ARTICLE

Acute Neonatal Effects of Cocaine Exposure During Pregnancy

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Objective: To identify associations between cocaine exposure during pregnancy and medical conditions in newborn infants from birth through hospital discharge.

Design: Multisite, prospective, randomized study.

Setting: Brown University, University of Miami, University of Tennessee (Memphis), and Wayne State University.

Subjects: A total of 717 cocaine-exposed infants and 7442 nonexposed infants.

Main Outcome Measures: Results of physical examination and conditions observed during hospitalization.

Results: Cocaine-exposed infants were about 1.2 weeks younger, weighed 536 g less, measured 2.6 cm shorter, and had head circumference 1.5 cm smaller than nonexposed infants (all $P<.001$). Results did not confirm previously reported abnormalities. Central and autonomic nervous system symptoms were more frequent in the exposed group: jittery/tremors (adjusted odds ratio, 2.17; 99% confidence interval, 1.44-3.29), high-pitched cry (2.44; 1.06-5.66), irritability (1.81; 1.18-2.80), excessive suck (3.58; 1.63-7.88), hyperalertness (7.78; 1.72-35.06), and autonomic instability (2.64; 1.17-5.95). No differences were detected in organ systems by ultrasound examination. Exposed infants had more infections (3.09; 1.76-5.45), including hepatitis (13.46; 7.46-24.29), syphilis (8.84; 3.74-20.88), and human immunodeficiency virus exposure (12.37; 2.20-69.51); were less often breastfed (0.26; 0.15-0.44); had more child protective services referrals (48.92; 28.77-83.20); and were more often not living with their biological mother (18.70; 10.53-33.20).

Conclusions: Central and autonomic nervous system symptoms were more frequent in the exposed cohort and persisted in an adjusted analysis. They were usually transient and may be a true cocaine effect. Abnormal anatomic outcomes previously reported were not confirmed. Increased infections, particularly sexually transmitted diseases, pose a serious public health challenge. Exposure increased involvement of child protective services and out-of-home placement.

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DRUG USE BY PREGNANT women remains a pervasive problem in American society. In 2002, 3% of all pregnant women aged 15 to 44 years exposed their fetus to 1 or more illicit drugs.[1] Attempts to isolate effects attributable to a specific drug exposure, such as cocaine, have often been confounded by the use of multiple drugs and limited access to large varied populations. Drug abusers are mobile, difficult to track over time, and often noncompliant.[2,3] From the mid-1980s into the early 1990s, a number of reports raised concerns about the potential teratogenic impact of fetal cocaine exposure during pregnancy. These observations included congenital anomalies,[4,5] growth retardation,[6-8] microcephaly,[9,10] central nervous system infarction,[11] seizures,[12] cortical atrophy and cysts,[13] intraventricular hemorrhage,[14,15] various neurologic impairments,[16,17] genitourinary tract and renal anomalies,[18-20] gastrointestinal tract defects,[21,22] limb deformities,[23] and respiratory insufficiency including sudden infant death syndrome.[24-27] A differential effect of drug exposure on preterm vs term infants has been suggested.[28] More recent studies and systematic reviews have emphasized potential effects on long-term neurodevelopment, behavior, and learning[29-33] while both the acute and chronic impacts of cocaine on growth remain.[32,34,35] How race, sex, drug dose, sociodemographics, and other important modifying variables impact ultimate outcome has recently been considered.[36,37] Well-designed, prospective studies that fail to identify significant drug effects, ie, negative studies, may be published less often and therefore not referenced.[38] This may result in a biased overreporting of less signifi-

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cant observations, as occurred in the early years of the crack and cocaine epidemic.

The Maternal Lifestyle Study (see page 833 for a list of institutions and investigators) was conceived and designed as a large multisite, prospective, randomized study, whose objective was to confirm or negate the null hypothesis that fetal cocaine exposure during pregnancy has no impact on acute maternal and infant medical outcomes, or on long-term neurodevelopmental infant outcomes.

Access to a large, multisite population was possible through the National Institute of Child Health and Human Development Neonatal Research Network, which, at the time the study was initiated, consisted of 12 major university research centers. The feasibility of successfully studying multicultural, multiethnic, sociodemographically varied populations with widespread use of drugs had been previously documented at several of the network participating centers.[39-41] Four of the 12 network sites were selected by competitive peer review to participate in the Maternal Lifestyle Study. A wide range of acute medical outcomes in cocaine-exposed and nonexposed infants, including sociodemographic circumstances and polydrug use, were assessed in infants recruited at these sites. Acute maternal pregnancy outcomes in these cohorts have already been reported.[42] This report presents identified associations between cocaine exposure during pregnancy and medical conditions in the newborn infant from birth through hospital discharge or death.

METHODS

Recruitment and screening occurred during a 2-year period at 4 centers: Brown University, Providence, RI; the University of Miami, Miami, Fla; the University of Tennessee, Memphis; and Wayne State University, Detroit, Mich. Informed maternal consent and institutional review board approval were required for participation. Reasons for noneligibility and nonenrollment are listed in **Figure 1**. Mothers who consented were more likely to be black (50.5% vs 46.5%), to be unmarried (62.3% vs 56.5%), and to have a history of drug use (13.0% vs 9.3%). Mothers who identified themselves as white consented equally often (44.4% vs 44.9%) while those who responded that they were of "other" race consented at lower rates (5.1% vs 8.6%). Differences in preterm delivery rate, abruptio placentae, prenatal care, and use of Medicaid between those who consented and those who did not were small. All low-birth-weight infants (<1500 g) were screened. Maternal and infant charts were reviewed to identify obvious protocol exclusions. Informed consent was usually obtained before or within 24 hours of delivery.

Initial screening included the mother's labor and delivery record, the newborn admission record, and a meconium sample. A detailed drug use questionnaire that addressed the mother's use of nicotine, alcohol, marijuana, cocaine, opiates, and other illicit drugs was given by research staff trained and certified in the reliable administration of all the study interviews. A Department of Health and Human Services Certificate of Confidentiality allowed for strict confidentiality regarding all drug use information, including the 2 states (Florida and Rhode Island) that had mandatory reporting statutes. The certificate did not, however, circumvent required reporting of child abuse, sexual abuse, or neglect.

