follow-up phase, 4 children died, 4 mothers lost custody and the children could not be traced, 6 families moved out of state, 7 mothers refused to participate, and 13 were lost to follow-up. The 261 subjects interviewed at the 1-year follow-up represented 89% of the birth cohort (N = 295). Two percent of the children were not in the custody of their biological mother at the 1-year follow-up. In these cases, the current caretaker was interviewed. The 1-year follow-up was conducted from 1989 through 1995.

One infant who was unable to be tested and one infant who was assessed at home under detrimental conditions were excluded from the BSID analyses. Thus, the final cohort for the growth and temperament analyses included 261 mothers and infants; the BSID analyses included 259 mothers and infants. The mothers who were not included in the 1-year analysis had less education at the initial prenatal interview than those who were included in the analysis (11.6 vs. 12.0 years, $p < .05$). There were no other significant differences in maternal sociodemographic, prenatal substance use, or infant birth characteristics between those who were included in this analysis and those who were not.

At birth, the mean gestational age was 39.7 weeks (range = 26 – 44). Six percent of the infants were premature (< 37 weeks). The mean birth weight was 3271.9 grams (range = 930–5600). At the 1-year follow-up, the median infant age at assessment was 13.8 months (mean = 14.6 months; range = 11 – 23; SD = 2.5). Ninety percent were seen by 18 months of age. Fifty-four

percent of the infants were male. The average weight was 23.4 pounds (range = 17.3 – 32), height was 30.6 inches (range = 26 – 35), and head circumference was 18.6 inches (range = 17–20). The mean Mental Development Index (MDI) and Psychomotor Development Index (PDI) of the BSID were 114 (range = 52 – 150; SD = 17) and 113 (range = 62 – 150; SD = 17), respectively.

At the 1-year follow-up, the women were, on average, 26.8 years old (range = 19 – 57), 54% were Caucasian, and 46% were African American. Women were of lower socioeconomic status, with a median family income of $550 per month and an average educational level of 12.1 years (range = 9 – 18). Twenty-seven percent of the women were married and 38% worked or went to school.

2.3. Substance Use Measurement

For each substance, women were asked about the usual, maximum, and minimum quantity and frequency of use. In addition, we developed a technique to enhance the accuracy of reporting of first trimester substance use. Women often do not change their substance use patterns until after they have confirmed their pregnancy, which may not occur until late in the first trimester. Therefore, we asked women detailed information about the time periods from conception to recognition, and from recognition to the diagnosis of the pregnancy, in order to get detailed substance use information for the first trimester. We also asked whether their use during these time periods was more like what they had reported for prior to pregnancy use or more like their reported first trimester use. This allowed calculation of substance use during each month of the first trimester and a weighted estimate of the average daily use for the first trimester. For second and third trimester use, women reported use over the entire trimester. These methods have also been used in our previous research on prenatal alcohol and marijuana exposure [27].

2.4. Data Analysis

The quantity of cocaine or crack use was reported by the women in lines, grams, or rocks. Reported use of lines or rocks was converted into gram equivalents in the following way: one line was estimated as 1/30th (0.03) of a gram; one rock of crack was estimated to be equivalent to 0.2 grams. These estimates were based on information from toxicology laboratories and law enforcement officials in Pittsburgh. Usual, maximum, and minimum quantity and frequency of cocaine/crack use were converted into the average number of grams per day. For descriptive purposes, cocaine use was converted back to lines per day. The alcohol and marijuana variables were expressed as average number of drinks or joints per day, respectively, and tobacco as number of cigarettes per day. These variables were ascertained separately for each trimester of pregnancy. For the multiple regressions, first trimester substance use variables were used as continuous variables. For the second and third trimester analyses, alcohol, marijuana, and tobacco use were continuous variables. Cocaine use was dichotomized into use/no use for the second and third trimester analyses because the number of women who used during these trimesters was small and did not adequately represent the spectrum of use for the regression analyses.

The outcome variables for the growth analyses were unadjusted weight, height, and head circumference. The analyses were also run using age- and gender-adjusted Z scores for weight, height, and head circumference [19], eliminating age and gender as covariates from the models. Age-adjusted scores were used for the MDI and PDI of the BSID for the infants who had been born prematurely (< 37 weeks). The IBR was analyzed using the factors defined by Matheny [55,56]: task orientation, affect, and activity. The ICQ variables were fussy/difficult, unadaptable, and persistent [7].

The first step in the analyses was to use stepwise multiple regression analyses to select significant covariates for the final model. To explore the stability of the variables entering the regression model, the initial significance level of entry and removal of the variables was set to 0.10. For the final model, only variables that were significant at an alpha level of 0.05 were retained. The covariates considered for inclusion in the analyses are listed in Table 1. They represent infant characteristics, maternal sociodemographic and psychosocial characteristics, environmental variables, and maternal prenatal and current substance use. These domains were selected because of their association with the outcomes and/or cocaine use, and based on findings in the literature and prior analyses of these data. A stepwise regression was used to obtain the most parsimonious set of covariates related to the outcomes.

In the second step of the analyses, PCE was forced into the model containing the significant covariates, regardless of its significance. Because this is a study of the effects of a potential teratogen, all regressions were run separately for the first, second, and third trimesters to assess the effects of exposure during each time period. For the final regression models, residuals and the modified Cook's statistic [22] were used to identify possible outliers and influential points. This report includes only those effects due to cocaine that remained stable after removal of the influential cases. There was one influential point for each of the following outcomes: fussy/difficult, unadaptable, persistent, and MDI. In addition, the tolerance of each predictor (a measure of intercorrelation among the predictors) was examined to assure that the effect size was not due to multicollinearity.

A descriptive group analysis was also conducted to investigate the impact of duration of cocaine use. Three groups were defined: women who abstained from cocaine throughout pregnancy ("Never") (N = 144); those who used first trimester only ("Stopped") (N = 61); and those who used both first and third trimesters ("Continued") (N = 28).

3. Results

3.1. Descriptive Analyses

The prevalence of cocaine/crack use is described in Table 2. For descriptive purposes, women who reported using one or more lines of powder cocaine per day, or the equivalent in crack, were classified as frequent users. Women who reported less than one line per day of cocaine (or the equivalent in crack) were classified as occasional users. Abstainers were women who did not use cocaine. During the first trimester, 18.4% of the women were frequent users. The prevalence of reported cocaine use declined over pregnancy. Only 13% of the women who used first trimester also used second and third trimester. By the third trimester, 6.2% of the women were frequent users. All of the women who used second and third trimester had used first trimester. The prevalence of frequent cocaine use did not change significantly during the first year postpartum from that of the third trimester.

