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Effects of cocaine/polydrug exposure and maternal psychological distress on infant birth outcomes☆

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Abstract

To assess teratogenic effects of cocaine exposure and maternal psychological distress on birth outcomes, we conducted a longitudinal prospective study of 415 infants (218 cocaine-exposed—CE, 197 nonexposed—NE). Drug exposure was determined through a combination of maternal self-report, urine, and meconium screens. Maternal psychological distress postpartum was evaluated through a standardized, normative, self-report assessment. An extensive set of confounding variables was controlled, including severity of exposure to alcohol, tobacco, marijuana and other drugs, maternal age, race, parity, number of prenatal care visits, educational, marital, and socioeconomic status, and verbal and nonverbal intelligence. CE infants were smaller on all birth parameters and more likely to be preterm, small for gestational age, and microcephalic than NE infants. Forty-one percent of cocaine users had clinically significant psychological symptoms, compared to 20% of a high-risk comparison group of noncocaine users. Consistent with a teratologic model, cocaine exposure independently predicted offspring birthweight, length, and head circumference. Maternal psychological distress self-reported postnatally also independently predicted head circumference. Tobacco, alcohol, and marijuana exposures were also significant independent predictors of some fetal growth parameters. In addition, maternal distress symptoms, which may be reflective of maternal mental health disorders or responses to stress, added significantly to the risk for poorer fetal growth.

Keywords: Depression; Anxiety; Drugs; Cocaine; Birth outcomes; Teratology; Alcohol; Marijuana; Tobacco

1. Introduction

Maternal cocaine use during pregnancy is a significant public health problem. In 1997, an estimated 1.5 million Americans were current users of cocaine and 66,000 pregnant women self-reported use of cocaine or crack [15]. Cocaine freely crosses the placenta [52] and its vasoconstrictive effects decrease uterine blood flow causing fetal hypoxemia [67,73], thus affecting fetal growth. Fetal growth, especially intrauterine brain growth retardation, can reflect altered central nervous system development, and provide evidence for neurotoxic and neuroteratogenic effects of cocaine exposure [67,72].

Consistent relationships have been demonstrated between fetal cocaine exposure and incidence of prematurity [11,62], low birthweight [11,61,47], reduced birth length [10,62,69], and small head circumference [4,35], suggesting teratogenic effects, but earlier studies failed to control for many relevant confounders [37]. Disproportionately reduced head circumference, a reflection of brain size, has been found in cocaine-exposed (CE) neonates [35], as well as depressed neonatal fat stores and lean body mass indicative of intrauterine growth retardation [21]. A large prospective study [75] found that maternal cocaine use was independently related to lower infant birthweight,

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length, and head circumference, but did not assess severity of exposure to a confounding variable, marijuana. In studies of small samples of CE infants, a dose–response relationship has been found between the magnitude of prenatal cocaine exposure and impaired fetal growth and head circumference when the concentration of the cocaine metabolite benzoylecgonine (BZE) was measured in meconium and hair samples [40,53]. In a large sample, direct effects of cocaine/polydrug use were found on fetal growth, [7] particularly birthweight, length, and ponderal index, which were sensitive to the frequency of use during pregnancy. However, alcohol and marijuana were confounded with cocaine exposure in this study.

In contrast, a study with greater control for confounding variables, [18], did not find relationships between level of cocaine exposure and head circumference or birth length after control for other drugs, although head and chest circumference were lower in infants exposed to both cocaine and tobacco. Similar effects of synergistic interactions between drugs have been reported in prior studies, which found a cocaine/alcohol interaction effect on birth length [62] and a cocaine/alcohol effect on head circumference [13]. Although maternal age and amount of prenatal care, found to be related to birth outcomes in prior studies [22,49,62], were not controlled in these studies, a recent, large, well-controlled prospective investigation [50,51] found that cocaine exposure in the first two trimesters of pregnancy predicted fetal growth retardation, irrespective of prenatal care.