Although recruitment addressed exposure to cocaine and/or opiates, all analyses presented herein are limited to the cocaine-only and the non–cocaine-exposed cohorts.

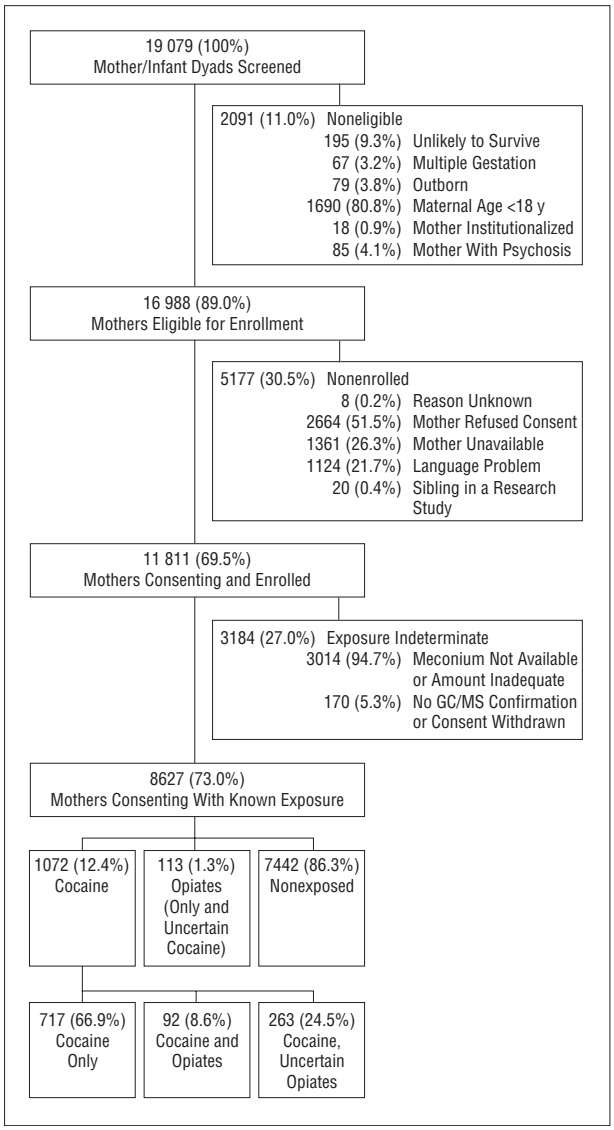

Figure 1. Screening, enrollment, exclusions, eligibility, consent, and exposure identification. GC/MS indicates gas chromatography–mass spectroscopy.

Cocaine exposure was defined by maternal admission of cocaine use at any time during this pregnancy or a positive enzyme-multiplied immunoassay technique (EMIT) screen for cocaine metabolites in the infant's meconium, confirmed by gas chromatography–mass spectroscopy, coupled with a negative EMIT screen for opiates. All analyses were performed by a central laboratory (El Sohly Laboratories Inc, Oxford, Miss)[43] after informed consent was obtained. A history of cocaine use recorded in the medical record was not sufficient to qualify as exposed. Mothers who denied use, but in whom the infant's meconium EMIT screen was positive and gas chromatography–mass spectroscopy analysis was not available, were excluded.[44] A nonexposure designation required both a maternal denial of use and a negative result of meconium screening. There were 3183 infants of consenting mothers whose exposure could not be determined primarily because of lack of gas chromatography–mass spectroscopy confirmation. This included 2760 in whom meconium was unavailable, 254 in whom the quantity of meconium collected was insufficient for any analysis, and 169 with a positive EMIT screen but who had insufficient amounts of meconium for gas chromatography–mass spectroscopy confirma-

Table 1. Cocaine Exposure by Source of Information, Birth Weight, Gestational Age, and Location of Clinic*

			Cocaine Meconium Results		Cocaine Use	
	No.	Cocaine Self-report	EMIT Screen Positive	GC/MS Positive	By Self-report *and* Meconium GC/MS Positive	By Self-report *or* Meconium GC/MS Positive
Total eligible	11 811	882 (7.5)	809 (6.8)	594 (5.0)	404 (3.4)	1072 (9.1)
Birth weight, g						
501-1500	755	95 (12.6)	67 (8.9)	39 (5.2)	23 (3.0)	111 (14.7)
1501-2500	2060	298 (14.5)	295 (14.3)	243 (11.8)	181 (8.8)	360 (17.5)
>2500	8996	489 (5.4)	447 (5.0)	312 (3.5)	200 (2.2)	601 (6.7)
Gestational age† (best OB), wk						
≤27	352	38 (10.8)	26 (7.4)	15 (4.3)	8 (2.3)	45 (12.8)
28-32	789	110 (13.9)	95 (12.0)	67 (8.5)	49 (6.2)	128 (16.2)
33-37	2739	354 (12.9)	302 (11.0)	253 (9.2)	197 (7.2)	410 (15.0)
≥38	7920	375 (4.7)	381 (4.8)	254 (3.2)	145 (1.8)	484 (6.1)
Location of clinic						
Detroit, Mich	2674	315 (11.8)	345 (12.9)	277 (10.4)	186 (7.0)	406 (15.2)
Memphis, Tenn	2809	296 (10.5)	199 (7.1)	164 (5.8)	124 (4.4)	336 (12.0)
Miami, Fla	2990	171 (5.7)	139 (4.6)	88 (2.9)	54 (1.8)	205 (6.9)
Providence, RI	3338	100 (3.0)	126 (3.8)	65 (1.9)	40 (1.2)	125 (3.7)

Abbreviations: EMIT, enzyme-multiplied immunoassay technique; GC/MS, gas chromatography–mass spectroscopy; OB, obstetric estimate.
*Data are presented as number (percentage) unless otherwise indicated.
†Eleven subjects had missing gestational ages.

tion.There was also 1 mother who withdrew consent. None of the mothers of these infants admitted cocaine use during pregnancy. Those mothers excluded because of indeterminate exposure were less likely to be black (47.5% vs 51.6%), were more likely to be married (40.7% vs 36.6%), and had a higher rate of preterm birth (7.8% vs 5.7%). As with mothers who refused consent, there were no important differences in their Medicaid insurance status, rate of prenatal care, or prevalence of abruptio placentae. Of the total 1072 infants with known exposure to cocaine, 717 (66.9%) were known to be exposed only to cocaine (Figure 1). The remaining cocaine-exposed infants were excluded as indeterminate. Use of alcohol, marijuana, and/or nicotine during pregnancy occurred in both groups (95% of those exposed, 42% of those nonexposed).