The sociodemographic characteristics and other substance use associated with first trimester cocaine use are shown in Table 3. Women who used cocaine during the first trimester were significantly more likely to be older, African American, single, less likely to be working or attending school, and to have lower incomes than the women who did not use first trimester. First trimester cocaine users were also more likely to use alcohol, cigarettes, marijuana, and other illicit drugs than were the first trimester non-cocaine users. For example, 55% of the women who used cocaine also used marijuana compared with 17% of the women who did not use cocaine, and the women who used cocaine drank an average of 2 drinks/day compared with 0.4 drinks/day for those who did not use cocaine. These same characteristics also applied to the women who continued to use during the third trimester (Table 3). One notable difference is that the women who continued to use cocaine in the third trimester were much more likely

to be African American than were the women who never used and than those who used cocaine first trimester and then discontinued their use later in pregnancy.

Infants who were exposed to cocaine during the first trimester had lower gestational age and birth weight compared to those infants who were not exposed during the first trimester (Table 4). They also were more likely to be premature and low birth weight, to have lower PDI scores, and to have been rated as more fussy/difficult and unadaptable by their mothers on the ICQ. The infants who were exposed throughout pregnancy had lower PDI scores and were rated as more fussy/difficult and unadaptable than were the infants who were exposed first trimester only or who were never exposed (Table 4).

As shown in Table 5, women who used cocaine/crack at the 1-year follow-up were older, less likely to be married, and more likely to report symptoms of hostility than were women who did not use cocaine at the 1-year phase. Cocaine users also provided less stimulating home environments, as measured by the PROCESS scale [18], and were more likely to use alcohol, cigarettes, and marijuana than were women who did not use cocaine at the 1-year phase.

3.2. Regression Analyses

3.2.1. Growth—There were no effects of prenatal cocaine/crack use on weight, height, or head circumference at the 1-year follow-up. Table 6 presents the results with the raw growth scores, controlling for age and gender. The same results were obtained using the Z scores. Two additional regression models were run, one including gestational age and one including birth weight: There were no changes from the original model in the effects of PCE. Significant predictors of increased growth included older child age at assessment, gender (male), and maternal height. Decreased growth was predicted by maternal depression, and prenatal tobacco and alcohol use. The amount of variance explained by the models that did not include birth weight or gestational age was 22% for weight, 47% for height, and 34% for head circumference. The effects of prenatal tobacco use on height at the 1-year assessment were no longer significant when birth weight was added to the model. Thus, the effects of prenatal tobacco exposure on height were mediated by the effects of tobacco use on birth weight.

3.2.2. BSID—PCE was not a significant predictor of the BSID mental development scores (Table 7). Significant predictors of higher MDI scores were higher scores on the PROCESS developmental stimulation scale, Caucasian race, and the examiner's judgement of the assessment as being an average to excellent indicator of the child's ability. Lower MDI scores were predicted by older age of the child at assessment, more children in the household, the presence of a male in the household, and prenatal alcohol use.

Second trimester cocaine use was a significant predictor of poorer psychomotor development scores, when controlling for all other significant covariates (Table 7). Lower PDI scores were also predicted by older age at assessment, prenatal alcohol exposure, and more children in the household. Prenatal cocaine use was not a significant predictor of the IBR factors. The amount of variance explained by the models was 31% for the MDI, 13% for the PDI, and from 2 to 4% for the IBR.

3.2.3. Temperament—Cocaine exposure during the first and second trimesters of pregnancy were significant predictors of the unadaptable factor of the Bates ICQ Scale (Table 8). Cocaine use during the second and third trimesters significantly predicted increased fussiness/difficultness. There were no significant effects of prenatal cocaine use on the persistent scale. Additional significant predictors of more difficult or unadaptable temperament scores included younger age of the child at assessment, lower maternal education, more hospitalizations, maternal depression, more children in the household, third trimester marijuana exposure, and higher levels of current maternal substance use. Less difficult temperament was predicted by

the presence of an adult male in the household and by more developmental stimulation in the home. The amount of variance explained by the models was 16%, 19%, and 11% for the unadaptable, fussy/difficult, and persistent scales, respectively.

4. Discussion

This is a report from an ongoing, longitudinal study of prenatal cocaine exposure. Women were enrolled prenatally and interviewed about their drug use at the end of each trimester of pregnancy. At birth, infants who were exposed to cocaine prenatally were smaller and had reduced gestational age compared to those who were not exposed [73]. The exposed infants also had poorer autonomic stability, state regulation, and motor maturity on the Brazelton Neonatal Behavioral Assessment Scale (BNBAS) at birth [72], and less mature brain development on EEG-sleep studies at both birth and 1 year of age [77]. These effects were associated both with cocaine use during early pregnancy and with continued use throughout pregnancy.

This report investigated the effects of PCE on infant growth, development, and temperament. The most consistent effects of prenatal cocaine use were on the maternal ratings of infant temperament. Infants who were exposed to cocaine during pregnancy were rated as more fussy/difficult and unadaptable than were infants who were not exposed to cocaine. These findings were significant after controlling for prenatal and current maternal use of alcohol, tobacco, and marijuana, for infant characteristics, and for maternal sociodemographic and environmental factors. The descriptive analyses showed that the infants who were exposed throughout pregnancy were the most affected; those exposed during the first trimester only were also affected. Although there have been only a few published reports investigating the effects of cocaine exposure on infant temperament, our findings are consistent with those that reported an increase in fussiness and difficultness as a result of prenatal cocaine use [32,58]. The effects of cocaine use on infant temperament may result from the changes in autonomic stability, state regulation, and brain maturation that were found at birth. These aspects of neonatal behavior and later infant temperament have been found to be related in other research. Green, Bax, and Tsitsikas [40] reported a significant relationship between BNBAS state control at 2 weeks and unadaptability at 6 months, and Tirosh and Scher [90] found that the BNBAS autonomic stability and state regulation clusters at birth predicted the unadaptability score of the ICQ at 4 months of age.