To date, no studies of the effects of cocaine exposure on birth outcomes have controlled for maternal distress symptoms, despite high levels of such symptoms noted in women who use cocaine and other drugs, including alcohol, and tobacco [5,6,38,63,74]. Strong relationships between maternal stress and poorer birth outcomes have been established in human [20,32,44,64,68], primate [41,43,55], and rodent [24,48] studies, but these have not been investigated in the context of drug or alcohol exposure in human studies.

The present study was designed to investigate birth outcomes associated with fetal cocaine exposure. Confounding variables known to have adverse effects on birth outcomes were controlled by design or statistical analysis, particularly socioeconomic and prenatal care factors [22,49,62], maternal age and parity, and, of greater importance, exposure to other substances, especially alcohol [14], marijuana [23], and tobacco [25]. In addition, maternal risk factors known to affect birth outcomes that have not consistently been considered in drug-exposed populations, such as maternal intellectual ability and psychological distress, were also controlled. Both timing [9] and amount [28] of all drug exposures were considered to avoid misattribution of cocaine effects due to unreliable assessment of self-report variables [27]. Meconium metabolite measures of exposure were quantified to classify exposure status and severity.

2. Method

2.1. Subjects

A total of 415 infants (218 CE, 197 NE) were recruited at birth to participate in a longitudinal study of the developmental sequelae of fetal drug exposure. Mothers and infants were recruited from a large, urban county teaching hospital, identified from a high-risk population screened for drug use. Urine samples were obtained immediately before or after labor and delivery and analyzed for the presence of cocaine metabolites, cannabinoids, opiates, PCP, and amphetamines. Urine toxicology screens for drugs were performed by the hospital on all women who received no prenatal care, appeared to be intoxicated or taking drugs, had a history of involvement with the Department of Human Services in previous pregnancies, or self-admitted or appeared to be high risk for drug use after interview by hospital staff. The Syva Emit method (Syva, Palo Alto, CA) was used for urine analysis. The specificity for BZE was 99% at a concentration of 0.3 mg/ml. Follow-up gas chromatography analyses were performed.

Infants also had the following meconium drug analyses for cocaine and its metabolites: BZE, *meta*-hydroxybenzoylecgonine (*m*-OH-BZE), cocaethylene, cannabinoids (THC), opiates, phencyclidine, amphetamines, and benzodiazepines [32,45]. Meconium was collected in the hospital from infants' diapers, and was scraped from the diaper with a wooden spatula and placed into a plastic container. To maximize the amount collected, specimens from multiple diapers of the same newborn were accumulated and kept refrigerated. The entire sample was then stirred for 5 min to insure homogeneity. Meconium analysis was conducted using gas chromatography-mass spectrometry (GC-MS). Concentrations were expressed as nanograms per gram (ng/g).

A nurse recruiter approached all screened women shortly before or after infant birth. Six hundred forty-seven mothers and their infants were identified, of whom 54 were excluded (20 cocaine-positive, 34 cocaine-negative). Reasons for exclusion included no meconium (15), Down syndrome (2), maternal psychiatric history (16), primary heroin use (2), HIV-positive (5), maternal IQ <50 (1) fetal alcohol syndrome (1), maternal age <19 years (2), infant medical illness (3), maternal chronic illness (4), and others (3). One hundred fifty-five mothers refused to participate (49 cocaine-positive, 106 cocaine-negative) and 23 (9 cocaine-positive, 14 cocaine-negative) did not show up at the enrollment visit. Therefore, 415 women and their infants enrolled in the study (218 cocaine-positive, 197 cocaine-negative). CE infants were identified by a positive response on any of the following measures: infant meconium, urine, or maternal urine positive for cocaine, maternal report to hospital staff, or maternal self-report during clinical interview. Comparison infants were drawn from the same high-risk population and were negative for indications of cocaine use, but varied in alcohol, marijuana, and tobacco use. For the majority of

comparison subjects, all of the above indicators were negative. For 11 (6%), meconium was unavailable, but all other screening and follow-up indicated no evidence of use.