A standardized physical and neurologic examination, made up of 62 specific items and including the New Ballard Score,[45] was performed within the first 24 hours of life by centrally trained and certified examiners from each site, who were masked to exposure status. Birth weight, length, and head circumference were measured and recorded. These same certified research personnel observed the "acute" course of these infants, which included the time from birth to infant death or discharge from the hospital. Seventy-seven individual conditions and/or diagnoses were recorded during the hospitalization. Detailed information on therapies, procedures, resuscitation, the length of stay, child protective services reporting, and proposed living situation was also collected. Information on medications administered to the mothers at delivery and complications of labor and delivery were assessed and reported previously.[42]

To compensate for and to protect against inflated type I error levels that may be caused by multiple comparisons, we decided a priori to report $P<.01$ as significant in these analyses. In addition, to reduce the number of reported outcomes and to eliminate redundancy, information from multiple sources was combined where this was deemed clinically valid, and outcomes with a prevalence of less than 1% in the nonexposed cohort and that had no occurrence in the cocaine-exposed cohort were dropped but are listed in the appropriate table footnotes. Outcome data were summarized by exposure groups, using frequency distributions (χ^2 tests) or means and standard deviations (unpaired 2-tailed t tests) when appropriate. The estimated odds ratios and 99% confidence intervals are presented as a summary of the unadjusted relationship between cocaine-exposure status and each outcome.

Statistically significant ($P<.01$) bivariate associations were subjected to multivariate modeling to obtain covariate-adjusted estimates. Linear and logistic regression models were fitted for continuous and binary outcomes, respectively. A standard set of 10 covariates plus cocaine use, chosen a priori for all multivariate analyses, was as follows: clinical site; race or ethnicity; sex; birth weight; being small for gestational age; the use of alcohol, tobacco, or marijuana during pregnancy; maternal age; and maternal education. Tobacco exposure was categorized at 3 levels as high use (≥0.5 pack per day), low use (any other use), and no use. Alcohol was categorized into 3 groups: alcohol use with bingeing, nonbingeing alcohol use, and no alcohol use. Marijuana was entered as a simple yes-no use variable. Race or ethnicity of the mother was based on self-identification as black, Hispanic, or white/other. Maternal age was based on whether the mother was 26 years or older, or younger than 26 years, at the time of delivery. Maternal education (<12 years or ≥12 years) was considered a surrogate for socioeconomic status. Being small for gestational age was entered into the model to adjust for the enhanced effect of low birth weight seen primarily in the near-full-term subjects in the study. Being small for gestational age was based on a birth weight of less than 10th percentile for gestational age.[46]

RESULTS

Of the 19 079 women screened, 16 988 (89.0%) were eligible for recruitment, and 11 811 of those (69.5%) consented (Figure 1). Meconium was analyzed in 8804 infants (74.5%). There were 3184 excluded infants (27.0%). Meconium quantity was insufficient for any screening analysis in 2760 and in an additional 254 infants to confirm a positive EMIT screen; no meconium was collected in 169 infants, and 1 mother withdrew consent. Maternal self-report alone identified 7.5% of infants as cocaine exposed, and meconium analysis identified a 5.0% exposure rate (**Table 1**). The total cocaine-exposure rate was 9.1%. Meconium analysis identified an additional 190

exposed infants (1.6%) not acknowledged by self-report. Cocaine-exposure rates at the various sites ranged between 3.7% and 15.2%. The exposure rate in the low-birth-weight population (≤2500 g) was more than double that of normal-birth-weight infants (16.7% vs 6.7%). Of mothers who admitted cocaine use during pregnancy, meconium testing was confirmatory in 66.2% of the cases where both meconium and self-report were available. Because maternal admission alone was sufficient to define an infant as exposed, meconium screens and confirmations were not run on all of these infants. However, as noted already, an additional 1.6% of exposed infants, whose mothers denied use during pregnancy, were identified by meconium analysis.

The 717 infants identified as exposed to cocaine only (Figure 1) were more often black (78.9% vs 46.3%) and their mothers were older (79.9% aged ≥26 years vs 48.3%) than the 7442 subjects in the nonexposed cohort (**Table 2**). The prevalence of prematurity (≤37 weeks' gestation) was significantly greater in the cocaine-exposed cohort (42.6% vs 24.2%). Use of tobacco (81.8% vs 19.7%), alcohol (73.0% vs 30.6%), and marijuana (39.2% vs 5.0%) were all greater ($P<.001$) in the cocaine-exposed cohort.

Table 3 lists the prevalence of specific physical findings and physiological observations assessed during the initial infant examination, as well as diagnoses and/or conditions observed during hospitalization. Abnormal physical findings were rare, with only tachypnea exceeding a 5% prevalence in either group. Two observations (flat philtrum and tachypnea) were significantly more frequent in the exposed cohort, but not after adjusting for covariates in a multivariable logistic regression model. The diagnoses of respiratory distress–transient tachypnea, apnea, retinopathy of prematurity, hepatitis, syphilis, human immunodeficiency virus–positive status, proven sepsis, and any infection were significantly more prevalent in the cocaine-exposed cohort. Hepatitis, syphilis, human immunodeficiency virus–positive status, and any infection remained significant after adjusting for covariates. These infections, determined during the hospitalization and based on laboratory confirmation, were consistent with the infection findings documented in the mothers.[42]

Several central and autonomic nervous system findings, which included hypertonia, jitteriness or tremors, high-pitched cry, difficulty arousing, irritability, excessive suck, and hyperalertness, were noted more frequently on the initial physical examination in the cocaine-exposed cohort (**Table 4**). During the hospitalization, the diagnoses of seizures and autonomic instability were more frequently noted in cocaine-exposed infants. When adjusted, all of these findings except hypertonia, difficulty arousing, and seizures remained significant in the exposed cohort.