We found an association between second trimester cocaine use and infant motor development in the regression analyses, and in the descriptive group analyses. This association between PCE and motor development has been reported previously by some researchers [34,82], but not by others [2,4,43,58]. This is an area that is in need of further investigation.

There were no significant relationships between prenatal cocaine use and infant size. The relationships between cocaine use and growth that were present at birth were no longer significant at the 1-year follow-up. This lack of effect of PCE on infant growth is consistent with previous research [34,35,42,47].

In addition to the association between PCE and temperament that was identified in this study, we have previously reported that first trimester cocaine use was a significant predictor of reduced gestational age [73] and neurobehavioral and neurophysiological changes at birth [72,77]. Brain development during pregnancy is characterized by a complex interaction of genetic, neurochemical, and environmental factors [29]. Animal models of PCE demonstrate a direct neurobiological link between PCE and deficits in behavior. Cocaine exposure during gestation can alter critical events during neural development. For example, PCE has a direct effect on the development of monoaminergic systems in rats [61,75,78,93], which play a crucial

regulatory role in neuronal proliferation and migration [14,51,53]. PCE has also been shown to delay cell proliferation and migration in rats, causing a disruption in cortical architecture [79,95]. Thus, the laboratory studies demonstrate that PCE can alter the normal course of neural development, which results in long-lasting effects on brain function and behavior. While the results of our study do not specify underlying mechanisms for the effects of PCE, animal studies have demonstrated direct effects of PCE on the developing nervous system, which may have further implications for brain structure and function.

We also found that continued cocaine use throughout pregnancy was associated with changes in neonatal neurobehavioral status [72] and infant temperament. It is not possible, however, to determine the independent effects of cocaine use during the third trimester in human samples because all of the third trimester users also used in the first trimester.

The validity of our findings is strengthened by their consistency with other reports in the literature. We found that gender and maternal height were associated with growth, as did Karlberg et al. [45] and Kuczmarski et al. [49]. We also found that prenatal tobacco exposure was a significant predictor of height during the infancy period, as did Day et al. [24]. Prenatal alcohol exposure was associated with head circumference during infancy, a finding reported by some researchers [6,26], but not others [37,66]. There were no effects of prenatal marijuana exposure on infant growth, a finding that is also consistent with the literature [24,39]. Predictors of cognitive development such as home environment and prenatal alcohol exposure have also been found by other investigators [69,83,89]. In fact, our finding of a relationship between prenatal alcohol exposure and the BSID MDI is supported by a meta-analysis conducted by Testa et al. [89]. We did not find an effect of prenatal marijuana exposure on infant cognitive development, consistent with the findings of Frank et al. [36] and Fried et al. [38]. Additional evidence of the validity of our findings is that the correlates of infant temperament in this study, e.g., maternal depression and home environment, have also been reported by other researchers [16,54,60,88].

Our findings of changes in neurobehavioral and neurophysiological function at birth and temperament at the 1-year assessment are consistent with the hypothesis that PCE affects arousal, attention, mood, and state regulation through changes in neurotransmitter systems [46,47,57,77]. This hypothesis has also been supported in animal studies [1,8,15,30,63,67, 85,86,92,94]. The prefrontal cortex is one site that is thought to control arousal, attention, and mood, as well as executive functioning (the ability to plan and carry out actions) [17,23]. As the children in this cohort develop, we use more specific measurements designed to assess the domains controlled by the prefrontal cortex in order to test this hypothesis.

This study represents an improvement over previous studies because of its prospective design, large number of subjects, and statistical control for confounding factors. The study design also allows us to assess light to moderate levels of PCE and the effect of the timing of exposure on infant development. Women enrolled in this project represent a healthy population from a prenatal clinic and all women received prenatal care by their fourth or fifth month of pregnancy. Additionally, all women were interviewed at the same time points and at frequent intervals to minimize recall bias. Furthermore, the interview techniques have been used in previous studies of substance use in pregnancy and have been shown to be reliable and valid [25,28,71].

A potential limitation of this study is that biological measures were not used to document drug use. While it is possible that some women who used drugs denied use on interview and were misclassified, this would reduce the differences between groups and would not affect the significant findings in this report. In addition, while urine screening can identify women who deny use, it fails to detect many cocaine users because of the short time period for detection, about 3 days [44,91]. Our interviews identified a higher percentage of users than did urine

screening [73], a finding also reported by Lester et al. [50] and Zuckerman et al. [96]. Detailed, confidential interviewing close to the time of use is an effective way to identify users and to characterize the quantity, timing, and pattern of use, especially during the first trimester [70, 74]. Moreover, our rates of cocaine use and our findings are comparable to reports from other studies of PCE.

Another issue to consider is whether the association between PCE and maternal ratings of infant temperament reflects the infant's behavior or the mother's perception of the infant's behavior. We found that PCE predicted the mother's ratings of the infant's behavior, but not the examiner's ratings. One possible explanation for this difference is that the ICQ [7] and the IBR [9] are measuring different aspects of the infant's behavior. On the ICQ, the mother is asked to rate how her infant typically acts in a variety of settings. The items focus on irritability and fussiness in different settings and on adaptation to new situations. By contrast, the examiner rates the infant on the IBR in terms of how s/he behaved solely during the BSID administration. In addition, the items reflect different aspects of behavior than are measured on the ICQ, for example, object orientation and activity. Another possible explanation for the different findings between the two measures is that women who use cocaine have different psychological characteristics than women who do not use cocaine and therefore they perceive their infant's behavior differently. PCE and depression were not related in our study, and other studies have also not found differences in psychological characteristics between women who used cocaine prenatally and those who did not [52,76,82]. Maternal depression was associated with infant temperament in our study, but when we controlled for maternal depression, PCE was still a significant predictor of temperament.

This study used the 1969 version of the BSID because the BSID-II was not available at the time these data were beginning to be collected. The outdated 1969 BSID norms contribute to inflated scores: The mean MDI and PDI scores for this sample were approximately one standard deviation above average. However, this does not affect the finding of an association between PCE and the BSID PDI scores.

This report of prenatal exposure to light to moderate levels of cocaine documents effects of cocaine use on infant temperament and motor development. The associations with temperament are particularly important as previous literature has shown that aspects of infant temperament, such as difficultness and unadaptability, are associated with later behavior problems [31,80,81]. Future reports from this cohort will address the development of the children at 3, 7, and 10 years of age, when we evaluated physical, cognitive, and behavioral development.