2.2. Procedures

Infants and their caregivers were seen as soon as possible after birth, at which time, the biologic mother was interviewed regarding drug use. For infants in foster care at birth, biologic mothers were seen at a separate visit. Infants were seen, on average, at the age of 1 month (corrected) [60]. An adaptation of the Maternal Post-Partum Questionnaire [59,65] was used to quantify maternal drug use. For the month prior to pregnancy and for each trimester of pregnancy, mothers were requested to recall frequency and amount of drug use. For marijuana, the number of joints per day, and for alcohol, the number of drinks of beer, wine, or hard liquor per day was computed with each drink equivalent to 0.5 oz of absolute alcohol. For cocaine, the number of rocks consumed and amount of money spent per day were noted. For each drug, except tobacco, the frequency of use was recorded on a Likert-type scale ranging from 0 (*not at all*) to 7 (*daily use*), which was then converted to reflect the average number of days per week a drug was used. For tobacco, the number of cigarettes smoked per day was recorded. The frequency of use was multiplied by the amount used per day to compute a severity of use score for the month prior to pregnancy and for each trimester. This score was then averaged for a total score for the prenatal exposure for each drug.

In a separate study, validity for the assessments of maternal self-report of severity of cocaine use and concentrations of cocaine metabolites in infant meconium was found in reasonable and significant correlations between the two measures for BZE (.57), *m*-OH-BZE (.51), cocaethylene (.32), and cocaine (.46) [3].

Demographic and medical characteristics at the time of infant birth were extracted from hospital records. These included maternal race, age, gravida, parity, number of prenatal care visits, infant APGAR scores, birthweight, length, head circumference, and estimated gestational age from the Ballard Scale.

At birth, all infants were scheduled for follow-up and seen for evaluation at the developmental research laboratories of the Department of Pediatrics. The Hobel Neonatal Risk Index [26] was computed from chart review as a measure of neonatal medical complications. At the initial visit, maternal socioeconomic status and maternal education were calculated, and maternal vocabulary was measured using the Peabody Picture Vocabulary Test—Revised (PPVT-R) [17]. Two subtests of the Weschler Adult Intelligence Scale—Revised (WAIS-R) [70], i.e., block design (BD) and picture completion (PC), were administered to obtain estimates of nonverbal intelligence.

Mothers were also administered the Brief Symptom Inventory [16], which yields a summary measure for the previous 7-day period of self-reported severity of psychological distress, the Global Severity Index (GSI). This scale measures nine psychiatric symptom patterns (somatic complaints, obsessive–compulsive behavior, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism) that possess consensually valid clinical significance. Cut-off scores identify persons whose symptoms reach severity levels suggesting the need for clinical intervention, i.e., higher than the 84th percentile (moderate) or higher than the 98th percentile (severe) compared with same-sex nonpatient norms.

The Institutional Review Boards of the participating hospitals approved this study, and maternal written informed consent in hospital was obtained either prior to or immediately after infant birth for both maternal and infant participation.

2.3. Statistical analysis

Prior to analysis, cocaine, cigarette, alcohol, and marijuana self-report measures, meconium variables, and GSI scores, which were positively skewed, were normalized by means of log $x+1$ transformation. Means and standard deviations are reported in terms of the original distribution, while transformations were used in analyses. The cocaine-negative and -positive mothers were compared on demographic variables and frequency and severity of drug use using t tests for continuous data and χ^2 analyses for categorical variables.

Spearman correlations assessed the relationship of severity of prenatal drug exposure to infant outcomes, based on

Table 1
Sample characteristics

Maternal	Cocaine ($n=218$)	Noncocaine ($n=197$)	t/χ^2	P
Race (non-White)	177 (81%)	156 (79%)	0.26	.60
Age (years)	29.6±5	25.7±5	−8.0	.0001
Parity	3.6±2	2.7±2	−4.6	.0001
Gravida	5.0±2	3.7±2	−5.9	.0001
Number of prenatal visits	5.1±5	8.7±5	7.7	.0001
No prenatal care	44 (20%)	19 (10%)	8.9	.003
Alcohol use	177 (86%)	122 (65%)	23.8	.001
Marijuana use	102 (50%)	25 (13%)	59.0	.001
Tobacco use	182 (88%)	79 (42%)	94.3	.001
Amphetamine use	5 (2%)	2 (1%)	1.05	.31
Barbiturate use	2 (1%)	1 (.5%)	0.25	.62
Benzodiazepine use	24 (15%)	0 (0%)	24.1	.001
Heroin use	5 (2%)	0 (0%)	4.6	.03
PCP	11 (5%)	0 (0%)	10.3	.001
Maternal employment	11 (5%)	42 (21%)	24.6	.001
Married	16 (7%)	34 (17%)	9.6	.002
Low socioeconomic status	213 (98%)	192 (98%)	0.2	.63
Education (<high school graduate)	103 (48%)	61 (31%)	11.8	.001
PPVT-R standard score	73.8±15	78.2±15	2.8	.005
WAIS-R BD score	6.8±2	7.2±2	1.7	.09
WAIS-R PC score	6.6±2	6.9±2	1.7	.09
GSI	0.81±.7	0.49±.5	−5.3	.0001