More screening and diagnostic echocardiograms of the heart, abdomen, and head were performed in the exposed cohort (odds ratio, 1.54; 99% confidence interval, 1.01-2.34) (**Table 5**), explained primarily by lower-birth-weight infants in that group. In addition, they were ordered by the infant's primary caretakers, who were usually aware of the infant's exposure status as well as the early literature that suggested that anatomic abnormalities might

Table 2. Characteristics of Subjects by Infant's Drug Exposure Status*

	No. (%)		
	Cocaine Exposed (n = 717)	Nonexposed (n = 7442)	Odds Ratio (99% CI)
Maternal Characteristics			
Race/ethnicity			
Black	566 (78.9)	3448 (46.3)	4.34 (3.40-5.54)
White	89 (12.4)	2196 (29.5)	0.34 (0.25-0.46)
Hispanic	52 (7.3)	1625 (21.8)	0.28 (0.19-0.41)
Other	10 (1.4)	173 (2.3)	0.59 (0.26-1.38)
Maternal age, y			
18-25	144 (20.1)	3848 (51.7)	0.23 (0.18-0.30)
26-35	492 (68.7)	3019 (40.6)	3.22 (2.59-3.99)
36-49	80 (11.2)	572 (7.7)	1.51 (1.09-2.09)
Marital status			
Married	72 (10.1)	2997 (40.4)	0.17 (0.12-0.23)
Single	616 (86.5)	4273 (57.6)	4.64 (3.48-6.18)
Divorced	24 (3.4)	143 (1.9)	1.76 (1.01-3.07)
Insurance			
Medicaid	618 (87.9)	4535 (61.1)	4.62 (3.41-6.26)
Self-pay	52 (7.4)	848 (11.4)	0.62 (0.42-0.91)
HMO/private	33 (4.7)	2034 (27.4)	0.13 (0.08-0.21)
Education, <12 y	360 (50.2)	2139 (28.7)	2.24 (1.83-2.74)
Worked in last year	163 (22.7)	3987 (53.6)	0.25 (0.20-0.32)
Prenatal care	542 (75.6)	7226 (97.1)	0.09 (0.07-0.12)
Infant Characteristics			
Location of birth			
Detroit, Mich	306 (42.7)	1920 (25.8)	2.14 (1.74-2.63)
Memphis, Tenn	208 (29.0)	1457 (19.6)	1.68 (1.34-2.10)
Miami, Fla	127 (17.7)	1850 (24.9)	0.65 (0.50-0.85)
Providence, RI	76 (10.6)	2215 (29.8)	0.28 (0.20-0.38)
Infant of male sex	362 (50.5)	3876 (52.1)	0.94 (0.77-1.15)
Gestational age, wk			
24-27	15 (2.1)	92 (1.3)	1.62 (0.79-3.35)
28-32	60 (8.4)	327 (4.6)	1.89 (1.29-2.75)
33-37	229 (32.1)	1277 (18.1)	2.13 (1.71-2.66)
38-44	409 (57.0)	5340 (75.9)	0.43 (0.35-0.53)
Background Drug Use			
Tobacco use during pregnancy			
High use, ≥0.5 pack/d	359 (50.2)	831 (11.2)	8.00 (6.46-9.92)
Some use, <0.5 pack/d	226 (31.6)	633 (8.5)	4.96 (3.93-6.26)
No use	130 (18.2)	5963 (80.3)	0.05 (0.04-0.07)
Alcohol use during pregnancy			
High use, ≥1 drink/wk	261 (36.4)	190 (2.6)	21.85 (16.59-28.77)
Moderate use, 1-3 drinks/mo	128 (17.9)	320 (4.3)	4.84 (3.62-6.47)
Low use, <1 drink/mo	134 (18.7)	1767 (23.7)	0.74 (0.57-0.95)
No use	194 (27.1)	5165 (69.4)	0.16 (0.13-0.20)
Alcohol bingeing during pregnancy	154 (21.5)	142 (1.9)	6.27 (4.49-8.75)
Marijuana use during pregnancy	281 (39.2)	374 (5.0)	12.18 (9.58-15.48)
Any tobacco, alcohol, or marijuana use during pregnancy	680 (94.8)	3114 (41.8)	25.54 (16.47-39.62)

Abbreviations: CI, confidence interval; HMO, health maintenance organization.

*The category totals do not always add up owing to a small number of missing values not obtainable at the time of the hospital interview.

Table 3. Prevalence of Physical Findings and Symptoms Observed on Initial Physical Examination or During Hospitalization by Infant's Drug Exposure Status*