Acknowledgements

This research was supported by the National Institute on Drug Abuse grant DA05460 (G. Richardson, Principal Investigator).

References

1. Akbari H, Kramer H, Whitaker-Azmitia P, Spear L, Azmitia E. Prenatal cocaine exposure disrupts the development of the serotonergic system. Brain Res 1992;572:57–63. [PubMed: 1535274]
2. Alessandri S, Bendersky M, Lewis M. Cognitive functioning in 8- to 18-month-old drug-exposed infants. Dev Psychol 1998;34:565–573. [PubMed: 9597365]
3. Arendt R, Angelopoulos J, Salvator A, Singer L. Motor development of cocaine-exposed children at age two years. Pediatrics 1999;103:86–92. [PubMed: 9917444]
4. Arendt R, Singer L, Angelopoulos J, Bass-Busdiecker O, Mascia J. Sensorimotor development in cocaine-exposed infants. Infant Behav Dev 1998;21:627–640.

5. Ballard J, Novak K, Driver B. A simplified score for assessment of fetal maturation of newly born infants. J Pediatr 1979;95:769–774. [PubMed: 490248]
6. Barr H, Streissguth A, Martin D, Herman C. Infant size at 8 months of age: relationship to maternal use of alcohol, nicotine, and caffeine during pregnancy. Pediatrics 1984;74:336–341. [PubMed: 6472964]
7. Bates J, Freeland C, Lounsbury M. Measurement of infant difficultness. Child Dev 1979;50:794–803. [PubMed: 498854]
8. Bayer L, Brown A, Mactutus C, Booze R, Strupp B. Prenatal cocaine exposure increases sensitivity to the attentional effects of the dopamine D1 agonist SKF81297. J Neurosci 2000;20:8902–8908. [PubMed: 11102500]
9. Bayley, N. Manual for the Bayley Scales of Infant Development. Psychological Corporation; New York: 1969.
10. Bayley, N. Manual for the Bayley Scales of Infant Development. 2. Psychological Corporation; New York: 1993.
11. Behnke M, Eyler F, Garvan C, Wobie K, Hou W. Cocaine exposure and developmental outcome from birth to 6 months. Neurotoxicol Teratol 2002;24:282–295.
12. Billman D, Nemeth P, Heimler R, Sasidharan P. Prenatal cocaine/polydrug exposure: Effect of race on outcome. J Perinatol 1996;16:366–369. [PubMed: 8915935]
13. Brown J, Bakeman R, Coles C, Platzman K, Lynch M. Prenatal cocaine exposure: A comparison of 2-year-old children in parental and nonparental care. Child Dev 2004;75:1282–1295. [PubMed: 15260878]
14. Buznikov G, Lambert H, Lauder J. Serotonin and serotonin-like substances as regulators of early embryogenesis and morphogenesis. Cell Tissue Res 2001;305:177–186. [PubMed: 11545255]
15. Cabrera-Vera T, Garcia F, Pinto W, Battaglia G. Neurochemical changes in brain serotonin eurons in immature and adult offspring prenatally exposed to cocaine. Brain Res 2000;870:1–9. [PubMed: 10869495]
16. Carey, W.; McDevitt, S. Prevention and Early Intervention: Individual Differences as Risk Factors for the Mental Health of Children. Brunner/Mazel Publishers; New York: 1994.
17. Casey B, Castellano F, Giedd J, Marsh W, Hamburger S, Schubert A, Vauss Y, Vaituzis A, Dickstein D, Sarfatti S, Rapoport J. Implication of right frontostriatal circuitry in response inhibition and attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 1997;36:374–383. [PubMed: 9055518]
18. Casey P, Bradley R, Nelson J, Whaley S. The clinical assessment of a child's social and physical environment during health visits. J Dev Behav Pediatr 1988;9:333–338. [PubMed: 3220952]
19. Centers for Disease Control and Prevention. Epi Info Version 3.4.1. www.cdc.gov/epiinfo
20. Chasnoff I, Griffith D, Freier C, Murray J. Cocaine/polydrug use in pregnancy: Two-year follow-up. Pediatrics 1992;89:284–289. [PubMed: 1370867]
21. Chiriboga C, Kuhn L, Wasserman G. Prenatal cocaine exposures and dose-related cocaine effects on infant tone and behavior. Neurotoxicol Teratol 2007;29:323–330. [PubMed: 17234383]
22. Cook, R.; Weisberg, S. Residuals and Influence in Regression. Chapman and Hall; New York: 1982.
23. Dahl R. The regulation of sleep and arousal: Development and psychopathology. Dev Psychopathol 1996;8:3–27.
24. Day N, Cornelius M, Goldschmidt L, Richardson G, Robles N, Taylor P. The effects of prenatal tobacco and marijuana use on offspring growth from birth through 3 years of age. Neurotoxicol Teratol 1992;14:407–414. [PubMed: 1488035]
25. Day N, Jasperse D, Richardson G, Robles N, Sambamoorthi U, Taylor P, Scher M, Stoffer D, Cornelius M. Prenatal exposure to alcohol: Effect on infant growth and morphologic characteristics. Pediatrics 1989;84:536–541. [PubMed: 2771556]
26. Day N, Richardson G, Robles N, Sambamoorthi U, Taylor P, Scher M, Stoffer D, Jasperse D, Cornelius M. Effect of prenatal alcohol exposure on growth and morphology of offspring at 8 months of age. Pediatrics 1990;85:748–752. [PubMed: 2330235]
27. Day, N.; Robles, N. Methodological issues in the measurement of substance use. In: Hutchings, DE., editor. Prenatal Abuse of Licit and Illicit Drugs. Ann N Y Acad Sci. 562. 1989. p. 8-13.