Table 2
Summary measures of tobacco, alcohol, marijuana, and cocaine by trimester

	Cocaine ($n=206$)	Noncocaine ($n=188$)	t	P
Number of cigarettes per day	11.6±11	4.4±8	−7.5	.0001
Alcohol use[a]				
Month prior	12.9±23	2.4±8	−5.8	.0001
Trimester 1	11.8±23	1.3±4	−6.0	.0001
Trimester 2	8.5±21	0.6±3	−5.1	.0001
Trimester 3	6.4±18	1.0±8	−3.8	.0005
Average	9.9±18	1.3±4	−6.2	.0001
Marijuana use[b]				
Month prior	1.6±4	1.5±10	−0.15	.88
Trimester 1	1.4±4	0.6±4	−2.2	.03
Trimester 2	1.3±4	0.2±2	−3.3	.001
Trimester 3	1.0±4	0.1±1	−3.1	.002
Average	1.3±4	0.6±4	−2.1	.04
Cocaine use[c]				
Month prior	31.1±68			
Trimester 1	32.1±67			
Trimester 2	25.7±67			
Trimester 3	11.1±27			
Average	23.3±44			

[a] Alcohol use=number of drinks per day×number of days per week.
[b] Marijuana use=number of joints per day×number of days per week.
[c] Cocaine use=number of rocks per day×number of days per week.

maternal self-report by trimester and concentration of cocaine metabolites in infant meconium. Hierarchical multiple regression analyses evaluated the predictive power of severity of cocaine exposure after control for confounders. Because of collinearity, all confounding variables other than drug variables and maternal distress were entered into regression models first to reduce the model, followed by stepwise entry of each drug variable with cocaine and maternal distress entered on the final steps. Drug interactions and moderating effects of other variables were assessed by adding interaction terms to the regression models after assessment of main drug effects. The following confounders were considered for analyses if they were related to the outcome at $P<.10$: gestational age, race,

Table 3
Infant outcomes

	Cocaine ($n=218$)	Noncocaine ($n=197$)	$F/t/\chi^2$	P
% Female	116 (53%)	101 (51%)	0.16	.70
Gestational age (weeks)	37.7±3	38.5±3	2.6	.008
Birthweight (g)[a]	2709±678	3086±703	31.1	.0001
Birth length (cm)[a]	47.2±4	49.9±4	14.2	.0001
Head circumference (cm)[a]	32.3±0.3	33.4±3	17.75	.0001
Hobel Neonatal Risk score	8.3±19	6.0±17	−1.3	.19
APGAR—1 min	8.0±2	7.9±2	−0.4	.69
APGAR—5 min	8.8±1	8.8±1	1.9	.85
Prematurity (<37 weeks)	64 (29%)	36 (18%)	7.0	.008
Small for gestational age	6 (12%)	4 (2%)	14.5	.001
Microcephaly[b]	32 (15%)	10 (5%)	10.5	.001

[a] P was adjusted for gestational age.
[b] Head circumference is <10th percentile for gestational age.