	No. (%)		Cocaine Exposed	
	Cocaine Exposed (n = 717)	Nonexposed (n = 7442)	Unadjusted Odds Ratio (99% CI)	Adjusted Odds Ratio (99% CI)
Initial Physical Examination				
Cardiac				
Arrhythmia	3 (0.4)	32 (0.4)	0.93 (0.20-4.42)	NA
Murmur	23 (3.2)	172 (2.3)	1.34 (0.75-2.39)	NA
Respiratory				
Tachypnea	46 (6.4)	272 (3.7)	1.73 (1.13-2.64)	1.15 (0.66-2.00)
Labored breathing	7 (1.0)	89 (1.2)	0.78 (0.28-2.15)	NA
Nasal flaring	11 (1.5)	96 (1.3)	1.14 (0.50-2.60)	NA
Retractions	34 (4.7)	271 (3.6)	1.26 (0.78-2.03)	NA
Face				
Epicanthal folds	1 (0.1)	20 (0.3)	0.50 (0.04-6.95)	NA
Flat philtrum	8 (1.1)	23 (0.3)	3.50 (1.21-10.12)	2.93 (0.98-8.73)†
Low-set/posterior ears	8 (1.1)	68 (0.9)	1.17 (0.44-3.08)	NA
Preauricular tags	2 (0.3)	12 (0.2)	1.66 (0.23-11.87)	NA
Micrognathia	3 (0.4)	10 (0.1)	2.99 (0.55-16.33)	NA
Cleft lip/palate	1 (0.1)	8 (0.1)	1.24 (0.08-19.10)	NA
Skeletal				
Clubfoot	1 (0.1)	11 (0.1)	0.90 (0.06-13.32)	NA
Genitourinary				
Hydrospadias	4 (0.6)	23 (0.3)	1.81 (0.45-7.33)	NA
Gastrointestinal				
Abdominal distention	5 (0.7)	32 (0.4)	1.56 (0.45-5.39)	NA
Abdominal wall defect	5 (0.7)	23 (0.3)	2.26 (0.63-8.11)	NA
During Hospitalization				
Respiratory				
Respiratory distress syndrome	48 (6.7)	400 (5.4)	1.26 (0.84-1.90)	NA
Bronchopulmonary dysplasia	15 (2.1)	110 (1.5)	1.42 (0.70-2.91)	NA
Respiratory distress/TTN	86 (12.0)	545 (7.3)	1.72 (1.26-2.37)	0.98 (0.65-1.47)
Apnea	54 (7.5)	353 (4.7)	1.64 (1.11-2.42)	0.68 (0.35-1.34)
Gastrointestinal				
Necrotizing enterocolitis	10 (1.4)	52 (0.7)	2.01 (0.82-4.92)	NA
Infection				
Cytomegaloviris	1 (0.1)	2 (<0.1)	5.19 (0.22-122.00)	NA
Herpes	2 (0.3)	4 (0.1)	5.20 (0.56-48.51)	NA
Hepatitis	4 (0.6)	1 (<0.1)	41.74 (2.34-744.77)	13.46 (7.46-24.29)†
Syphilis	51 (7.1)	38 (0.5)	14.92 (8.51-26.16)	8.84 (3.74-20.88)
HIV-positive status	6 (0.8)	4 (0.1)	15.69 (2.97-83.00)	12.37 (2.20-69.51)†
Proven sepsis	22 (3.1)	122 (1.6)	1.90 (1.04-3.48)	0.93 (0.39-2.22)
Any infection	76 (10.6)	167 (2.2)	5.16 (3.56-7.49)	3.09 (1.76-5.45)
Syndromes/malformations				
Down syndrome	2 (0.3)	6 (0.1)	3.47 (0.42-28.46)	NA
Any syndrome/malformation	2 (0.3)	33 (0.4)	0.63 (0.10-4.11)	NA
Sensory				
Retinopathy of prematurity	24 (3.3)	128 (1.7)	1.97 (1.10-3.54)	1.11 (0.35-3.48)

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; NA, not applicable; TTN, transient tachypnea of the newborn.
*Observations that were rare (<1%) in the nonexposed cohort and were not seen in the cocaine-exposed cohort included missing digits, prune belly, intestinal atresia, renal mass, meconium peritonitis, tracheoesophageal fistula, Potter syndrome, fetal alcohol syndrome, trisomy 13, trisomy 18, and limb reductions.
†Model fit with only birth weight and cocaine exposure because of modeling limitations.

be associated with intrauterine cocaine exposure. Despite this increased surveillance, no ultrasound diagnoses were more prevalent in the cocaine-exposed group.

The cocaine-exposed infants were significantly smaller ($P<.001$) in all growth measures before and after adjustment (**Table 6**). They were 536 g lighter at birth, were 2.6 cm shorter, and had a 1.5-cm smaller head circumference. Gestational age was significantly lower by 8.4 days (1.2 weeks) in the cocaine-exposed group (as measured by the revised Ballard examination[45]). The prevalence of being small for gestational age was more than double in the cocaine-exposed cohort (29.4% vs 13.5%). The relationship between birth weight and gestational age is complex. **Figure 2** displays that relationship by contrasting birth weights at various gestational ages in the 2 study groups on the basis of the birth weight categories (501-1500, 1501-2500, and >2500 g). The negative effect of cocaine exposure was most evident in the heavier, later-gestation infants.

Delivery room resuscitation and intubation occurred more frequently in the cocaine-exposed infants (**Table 7**). Similarly, exposed infants received more therapies and

Table 4. Prevalence of CNS and ANS Findings and Symptoms Observed on Initial Physical Examination or by Chart Review at Death or Discharge by Infant's Drug Exposure Status*

	No. (%)		Cocaine Exposed	
	Cocaine Exposed (n = 717)	Nonexposed (n = 7442)	Unadjusted Odds Ratio (99% CI)	Adjusted Odds Ratio (99% CI)
Initial Physical Examination				
CNS				
Hyperactive	3 (0.4)	18 (0.2)	1.66 (0.33-8.28)	NA
Hypertonia	14 (2.0)	54 (0.7)	2.60 (1.19-5.67)	1.90 (0.67-5.40)
Hypotonia	13 (1.8)	168 (2.3)	0.76 (0.36-1.61)	NA
Jittery/tremors	104 (14.5)	420 (5.6)	2.70 (2.00-3.66)	2.17 (1.44-3.29)
High-pitched cry	21 (2.9)	103 (1.4)	2.04 (1.10-3.82)	2.44 (1.06-5.66)
Weak cry	7 (1.0)	65 (0.9)	1.06 (0.38-2.98)	NA
Abnormal posture	3 (0.4)	9 (0.1)	3.31 (0.59-18.52)	NA
Difficult to console	14 (2.0)	68 (0.9)	2.06 (0.96-4.42)	NA
Difficult to arouse	9 (1.3)	27 (0.4)	3.34 (1.23-9.04)	2.83 (0.68-11.70)
Irritability	87 (12.1)	407 (5.5)	2.28 (1.65-3.15)	1.81 (1.18-2.80)
Lethargy	18 (2.5)	137 (1.8)	1.31 (0.68-2.52)	NA
Fisting	19 (2.6)	205 (2.8)	0.92 (0.49-1.72)	NA
Cortical thumb	14 (2.0)	194 (2.6)	0.71 (0.35-1.46)	NA
ANS				
Sneezing	24 (3.3)	220 (3.0)	1.09 (0.62-1.91)	NA
Hiccoughing	1 (0.1)	42 (0.6)	0.24 (0.02-3.19)	NA
Mottling	4 (0.6)	67 (0.9)	0.59 (0.16-2.23)	NA
Bradycardia	5 (0.7)	24 (0.3)	2.08 (0.58-7.39)	NA
Tachycardia	6 (0.8)	67 (0.9)	0.89 (0.29-2.67)	NA
Poor suck	28 (3.9)	190 (2.6)	1.48 (0.87-2.52)	NA
Excessive suck	16 (2.2)	47 (0.6)	3.43 (1.62-7.28)	3.58 (1.63-7.88)†
Nasal stuffiness	19 (2.6)	121 (1.6)	1.57 (0.83-2.99)	NA
Hyperthermia	1 (0.1)	8 (0.1)	1.24 (0.08-19.11)	NA
Hypothermia	3 (0.4)	19 (0.3)	1.57 (0.32-7.80)	NA
Hyperalertness	6 (0.8)	7 (0.1)	8.57 (2.04-36.05)	7.78 (1.72-35.06)†
During Hospitalization				
CNS				
Seizures	12 (1.7)	36 (0.5)	3.50 (1.47-8.31)	1.23 (0.40-3.81)
Hydrocephalus	1 (0.1)	16 (0.2)	0.65 (0.05-9.24)	NA
ANS				
Autonomic instability	27 (3.8)	84 (1.1)	3.43 (1.92-6.11)	2.64 (1.17-5.95)