28. Day N, Sambamoorthi U, Taylor P, Richardson G, Robles N, Jhon Y, Scher M, Stoffer D, Cornelius M, Jasperse D. Prenatal marijuana use and neonatal outcome. Neurotoxicol Teratol 1991;13:329–334. [PubMed: 1886543]
29. Doe C, Sanes J. Development: Neural development in the millennium. Curr Opin Neurobiol 2000;10:31. [PubMed: 10733275]
30. Dow-Edwards D, Freed L, Fico T. Structural and functional effects of prenatal cocaine exposure in adult rat brain. Brain Res 1990;57:263–268.
31. Earls F, Jung K. Temperament and home environment characteristics as causal factors in the early development of childhood psychopathology. J Am Acad Child Adolesc Psychiatry 1987;26:491–498. [PubMed: 3654499]
32. Edmondson R, Smith T. Temperament and behavior of infants prenatally exposed to drugs: Clinical implications for the mother-infant dyad. Infant Mental Health Journal 1994;15:368–379.
33. Eyler F, Behnke M, Conlon M, Woods N, Frentzen B. Prenatal cocaine use: A comparison of neonates matched on maternal risk factors. Neurotoxicol Teratol 1994;16:81–87. [PubMed: 8183193]
34. Fetters L, Tronick E. Neuromotor development of cocaine-exposed and control infants from birth through 15 months: Poor and poorer performance. Pediatrics 1996;98:938–943. [PubMed: 8909489]
35. Frank D, Augustyn M, Knight W, Pell T, Zuckerman B. Growth, development, and behavior in early childhood following prenatal cocaine exposure: A systematic review. JAMA 2001;285:1613–1625. [PubMed: 11268270]
36. Frank D, Jacobs R, Beeghly M, Augustyn M, Bellinger D, Cabral H, Heeren T. Level of prenatal cocaine exposure and scores on the Bayley Scales of Infant Development: Modifying effects of caregiver, early intervention, and birth weight. Pediatrics 2002;110:1143–1152. [PubMed: 12456912]
37. Fried P, O'Connell C. A comparison of the effects of prenatal exposure to tobacco, alcohol, cannabis and caffeine on birth size and subsequent growth. Neurotoxicol Teratol 1987;9:79–85. [PubMed: 3657756]
38. Fried P, Watkinson B. 12- and 24-month neurobehavioural follow-up of children prenatally exposed to marihuana, cigarettes and alcohol. Neurotoxicol Teratol 1988;10:305–313. [PubMed: 3226373]
39. Fried P, Watkinson B, Gray R. Growth from birth to early adolescence in offspring prenatally exposed to cigarettes and marijuana. Neurotoxicol Teratol 1999;21:513–525. [PubMed: 10492386]
40. Green J, Bax M, Tsitsikas H. Neonatal behavior and early temperament: A longitudinal study of the first six months of life. Am J Orthopsychiatry 1989;59:82–93. [PubMed: 2929731]
41. Hurt H, Brodsky N, Betancourt L, Braitman L, Malmud E, Giannetta J. Cocaine-exposed children: Follow-up through 30 months. J Dev Behav Pediatr 1995;16:29–35. [PubMed: 7730454]
42. Jacobson J, Jacobson S, Sokol R. Effects of prenatal exposure to alcohol, smoking, and illicit drugs on postpartum somatic growth. Alcohol Clin Exp Res 1994;18:317–323. [PubMed: 8048733]
43. Jacobson J, Jacobson S, Sokol R, Martier S, Chiodo L. New evidence for neurobehavioral effects of in utero cocaine exposure. J Pediatr 1996;129:581–590. [PubMed: 8859266]
44. Julien, R. A Primer of Drug Action. 7. W.H. Freeman Company; New York: 1995.
45. Karlberg J, Lawrence C, Albertsson-Wikland K. Prediction of final height in short, normal and tall children. Acta Paediatr Suppl 1994;406:3–10. [PubMed: 7734809]
46. Karmel B, Gardner J. Prenatal cocaine exposure effects on arousal-modulated attention during the neonatal period. Dev Psychobiol 1996;29:463–480. [PubMed: 8809496]
47. Karmel B, Gardner J, Freedland R. Arousal-modulated attention at four months as a function of intrauterine cocaine exposure and central nervous system injury. J Pediatr Psychol 1996;21:821–832. [PubMed: 8990726]
48. Kilbride H, Castor C, Hoffman E, Fuger K. Thirty-six-month outcome of prenatal cocaine exposure for term or near-term infants: Impact of early case management. J Dev Behav Pediatr 2000;21:19–26. [PubMed: 10706345]
49. Kuczmarski R, Ogden C, Grummer-Strawn L, Flegal K, Guo S, Wei R, Mei Z, Curtin L, Roche A, Johnson C. CDC growth charts: United States. Adv Data 2000;31:1–27. [PubMed: 11183293]