Table 4
Spearman correlations of maternal self-report of drug use with birth outcomes ($n=379$)

	Head circumference	Birthweight	Birth length	Gestational age
Average number of cigarettes per day	−.20¶	−.26¶	−.20¶	−.13*
Alcohol average[a]	−.19‡	−.21¶	−.18‡	−.05
Marijuana average[b]	−.10*	−.15†	−.11*	−.06
Cocaine average[c]	−.30¶	−.31¶	−.27¶	−.17‡

[a] Alcohol use=number of drinks per day × number of days per week.
[b] Marijuana use=number of joints per day × number of days per week.
[c] Cocaine use=number of rocks per day × number of days per week.
* $P<.05$.
† $P<.01$.
‡ $P<.001$.
¶ $P<.0001$.

gender, parity, number of prenatal care visits, maternal age, years of education, marital status, vocabulary score, WAIS-R BD and PC scores, GSI score, and summary measures of cigarette, alcohol, and marijuana exposure by trimester and/or averaged over pregnancy.

After these analyses, the potentially mediating effects of infant size (birthweight and length) on head circumference and of birth length on weight were evaluated by adding them to the regression models.

3. Results

3.1. Sample characteristics

Demographic and medical characteristics of the CE and NE infants are presented in Table 1. Cocaine-using women were older, had more children, and received less prenatal care. The majority of both groups were African American of

Table 5
Correlations of confounders with outcomes

	n	Gestational age	Birthweight	Length	Head circumference
Gender	415	.02	.10†	.11†	.11†
Race	415	−.07	−.12†	−.10†	−.19¶
Maternal age	415	−.04	−.12†	−.11†	−.15‡
Parity	415	−.10†	−.13‡	−.16¶	−.12†
Number of prenatal visits	413	.22¶	.26¶	.27¶	.16¶
Maternal education	415	−.04	.01	−.01	−.02
Socioeconomic status	414	.04	.05	.05	−.02
Marital status	391	.09	−.06	.07	.07
PPVT-R score	393	.02	.07	.10†	.06
WAIS-R BD score	397	.08*	0.07	.10†	.09*
WAIS-R PC score	397	.02	.03	−.01	.02
GSI	382	−.03	−.14‡	−.13†	−0.09*

* $P<.10$.
† $P<.05$.
‡ $P<.01$.
¶ $P<.001$.

Table 6
Effects of level of cocaine exposure on head circumference

Predictor	β (S.E.)	*t*	*P*
Race	−.77 (.27)	−3.58	.001
Maternal age	−.02 (.02)	−1.11	.26
Gender	.39 (.16)	2.51	.02
Log average cigarettes per day	−.05 (.08)	−0.66	.51
Log marijuana (Trimester 1)	−.18 (.12)	−1.48	.14
Log cocaine average	−.15 (.06)	−2.35	.02
Gestational age	.58 (.03)	19.92	.0001
GSI	−.50 (.26)	−1.99	.05

$F(8,367) = 65.2$, $P < .0001$, $R^2 = .59$.

low income status. Cocaine-using women had less education, lower vocabulary scores, were more likely to be unemployed, to use other substances of abuse, to report more psychological distress symptoms, and were less likely to be married. There were trends for lower BD and PC scores for cocaine-using women.

Table 2 shows the summary measures of frequency and severity of drug use for alcohol, marijuana, tobacco, and cocaine for both groups for the month prior to and during each trimester of pregnancy. The highest average use throughout pregnancy in the sample includes 80 cigarettes/day, 21 joints/week, 111 drinks/week, and 368 "rocks" of cocaine/week. The means and ranges of the concentration of cocaine metabolites in meconium were as follows: cocaine: 142 ng/g (0–3112); cocaethylene: 18 ng/g (0–419); BZE: 14 ng/g (552–9998); *m*-OH-BZE: 264 ng/g (0–9998).

3.2. Birth and maternal psychological outcomes

CE infants were smaller on all birth parameters and more likely to be preterm, have low birthweight, be small for gestational age, and microcephalic (see Table 3). After controlling for gestational age, CE infants weighed 230 g less, were 1.1 cm smaller in length, and 0.6 cm smaller in head circumference than NE infants. CE infants had three times the rate of microcephaly than NE infants.

Correlations of maternal self-report of severity of drug use with birth outcomes are presented in Table 4. Higher cigarette and cocaine exposures were significantly negatively related to all birth outcomes. Higher alcohol and marijuana exposures were related to poorer fetal growth on all parameters except gestational age.