Abbreviations: ANS, autonomic nervous system; CI, confidence interval; CNS, central nervous system; NA, not applicable.
*Observations that were rare (<1%) in the nonexposed cohort and were not seen in the cocaine-exposed cohort included encephalocele, meningomyelocele, microphthalmia, pavulonization, hypoxic-ischemic encephalopathy, sunset sign, nystagmus, strabismus, and sweating.
†Model fit with only birth weight and cocaine exposure because of modeling limitations.

underwent more procedures, but adjustment for other explanatory factors eliminated these differences. Cocaine-exposed infants were less often breastfed even after correcting for the birth weight differences between exposed and nonexposed infants. The increased admissions of exposed infants to neonatal intensive care or special care units was again related to the higher prevalence of low-birth-weight infants in the exposed cohort. There was no difference in survival (99.6% vs 99.7%), but the duration of hospitalization for infants who died (13.0 vs 56.2 days) was significantly shorter ($P = .008$) for the cocaine-exposed infants, again explained primarily by the birth weight disparity between the 2 groups. Exposed infants who survived were 48 times more likely to be kept in the hospital, labeled as "boarder infants," resulting in extended hospital stays (17.6% vs 0.5%) (Table 7).

Exposed infants were 49 times more likely to be involved with child protective services (38.5% vs 1.0%) and 19 times more often were discharged to the care of someone other than their mothers (18.8% vs 1.0%). Mothers of exposed infants were 6 times more likely to consider adoption as a permanent placement for their infants (2.1% vs 0.4%) (**Table 8**).

COMMENT

The teratogenic and toxic potential of fetal exposure to cocaine remains controversial. The Maternal Lifestyle Study attempted to clarify some of the ambiguity surrounding this important public health problem. The strengths of this study include its large sample size and extensive training and certification of research teams at each site to ensure consistency and reliability of both assessments and data collection. The multisite nature of this collaboration provided a multicultural, multiethnic population that included broad-based sociodemographic characteristics. The definition of cocaine-exposure status was

Table 5. Screening and/or Diagnostic ECHO Examinations Performed*

	No. (%)		Cocaine Exposed	
	Cocaine Exposed (n = 717)	Nonexposed (n = 7442)	Unadjusted Odds Ratio (99% CI)	Adjusted Odds Ratio (99% CI)
Cardiac ECHO				
ECHO done	46 (6.4)	318 (4.3)	1.54 (1.01-2.34)	1.02 (0.58-1.78)
Findings†				
Abnormal ECHO	32 (69.6)	246 (77.4)	0.67 (0.27-1.64)	NA
Transposition	1 (2.2)	3 (0.9)	2.33 (0.12-46.98)	NA
Pulmonary atresia	0 (0.0)	4 (1.3)	NA	
Pulmonary stenosis	6 (13.0)	36 (11.3)	1.18 (0.35-3.97)	NA
Ventricular septal defect	3 (6.5)	37 (11.6)	0.53 (0.11-3.63)	NA
Atrial septal defect	7 (15.2)	39 (12.3)	1.28 (0.41-4.04)	NA
Patent ductus arteriosus	19 (41.3)	165 (51.9)	0.65 (0.29-1.49)	NA
Other cardiac abnormalities	14 (30.4)	81 (25.5)	1.28 (0.53-3.12)	NA
Abdominal ECHO				
ECHO done	58 (8.1)	199 (2.7)	3.20 (2.15-4.77)	3.21 (1.81-5.66)
Findings†				
Abnormal ECHO	13 (22.4)	40 (20.1)	1.15 (0.45-2.91)	NA
Renal agenesis/dysgenesis	0 (0.0)	3 (1.5)	NA	
Hydronephrosis	7 (12.1)	19 (9.5)	1.30 (0.39-4.36)	NA
Ectopic kidney	2 (3.4)	1 (0.5)	7.07 (0.29-169.83)	NA
Abnormal collecting system	3 (5.2)	17 (8.5)	0.58 (0.11-3.07)	NA
Cystic kidney	0 (0.0)	6 (3.0)	NA	
CNS ECHO				
ECHO done	132 (18.4)	711 (9.6)	2.14 (1.63-2.79)	1.18 (0.73-1.90)
Findings†				
Abnormal ECHO	39 (29.5)	219 (30.8)	0.94 (0.55-1.60)	NA
Subependymal hemorrhage	29 (22.0)	136 (19.1)	1.19 (0.66-2.15)	NA
Intraventricular hemorrhage	10 (7.6)	53 (7.5)	1.02 (0.40-2.56)	NA
Parenchymal hemorrhage	1 (0.8)	6 (0.8)	0.90 (0.05-14.63)	NA
Cysts/lucencies	8 (6.1)	51 (7.2)	0.83 (0.30-2.29)	NA
Periventricular leukomalacia	1 (0.8)	12 (1.7)	0.44 (0.03-6.56)	NA
Ventriculomegaly	7 (5.3)	35 (4.9)	1.08 (0.36-3.23)	NA

Abbreviations: CI, confidence interval; CNS, central nervous system; ECHO, echocardiogram; NA, not applicable.