50. Lester B, ElSohly M, Wright L, Smeriglio V, Verter J, Bauer C, Shankaran S, Bada H, Walls H, Huestis M, Finnegan L, Maza P. The Maternal Lifestyle Study: Drug use by meconium toxicology and maternal self-report. Pediatrics 2001;107:309–317. [PubMed: 11158464]
51. Levitt P. Prenatal effects of drugs of abuse on brain development. Drug Alcohol Depend 1998;51:109–125. [PubMed: 9716934]
52. Lewis M, Misra S, Johnson H, Rosen T. Neurological and developmental outcomes of prenatally cocaine-exposed offspring from 12 to 36 months. Am J Drug Alcohol Abuse 2004;30:299–320. [PubMed: 15230078]
53. Lidow M, Wang F. Neurotransmitter receptors in the developing cerebral cortex. Crit Rev Neurobiol 1995;9:395–418. [PubMed: 8829853]
54. Mangelsdorf, S.; Schoppe, S.; Buur, H. The meaning of parental reports: A contextual approach to the study of temperament and behavior problems in childhood. In: Molfese, V.; Molfese, D., editors. Temperament and Personality Development Across the Life Span. L. Erlbaum Associates Publishers; Mahwah, NJ: 2000. p. 121-140.
55. Matheny A. Bayley's Infant Behavior Record: Behavioral components and twin analyses. Child Dev 1980;51:1157–1167. [PubMed: 7193557]
56. Matheny A. A longitudinal twin study of stability of components from Bayley's Infant Behavior Record. Child Dev 1983;54:356–360. [PubMed: 6683619]
57. Mayes L. Developing brain and in utero cocaine exposure: Effects on neural ontogeny. Dev Psychopathol 1999;11:685–714. [PubMed: 10624721]
58. Mayes L, Bornstein M, Chawarska K, Granger R. Information processing and developmental assessments in 3-month-old infants exposed prenatally to cocaine. Pediatrics 1995;95:539–545. [PubMed: 7700755]
59. Mayes L, Cicchetti D, Acharyya S, Zhang H. Developmental trajectories of cocaine-and-other-drug-exposed and non-cocaine-exposed children. J Dev Behav Pediatr 2003;24:323–335. [PubMed: 14578693]
60. Messinger D, Bauer C, Das A, Seifer R, Lester B, Lagasse L, Wright L, Shankaran S, Bada H, Smeriglio V, Langer J, Beeghly M, Poole W. The Maternal Lifestyle Study: Cognitive, motor, and behavioral outcomes of cocaine-exposed and opiate-exposed infants through three years of age. Pediatrics 2004;113:1677–1685. [PubMed: 15173491]
61. Meyer J, Shearman L, Collins L, Maguire R. Cocaine binding sites in fetal rat brain: Implications for prenatal cocaine action. Psychopharmacology 1993;112:445–51. [PubMed: 7871055]
62. Miller-Loncar C, Lester B, Seifer R, Lagasse L, Bauer C, Shankaran S, Bada H, Wright L, Smeriglio V, Bigsby R, Liu J. Predictors of motor development in children prenatally exposed to cocaine. Neurotoxicol Teratol 2005;27:213–220. [PubMed: 15734272]
63. Morrow B, Elsworth J, Roth R. Male rats exposed to cocaine in utero demonstrate elevated expression of fos in the prefrontal cortex in response to environment. Neuropsychopharmacology 2002;26:275–285. [PubMed: 11850142]
64. National Institute on Drug Abuse. National Institutes of Health Publication No. 96-3819. Rockville, MD: 1996. National Pregnancy and Health Survey: Drug Use Among Women Delivering Livebirths: 1992.
65. Noland J, Singer L, Mehta S, Super D. Prenatal cocaine/polydrug exposure and infant performance on an executive functioning task. Dev Neuropsychol 2003;24:499–517. [PubMed: 12850756]
66. O'Connor M, Brill N, Sigman M. Alcohol use in primiparous women older than 30 years of age: relation to infant development. Pediatrics 1986;78:444–450. [PubMed: 3748678]
67. Overstreet D, Moy S, Lubin D, Gause L, Lieberman J, Johns J. Enduring effects of prenatal cocaine administration on emotional behavior in rats. Physiol Behav 2000;70:149–156. [PubMed: 10978490]
68. Radloff L. The CES-D scale: A self-report depression scale for research in the general population. Applied Psychological Measurement 1977;1:385–401.
69. Richardson G, Day N, Goldschmidt L. Prenatal alcohol, marijuana, and tobacco use: Infant mental and motor development. Neurotoxicol Teratol 1995;17:479–487. [PubMed: 7565494]
70. Richardson G, Day N, McGauhey P. The impact of prenatal marijuana and cocaine use on the infant and child. Clin Obstet Gynecol 1993;36:302–318. [PubMed: 8513626]

71. Richardson G, Day N, Taylor P. The effect of prenatal alcohol, marijuana, and tobacco exposure on neonatal behavior. Infant Behav Dev 1989;12:199–209.
72. Richardson G, Hamel S, Goldschmidt L, Day N. Effects of prenatal cocaine use on neonatal neurobehavioral status. Neurotoxicol Teratol 1996;18:519–528. [PubMed: 8888016]
73. Richardson G, Hamel S, Goldschmidt L, Day N. Growth of infants prenatally exposed to cocaine/crack: A comparison of a prenatal care and a no prenatal care sample. Pediatrics 1999;104:e18. [PubMed: 10429136]
74. Richardson, G.; Huestis, M.; Day, N. Assessing in utero exposure to cannabis and cocaine. In: Bellinger, DC., editor. Human Developmental Neurotoxicology. Taylor & Francis Group; New York: 2006. p. 287-302.
75. Ronnekleiv O, Fang Y, Choi W, Chai L. Changes in the midbrain-rostral forebrain dopamine circuitry in the cocaine-exposed primate fetal brain. Ann N Y Acad Sci 1998;846:165–181. [PubMed: 9668406]
76. Salisbury A, Lester B, Seifer R, LaGasse L, Bauer C, Shankaran S, Bada H, Wright L, Liu J, Poole K. Prenatal cocaine use and maternal depression: effects on infant neurobehavior. Neurotoxicol Teratol 2007;29:331–340. [PubMed: 17258430]
77. Scher M, Richardson G, Day N. Effects of prenatal cocaine/crack exposure on EEG-sleep studies at birth and one year. Pediatrics 2000;105:39–48. [PubMed: 10617702]
78. Seidler F, Slotkin T. Fetal cocaine exposure causes persistent noradrenergic hyperactivity in rat brain regions: Effects on neurotransmitter turnover and receptors. J Pharmacol Exp Ther 1992;263:413–421. [PubMed: 1331397]
79. Seidler F, Temple S, McCook E, Slotkin T. Cocaine inhibits central noradrenergic and dopaminergic activity during the critical developmental period in which catecholamines influence cell development. Brain Research 1995;85:48–53. [PubMed: 7781166]
80. Shaw D, Owens E, Giovannelli J, Winslow E. Infant and toddler pathways leading to early externalizing disorders. J Am Acad Child Adolesc Psychiatry 2001;40:36–43. [PubMed: 11195559]
81. Shaw D, Vondra J, Hommerding K, Keenan K, Dunn M. Chronic family adversity and early child behavior problems: A longitudinal study of low income families. J Child Psychol Psychiatry 1994;35:1109–1122. [PubMed: 7995846]
82. Singer L, Arendt R, Farkas K, Minnes S, Huang J, Yamashita T. Relationship of prenatal cocaine exposure and maternal postpartum psychological distress to child developmental outcome. Dev Psychopathol 1997;9:473–489. [PubMed: 9327234]
83. Singer L, Arendt R, Minnes S, Farkas K, Salvator A, Kirchner H, Kliegman R. Cognitive and motor outcomes of cocaine-exposed infants. JAMA 2002;287:1952–1960. [PubMed: 11960537]
84. Spielberger, C.; Gorsuch, R.; Lushene, R. Manual for the State-Trait Anxiety Inventory. Consulting Psychologists Press, Inc; Palo Alto, CA: 1970.
85. Stanwood, G.; Levitt, P. The effects of cocaine on the developing nervous system. In: Nelson, CA.; Luciana, M., editors. Handbook of Developmental Cognitive Neuroscience. MIT Press; Cambridge, MA: 2001. p. 519-536.
86. Stanwood G, Washington R, Shumsky J, Levitt P. Prenatal cocaine exposure produces consistent developmental alterations in dopamine-rich regions of the cerebral cortex. Neuroscience 2001;106:5–14. [PubMed: 11564412]
87. Substance Abuse and Mental Health Services Administration. Results from the 2003 National Survey on Drug Use and Health: National Findings, DHHS Publication No. SMA 04-3964. Office of Applied Studies; Rockville, MD: 2004.
88. Sugawara M, Kitamura T, Toda M, Shima S. Longitudinal relationship between maternal depression and infant temperament in a Japanese population. J Clin Psychol 1999;55:869–880. [PubMed: 10866022]
89. Testa M, Quigley B, Eiden R. The effects of prenatal alcohol exposure on infant mental development: A meta-analytical review. Alcohol Alcohol 2003;38:295–304. [PubMed: 12814894]
90. Tirosh, E.; Scher, A. Neonatal behavior: Physiological, temperamental, and developmental correlates in infancy. In: Anastasiow, N.; Harel, S., editors. At-Risk Infants: Interventions, Families, and Research. Paul H. Brookes Publishing; Baltimore, MD: 1993. p. 137-143.