Table 7
Effects of level of cocaine exposure on birthweight

Predictor	β (S.E.)	*t*	*P*
Maternal age	1.42 (4.2)	0.34	.74
Number of prenatal visits	4.74 (4.6)	1.04	.30
Gender	100.62 (42.3)	2.31	.02
Log average cigarettes per day	−31.78 (19.0)	−1.67	.10
Log alcohol (Trimester 3)	−84.00 (22.8)	−3.69	.0003
Log cocaine average	−39.10 (17.0)	−2.28	.02
Gestational age	174.6 (7.57)	23.07	.0001
GSI	−116.18 (67.0)	−1.74	.08

$F(8,371) = 87.7$, $P < .0001$, $R^2 = .65$.

Table 8
Effects of level of cocaine exposure on birth length

Predictor	β (S.E.)	*t*	*P*
Maternal age	.001 (.03)	0.02	.98
Number of prenatal visits	.06 (.03)	2.40	.02
Gender	.71 (.26)	2.73	.01
Log average cigarettes per day	−.03 (.13)	−0.26	.80
Log alcohol (Trimester 3)	−.28 (.14)	−2.07	.04
Log marijuana (Trimester 3)	−.47 (.27)	−1.76	.08
Log cocaine average	−.22 (.10)	−2.11	.05
Gestational age	.95 (.05)	20.12	.0001

$F(8,381) = 67.7$, $P < .0001$, $R^2 = .59$.

Cocaine-using women had greater severity of psychological distress symptoms (see Table 1) and were more likely to have clinically significant symptoms (> the 84th percentile) than non-cocaine-using women (41% vs. 20%, $\chi^2 = 19.3$, $P < .001$). Clinically significant depressive symptoms were reported by 36% of cocaine-using women compared to 16% of non-cocaine-using women ($\chi^2 = 19.6$, $P < .001$) and severe symptoms (> the 98th percentile) were reported by 15% of cocaine users compared to 6% of nonusers ($\chi^2 = 8.4$, $P < .004$). Similar patterns were seen for moderate anxiety (27% vs. 11%, $\chi^2 = 14.4$, $P < .001$) and severe anxiety (9% vs. 3%, $\chi^2 = 5.5$, $P < .02$). Symptoms of paranoid ideation and psychoticism were prominent, with 54% of cocaine users vs. 27% of nonusers reporting clinically significant symptoms of psychoticism ($\chi^2 = 27.2$, $P < .001$) and 53% of users vs. 30% of nonusers presenting with significant symptoms of paranoia ($\chi^2 = 25.1$, $P < .01$).

Confounding variables related to infant birth outcomes are shown in Table 5. Although there were no group differences in race and gender, these variables were retained in the model to assess their potential to moderate cocaine effects. Better maternal intellectual functioning was related to better fetal growth. Specifically, higher maternal vocabulary and BD scores were related to greater birth length, and there was a nonsignificant trend for BD score to be associated with larger head circumference and longer gestation. Infants of mothers who had more prenatal care visits had better outcomes on all growth parameters, while higher levels of maternal psychological distress, older maternal age, greater parity, non-White race, and female gender were all related to poorer growth.

3.3. Results of multiple regression analyses

When regression analyses controlling for all confounding and/or mediating variables were conducted, significant

Table 9
Effects of level of drug exposure on gestational age

Predictor	β (S.E.)	*t*	*P*
Number of prenatal visits	.23 (.03)	3.52	.0005
Log cigarettes average	−.23 (.11)	−2.03	.04

$F(2,389) = 10.4$, $P < .0001$, $R^2 = .05$.

Table 10
Spearman correlations of concentration (ng/g) of cocaine metabolites in meconium with birth outcomes ($n = 341$)

	Cocaine	BZE	*m*-OH-BZE
Birthweight	−.14*	−.20‡	−.17†
Birth length	−.12*	−.17†	−.13*
Head circumference	−.19‡	−.21‡	−.20†
Gestational age	−.04	−.08	−.07

* $P < .05$.
† $P < .01$.
‡ $P < .001$.

independent effects of severity of cocaine exposure to predict lower birthweight, length, and smaller head circumference were found (see Tables 6–8). The effects of cocaine on head circumference remained even after adjustment for infant gestational age and length, indicating differential effects on head size beyond those of general growth retardation.