*ECHO results that were reported in less than 1% of the nonexposed population and were not observed in the cocaine-exposed cohort included tetralogy of Fallot, total anomalous pulmonary venous return, hypoplastic left ventricle, hypoplastic right ventricle, myocardial dysfunction, horseshoe kidney, posterior urethral valves, duplication, subarachnoid hemorrhage, and cerebral infarct.

†Percentages are calculated from the number of subjects in whom the ECHO study was done.

Table 6. Growth and Gestational Age Measures on Newborn Initial Physical Examination by Infant's Drug Exposure Status

				Linear Regression Multivariate Modeling Results*				Logistic Regression Multivariate Modeling Results, Cocaine Exposed*	
				Cocaine Exposed					
	Cocaine Exposed (n = 717)	Nonexposed (n = 7442)	Unadjusted *P* Value	Parameter Estimate	Adjusted *P* Value	Adjusted Mean	Nonexposed, Adjusted Mean	Unadjusted Odds Ratio (99% CI)	Adjusted Odds Ratio (99% CI)
Birth weight, mean ± SD, g	2531 ± 695	3067 ± 776	<.001	–322	<.001	2695	3018	NA	NA
Length at birth, mean ± SD, cm	46.3 ± 4.4	48.9 ± 4.5	<.001	–1.7	<.001	47.1	48.8	NA	NA
Head circumference at birth, mean ± SD, cm	31.9 ± 2.8	33.4 ± 2.7	<.001	–1.0	<.001	32.4	33.4	NA	NA
Gestational age, mean ± SD, wk	37.1 ± 3.4	38.3 ± 3.0	<.001	–0.93	<.001	37.4	38.3	NA	NA
Small for gestational age, No. (%)†	211 (29.4)	1001 (13.5)	<.001	NA	NA	NA	NA	2.70 (2.15-3.40)	1.66 (1.24-2.22)

Abbreviations: CI, confidence interval; NA, not applicable.

*These models exclude birth weight as a covariate.

†Defined as less than the 10th percentile by Alexander et al.[46]

reliable, based on self-report of cocaine use during pregnancy or demonstration of cocaine metabolites in meconium by means of state-of-the-art technology performed by a centralized facility. Testing of meconium, rather than urine, is hypothesized to reliably detect drug metabolites over a longer period of use during pregnancy. An additional 190 cocaine-exposed infants were identified by meconium analysis from mothers who denied drug use. There was no incentive to falsely admit the use of an illegal substance; however, the reverse was not true. Therefore, a negative meconium sample was required for the definition of nonexposure in mothers who denied use.

The important issues of multiple exposures to alcohol, tobacco, and/or marijuana, as well as the level of their use, were specifically addressed with the multivariate analyses. Both study cohorts had significant exposures to these 3 drugs, with more than 40% of the non–cocaine-exposed mothers also admitting to use. The impact of socioeconomic status and of a drug culture environment on outcome is complex, but important confounders and these variables were also addressed in the analyses. Unfortunately, not all potential confounders were eliminated. Since consent was required, it remains possible that particularly heavy users or those who used multiple drugs might be more likely to refuse participation. Because mothers were enrolled at or around the time of delivery, substance use early in pregnancy could have escaped detection.

This study contradicts the early reports of an increased prevalence of congenital anomalies. The increased central and autonomic nervous system dysfunction seen in the exposed cohort was mild, including soft signs such as irritability, jitteriness, tremors, high-pitched cry, and excessive suck. Although the cocaine-exposed cohort included more premature, low-birth-weight infants, who often exhibit mild, transient neurologic findings, most of the central nervous system findings remained significant after adjusting for birth weight, suggesting a true cocaine effect as reported by Chiriboga et al.[13,16] These rather subtle, acute neurologic findings support the findings of more recent reports, which suggest potential long-term neurodevelopmental, behavioral, and learning effects of cocaine exposure, rather than any acute teratogenic impact. More ultrasound examinations were ordered by the primary physician in the exposed cohort. The higher prevalence of premature infants in the exposed cohort, who have more complex illnesses, longer hospital stays, and more diagnostic tests such as echocardiograms, may also help to explain this difference. It is also true, however, that the clinicians who ordered these examinations were often aware of the infant's exposure status as well as the literature that equated cocaine exposure with the possible teratogenicity of various organ systems. Of note is that the ultrasound studies of the head were read centrally by expert ultrasonographers who were masked to exposure status. However, despite this heightened scrutiny, no differential structural abnormalities of the heart, gastrointestinal tract, kidneys, or brain were documented by these detailed examinations. These findings strongly support the conclusion that cocaine has no obvious anatomic teratogenic impact.

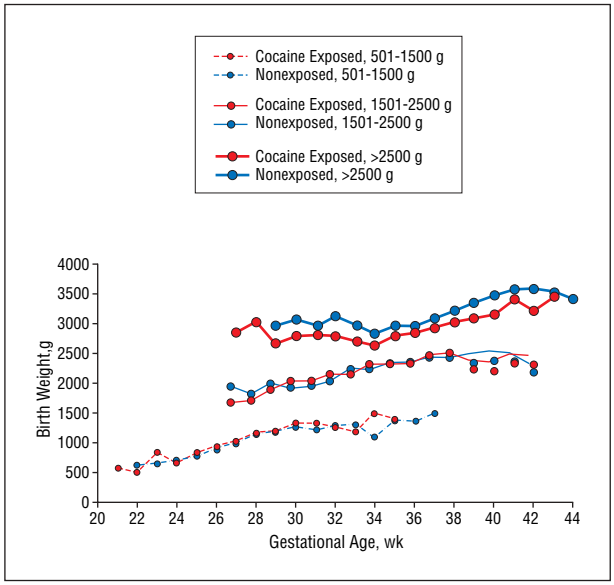

Figure 2. Birth weights by gestational ages (using best obstetric estimate) in the 2 study groups within birth weight categories (501-1500 g, 1501-2500 g, and >2500 g).

All measures of growth were affected by cocaine exposure, and this growth restriction was most evident in the larger, more mature infants. Growth failure as gestation progresses may relate to the vasoconstrictive impact of cocaine on the normally aging placenta, accelerating its demise and resulting in not only shorter gestations (prematurity) but also in increasing overall growth inhibition (small for gestational age) as term approaches.