91. Verebey, K. Cocaine abuse detection by laboratory methods. In: Washton, AM.; Gold, MS., editors. Cocaine - A Clinician's Handbook. Guilford Press; New York: 1987. p. 214-228.

92. Wang XH, Levitt P, Grayson D, Murphy E. Intrauterine cocaine exposure of rabbits: Persistent elevation of GABA-immunoreactive neurons in anterior cingulate cortex but not visual cortex. Brain Research 1995;689:32–46. [PubMed: 8528704]

93. Whitaker-Azmitia P. Role of the neurotrophic properties of serotonin in the delay of brain maturation induced by cocaine. Ann N Y Acad Sci 1998;846:158–164. [PubMed: 9668405]

94. Willford J, Segar T, Barron S. The behavioral response to novelty is altered in rats neonatally exposed to cocaine. Dev Psychobiol 1999;35:343–351. [PubMed: 10573573]

95. Zachor D, Cherkes J, Fay C, Ocrant I. Cocaine differentially inhibits neuronal differentiation and proliferation in vitro. J Clin Invest 1994;93:1179–1185. [PubMed: 8132758]

96. Zuckerman B, Frank D, Hingson R, Amaro H, Levenson S, Kayne H, Parker S, Vinci R, Aboagye K, Fried L, Cabral H, Timperi R, Bauchner H. Effects of maternal marijuana and cocaine use on fetal growth. N Engl J Med 1989;320:762–768. [PubMed: 2784193]

Table 1

Variables considered for inclusion in analyses

Infant Characteristics
Age at assessment
Gender
Number of illnesses
Number of injuries
Number of hospitalizations
Current Maternal Characteristics
Age
Race
Education
Marital status
Work status
Social support
Depression
Height
Current Environmental Characteristics
Number of children in the household
Adult male in the household
PROCESS developmental stimulation
Family income
Adequacy of the BSID[a]
Current Substance Use
Cocaine
Alcohol
Tobacco
Marijuana
Other illicit drugs
Prenatal Substance Use (for each trimester)
Cocaine
Alcohol
Tobacco
Marijuana
Other illicit drugs

[a] IBR judgement of test as being indicator of child's characteristics

Table 2

Prevalence of Cocaine Use (%)

Time Period	Level of Use		
	None	Occasional[a]	Frequent[b]
Year prior to pregnancy (N = 261)	55.6	23.4	21.1
First trimester (N = 261)	59.0	22.6	18.4
Second trimester (N = 234)	92.7	3.0	4.3
Third trimester (N = 258)	89.1	4.7	6.2
One-year follow-up (N = 261)	85.1	7.7	7.3

[a] Occasional: > 0 and < 1 line/day or gram equivalent of crack

[b] Frequent: ≥1 line/day of cocaine or gram equivalent of crack

Table 3

Prenatal Maternal Characteristics Associated with Prenatal Cocaine Use

First Trimester Characteristics	No cocaine use 1st trimester N = 154	Cocaine use 1st trimester N= 107
Mean Age (yrs)	24.0	26.3***
Mean Education (yrs)	12.1	11.9
% Caucasian	59.7	44.9*
% Married	27.3	13.1**
% Work/Attend School	46.8	33.6*
% Income < $500/month	40.5	60.4**
% Drink Alcohol	56.5	89.7***
Mean # Drinks/Day	.36	2.0***
% Smoke Cigarettes	44.2	74.8***
Mean # Cigarettes/Day	6.2	10.6***
% Use Marijuana	16.9	55.1***
Mean # Joints/Day	.07	.49***
% Use Other Drugs (excluding cocaine)	3.2	11.2**

Third Trimester Characteristics	Never Used[a] N = 144	Stopped[b] N = 61	Continued[c] N = 28
Mean Education (yrs)	12.1	12.0	11.9
% Caucasian	61.8	62.3	10.7***
% Married	31.2	16.4	10.7**
% Work/Attend School	16.0	11.5	7.1
% Income < $500/month	43.6	60.7	78.6***
% Drink Alcohol	31.9	52.5	60.7***
Mean # Drinks/Day	.05	.13	1.2***
% Smoke Cigarettes	37.3	67.2	77.8***
Mean # Cigarettes/Day	5.6	9.0	8.6*
% Use Marijuana	6.2	16.4	32.1***
Mean # Joints/Day	.02	.11	.07*

[a] Did not use cocaine during any trimester

[b] Used cocaine first trimester only

[c] Used cocaine both first and third trimesters

* $p < .05$

** $p < .01$

*** $p < .001$

Table 4

Infant Characteristics Associated with Prenatal Cocaine Use

	No cocaine use 1st trimester N = 154	**Cocaine use 1st trimester N= 107**
Gestational age (wks)	40.0	39.3**
Birth weight (gms)	3361.2	3143.3**
% Premature (< 37 wks)	3.2	10.3**
% Low birth weight (<2500 gms)	5.2	12.1**
Age (mos)[a]	14.5	14.6
Weight (lbs)[a]	23.5	23.3
Height (ins)[a]	30.7	30.5
Head circumference (ins)[a]	18.6	18.6
BSID Mental Development Index[a]	115.3	112.9
BSID Psychomotor Development Index[a]	114.7	110.7*
ICQ Scale: Fussy/Difficult[a]	29.2	31.0**
ICQ Scale: Unadaptable[a]	15.7	17.3**
ICQ Scale: Persistent[a]	13.0	13.9*