Independent effects of other drugs were also found. After control for all other factors, Trimester 3 alcohol exposure predicted lower birth length and weight, and average cigarette exposure predicted gestational age (Table 9). There were nonsignificant trends for Trimester 3 marijuana exposure to predict lower birth length and cigarette exposure to predict birthweight.

Severity of maternal psychological distress predicted smaller head circumference after control for all drugs and other confounding variables. There was a nonsignificant trend for maternal distress to predict lower birthweight as well.

Other factors also independently predicted adverse growth outcomes. Fewer prenatal visits predicted shorter birth length and lower gestational age. Non-White race predicted smaller head circumference and female gender predicted smaller growth on all parameters. There were no interaction effects of drugs or confounding variables, and all main effects were significant after interaction terms were entered into the models.

In addition to maternal self-report measures of drug use, quantification of some cocaine metabolites from infant meconium was related to birth outcomes. Higher concentrations of cocaine, BZE, and *m*-OH-BZE were all significantly related to lower birthweight, length, and head circumference (see Table 10). Neither cocaethylene, the cocaine metabolite formed in the presence of alcohol [32], nor THC, the marijuana metabolite, was related to any birth outcome.

4. Discussion

After control for confounding drugs, lifestyle, and maternal intellectual and psychological factors, fetal cocaine exposure significantly predicted poorer birth outcomes, consistent with a teratologic model [72]. Moreover, lower birthweight, head circumference, and length were all linearly related to higher exposure levels by maternal report, as well as to higher concentrations of metabolites of cocaine, BZE, and *m*-OH-BZE in meconium, indicating that greater exposure was related to poorer outcomes. Head circumference was negatively affected even after control for depressed infant body size, corroborating a prior study, which found that fetal cocaine exposure was related to asymmetrical intrauterine growth retardation [35].

Intrauterine somatic and brain growth retardation are likely manifestations of neuroteratogenic effects of prenatal cocaine exposure [72]. Cocaine may induce significant teratogenic effects on the developing brain, as demonstrated in basic cellular and animal studies. In addition to known vascular effects, cocaine may independently cause a direct toxic effect at the neuronal cell level that would impair cortical development [33,34]. In primates, structural abnormalities have been demonstrated throughout the cerebral cortex in the brains of monkeys exposed prenatally to cocaine [70]. These abnormalities include a reduction in the number of cortical cells, inappropriate positioning of cortical neurons, and a reduction in levels of monoamines in laminae of multiple regions of the fetal cerebral wall [71].

Somatic growth deficits have been seen in response to cocaine treatment in rats [42]. Alterations of brain structure and function, including disturbances in brain growth and disruption of neocortical cytoarchitecture have been demonstrated in mouse models as well [42]. Prenatal cocaine administration has produced decreased cell proliferation, retarded neurite outgrowth, and delayed astroglial maturation in rat models [12]. Our findings are consistent with those of animal models, which, if generalizable to humans, indicate significant teratogenic effects of cocaine on fetal brain development and significant risk for later learning problems. These findings are also consistent with emerging, well-controlled studies of prenatally cocaine-exposed infants that have found neonatal neurobehavioral deficits [13,60], sensorimotor delays [2,59], and early cognitive and language problems [1,28,61].

Other drug effects were also important. Negative effects of alcohol and cigarette exposure on birthweight and of alcohol and marijuana on birth length remained after control for all other factors. Prenatal alcohol exposure has been related to lower birthweights and lengths in prior studies of birth outcomes [14]. In a similar low-socioeconomic status population, independent relationships were also found among prenatal marijuana exposure, birthweight, and length [75], but such effects were not found in a more middle-class sample [23].

Severity of maternal psychological distress symptoms postpartum predicted lower head circumference and birthweight, reflecting similar relationships found in non-drug-exposed infants [8,20,31,41,44,64]. Such symptoms postpartum may be predictive of fetal growth because they may be related to maternal distress symptoms during preg-

nancy, may reflect responses to life stressors during pregnancy and in the postpartum period, or they may reflect underlying maternal psychopathology. In a large, population-based study in Denmark, pregnant women experiencing moderate to severe stress had infants with smaller head circumferences [36]. Lower birthweights in non-drug-exposed infants have been found to be more likely to occur after stressful life events, while heavier birthweights were more likely after an intervention to reduce maternal anxiety during pregnancy [20]. Lower offspring birthweights after prenatal maternal stress have also been demonstrated in rodent models [24,48] and in nonhuman primates, even when gestational age and nutritional intake were not affected [55]. Moreover, alcohol exposure has been found to exacerbate the harmful effects of prenatal stress on birthweight in rhesus monkeys [57].

To date, there is increasing evidence that maternal psychological distress may impact gestation, as well as postpartum development [54]. Mechanisms by which maternal stress may affect fetal development have been shown to occur at the biochemical level through effects on the hypothalamic–pituitary–adrenal axis [46,54,56]. Because drug-using women are more likely than non-drug-using women to have comorbid psychological disorders [6,29,30,38,63], the role of maternal psychological distress symptoms in affecting fetal vulnerability to drug effects warrants further investigation. For example, in the sample studied here, maternal psychological distress as measured in this study was also related to offspring attentional abnormalities and sensory asymmetries in the neonatal period [60], consistent with preclinical studies [55,57].

The present study is consistent with others that indicate a high prevalence of psychiatric illness among adult substance abusers, especially antisocial personality disorder, anxiety, and affective disorders [29,30]. For women substance abusers, rates are particularly elevated for antisocial disorders, posttraumatic stress, mania, schizophrenia, and major depression [30]. This study highlights the need to address the mental health symptoms of women during pregnancy, the need to provide substance abuse assessment and intervention to pregnant women, and especially, to integrate mental health treatment into substance abuse services for pregnant women. Although the coordination of alcohol, drug abuse, and mental health services has long been advocated, the ability of pregnant women, especially poor, minority women, to access such services remains an unrealized goal [66]. In addition to the physiologic effects of maternal substance abuse and psychological distress demonstrated here, the harmful effects of these conditions on maternal–child interactions and subsequent child development have been documented [19,39,58].

The present study has several advantages that may have increased the likelihood of detecting significant drug effects. Maternal drug status was determined through both biologic (meconium and urine screen) and clinical means, enhancing reliability of classification [3,75]. In contrast to prior studies, we assessed a comprehensive set of potentially confounding variables, including maternal age, parity, intelligence, and level of prenatal care. Severity of exposure to all drugs was quantified to reduce the possibility of spuriously attributing effects of other drugs to cocaine. It should be noted, however, that although independent effects of cocaine were found, all CE infants were polydrug-exposed and, in human studies, the effects of cocaine can be separated only statistically from those of other drugs.

Other limitations of the study should be considered. Psychological distress and associated personality factors were not assessed during pregnancy, but after infant birth, when women may be particularly vulnerable due to hormonal and social factors [64]. Moreover, only a brief screening instrument was used to assess maternal distress symptoms in this study; thus, evidence for maternal psychopathology cannot be construed from the findings.

Although the relationship found between a postnatal measure of maternal distress and fetal growth in this sample is interesting, these data should be considered preliminary and heuristic, as other studies have linked similar findings of maternal anxiety and depression to the impact of preterm, lower-birthweight birth on the caregiver [64]. Future studies should be conducted with better prospective designs, assessing maternal stress prenatally. Utilization of more specific measures of maternal psychopathology in combination with physiologic measures may provide evidence for the hypothesized linkages between fetal growth, maternal distress, and underlying brain physiology.

In summary, the present study found significant effects of cocaine/polydrug exposure and severity of maternal psychological distress symptoms on fetal growth, with heavier exposure and greater maternal distress related to poorer growth, even after control for effects of other drugs and potential confounders. In particular, differential effects on head circumference, an indicator of brain growth, raise concerns about the long-term cognitive development of CE infants.

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