	Never[b] N = 144	Stopped[c] N = 61	Continued[d] N = 28
Gestational age (wks)	40.1	40.1	39.3**
Birth weight (gms)	3359.9	3345.6	3056.0**
% Premature (< 37 wks)	3.5	3.3	14.3**
% Low birth weight (<2500 gms)	5.6	4.9	14.3
Age (mos)[a]	14.5	14.5	15.9**
Weight (lbs)[a]	23.5	23.2	24.2
Height (ins)[a]	30.7	30.8	30.9
Head circumference (ins)[a]	18.6	18.6	18.7
BSID Mental Development Index[a]	115.6	114.5	109.6
BSID Psychomotor Development Index[a]	115.4	112.9	108.3*
ICQ Scale: Fussy/Difficult[a]	29.1	29.5	33.5***
ICQ Scale: Unadaptable[a]	15.7	16.6	18.3**
ICQ Scale: Persistent[a]	13.0	13.5	14.4*

[a] Measured at 1-year follow-up phase

[b] Did not use cocaine during any trimester

[c] Used cocaine first trimester only

[d] Used cocaine both first and third trimesters

* $p < .10$

** $p < .05$

*** $p < .01$

Table 5

Current Maternal Characteristics Associated with Cocaine Use at 1-Year Follow-Up

	No Cocaine Use N= 222	Cocaine Use N= 39
Mean Age (yrs)	26.6	28.2*
Mean Education (yrs)	12.2	12.0
% Caucasian	53.4	58.3
% Married	29.7	13.9*
% Work/Attend School	40.2	27.8
Mean Income/Month ($)	847	795
Depression (total CES-D score) [68]	19.6	22.1
Hostility (total STAI score) [84]	17.4	20.7**
PROCESS Developmental Stim. [18]	45.2	43.2*
% Drink Alcohol	76.1	94.9**
Mean # Drinks/Day	.76	2.4**
% Smoke Cigarettes	51.8	89.7***
Mean # Cigarettes/Day	7.9	14.4***
% Use Marijuana	23.9	61.5***
Mean # Joints/Day	.13	.17***
% Use Other Drugs (excluding cocaine)	7.7	12.8

* $p < .05$

** $p < .01$

*** $p < .001$

Table 6

Significant Predictors of Growth[a]

	Raw Beta	Standardized Regression Coefficient
Weight (Total R^2 = .22)		
Child age at assessment	.41	.33
Gender[b]	1.31	.22
Maternal height	.19	.19
Maternal depression	−.04	−.15
Height (Total R^2 = .47)		
Child age at assessment	10.72	.63
Maternal height	2.50	.17
Gender	11.20	.13
Maternal depression	−.52	−.12
Prenatal tobacco use		
1st trimester	−.61	−.14
2nd trimester	−.44	−.09
3rd trimester	−.42	−.09
Head Circumference (Total R^2 = .34)		
Gender	13.41	.43
Child age at assessment	2.11	.33
Maternal height	1.01	.18
Prenatal alcohol use (2nd trimester)	−6.37	−.14

[a] Listed in order of standardized regression coefficient, an indication of the magnitude of the effect.

[b] 0=female; 1=male

Table 7

Significant Predictors of the Bayley Scales of Infant Development[a]

	Raw Beta	Standardized Regression Coefficient
Mental Development Index (MDI) (Total R^2 = .31)		
Child age at assessment	−2.32	−.36
Adequacy of the BSID[b]	−13.70	−.22
Developmental stimulation[c]	.83	.21
Race[d]	4.60	.14
Prenatal alcohol use		
1st trimester	−3.78	−.14
3rd trimester	−5.70	−.12
Man in household[e]	−3.92	−.12
Number of children in household	−1.48	−.10
Psychomotor Development Index (PDI) (Total R^2 =.13)		
Child age at assessment	−1.25	−.20
Prenatal alcohol use		
1st trimester	−4.28	−.17
2nd trimester	−7.19	−.16
3rd trimester	−6.24	−.13
Prenatal cocaine use		
2nd trimester	−7.32	−.12
Number of children in household	−1.69	−.11
Infant Behavior Record (IBR) Task (Total R^2 = .04)		
Number of hospitalizations	.71	.13
Current maternal marijuana use	−1.36	−.13
Affect (Total R^2 = .02)		
Prenatal marijuana use		
1st trimester	−1.22	−.13
2nd trimester	−4.37	−.17
3rd trimester	−2.82	−.13
Activity (Total R^2 = .03)		
Child age at assessment	.15	.17

[a] Listed in order of standardized regression coefficient, an indication of the magnitude of the effect.

[b] IBR judgement of test as being indicator of child's characteristics (0=average to excellent; 1 = minimal or fairly adequate)

[c] PROCESS Scale [18]

[d] 0=African American; 1=Caucasian

[e] 0=not present; 1=present

Table 8

Significant Predictors of the Infant Characteristics Questionnaire[ab]

	Raw Beta	Standardized Regression Coefficient
Unadaptable (Total R^2 = .16)		
Number of children in household	.87	.18
Current maternal alcohol use	1.59	.17
Maternal education	−.60	−.16
Developmental stimulation[c]	−.18	−.15
Prenatal cocaine use		
1st trimester	1.60	.14
2nd trimester	2.33	.13
Prenatal marijuana use (3rd Trimester)	3.79	.11
Fussy/Difficult (Total R^2 = .19)		
Maternal depression	.16	.22
Current maternal alcohol use	2.33	.19
Number of hospitalizations	2.39	.17
Developmental stimulation	−.24	−.15
Child age at assessment	−.38	−.14
Marital status[d]	1.77	.12
Prenatal cocaine use		
2nd trimester	2.99	.12
3rd trimester	2.61	.12
Persistent (Total R^2 = .11)		
Maternal depression	.06	.22
Man in household	−.83	−.14
Current maternal tobacco use	.04	.13

[a] Listed in order of standardized regression coefficient, an indication of the magnitude of the effect.

[b] Bates et al. [7]

[c] PROCESS Scale [18]

[d] 0=Not married; 1=Married