An extremely important finding of this study is the increased prevalence of infectious diagnoses, particularly sexually associated infections that were previously reported in these mothers.[42] Although human immunodeficiency virus–positive exposure status had a very low overall prevalence in this study (0.1%), it occurred almost 16 times more often in infants born to cocaine-abusing women, a clear documentation of the increased risk of an often fatal infection. Similarly, a diagnosis of hepatitis occurred about 42 times more often in cocaine-exposed infants, and syphilis was 15 times as common. The morbidity and mortality associated with these diseases may have a significant impact on both health care utilization and long-term developmental outcome. The increased use of both medical (intensive care, procedures, therapies, length of stay, etc) and social (referrals to child protective services, adoption, and foster care) services by the cocaine-exposed cohort is significant. The hospital utilization findings are reflective of cocaine's effect on both gestation and birth weight, whereas the social impact as reflected through child protective services involvement and the infant's living situation is a direct effect of the mother's cocaine use. The serious infectious exposures associated with prenatal cocaine abuse and the burden and cost imposed on the criminal and social justice systems are important short-term outcomes that have obvious long-term implications and have not been previously addressed. Being classified as a boarder infant was 48 times more likely in cocaine-exposed infants, resulting in extended hospital stays. Cocaine-exposed infants were

Table 7. Procedures and Treatments During Hospitalization and Discharge or Death Information by Infant's Drug Exposure Status

	No. (%)		Cocaine Exposed	
	Cocaine Exposed (n = 717)	Nonexposed (n = 7442)	Unadjusted Odds Ratio (99% CI)	Adjusted Odds Ratio (99% CI)
Resuscitation (at birth)				
Any DR resuscitation	76 (10.6)	540 (7.3)	1.52 (1.09-2.11)	0.94 (0.59-1.49)
Intubation	73 (10.2)	520 (7.0)	1.51 (1.07-2.12)	0.92 (0.57-1.47)
Therapies				
Any therapy administered	340 (47.4)	2154 (28.9)	2.21 (1.81-2.71)	1.27 (0.95-1.68)
Procedures				
Any procedure used	293 (40.9)	2032 (27.3)	1.84 (1.50-2.26)	1.12 (0.84-1.50)
Feeding				
Formula feedings	710 (99.0)	6510 (87.5)	14.49 (5.42-38.70)	4.66 (1.57-13.79)
Breast milk feedings	31 (4.3)	2146 (28.8)	0.11 (0.07-0.18)	0.26 (0.15-0.44)
Nursery stay				
Intermediate-special care	221 (30.8)	1416 (19.0)	1.90 (1.52-2.37)	0.93 (0.67-1.29)
Neonatal intensive care unit	149 (20.8)	1121 (15.1)	1.48 (1.15-1.90)	0.83 (0.56-1.22)
Boarder infant	126 (17.6)	39 (0.5)	40.46 (24.92-65.70)	47.72 (23.75-95.91)
Discharge				
Discharged home	712 (99.3)	7417 (99.7)	0.46 (0.13-1.64)	NA
Days to discharge, mean ± SD	11.4 ± 19.2	7.0 ± 16.2	<.001*	.84†
Death				
Died before discharge	3 (0.4)	20 (0.3)	1.56 (0.32-7.71)	NA
Days to death, mean ± SD	13.0 ± 2.6	56.2 ± 64.6	.008*	.72†

Abbreviations: CI, confidence interval; DR, delivery room; NA, not applicable.
*P value by unpaired 2-tailed t test.
†P value for cocaine-use parameter estimate in regression model.

Table 8. Infant CPS Involvement and Living Situation at Discharge by Infant's Drug Exposure Status

	No. (%)		Cocaine Exposed	
	Cocaine Exposed (n = 717)*	Nonexposed (n = 7442)*	Unadjusted Odds Ratio (99% CI)	Adjusted Odds Ratio (99% CI)
CPS Involvement				
CPS report/referral for study subject	275 (38.5)	74 (1.0)	62.18 (43.37-89.15)	48.92 (28.77-83.20)
Reason(s) for this referral (% of referred)				
Previous CPS report	55 (20.0)	22 (29.7)	0.59 (0.28-1.27)	NA
In utero drug exposure	256 (93.1)	36 (48.6)	14.22 (6.04-33.50)	24.45 (6.31-94.74)
Maternal abandonment	34 (12.4)	11 (14.9)	0.81 (0.31-2.12)	NA
Mother though incapable of caring for child	5 (1.8)	4 (5.4)	0.32 (0.06-1.89)	NA
Maternal alcohol or drug use	244 (88.7)	38 (51.4)	7.46 (3.44-16.18)	6.43 (2.45-16.90)
Mother's social or economic circumstances	78 (28.4)	29 (39.2)	0.61 (0.30-1.24)	NA
Mother's physical or mental condition	17 (6.2)	10 (13.5)	0.42 (0.14-1.25)	NA
Infant in out-of-home placement (% of infants with a CPS report)	96 (44.7)	17 (34.7)	1.52 (0.65-3.55)	NA
Previous CPS report/referral for other children	160 (22.3)	90 (1.2)	23.46 (16.40-33.55)	13.28 (7.93-22.24)
Living Situation at Discharge				
Living with biological mother	580 (81.2)	7350 (99.0)	0.04 (0.03-0.06)	0.05 (0.03-0.10)
Living elsewhere†				
Home of biological father	6 (4.5)	15 (21.7)	0.17 (0.05-0.63)	0.09 (0.01-0.88)
Home of other relative	38 (28.6)	14 (20.3)	1.57 (0.63-3.93)	NA
Home of friend of parent	0 (0.0)	1 (1.4)	NA	NA
Home of foster/preadoptive parents	61 (45.9)	36 (52.2)	0.78 (0.36-1.67)	NA
Congregate care facility	28 (21.1)	2 (2.9)	8.93 (1.30-61.41)	9.69 (1.37-68.65)‡
Unknown	0 (0.0)	1 (1.4)	NA	NA
Mother wishes to put infant up for adoption	15 (2.1)	26 (0.4)	6.10 (2.63-14.16)	5.65 (1.72-18.53)
Adoption has been initiated	9 (60.0)	21 (80.8)	0.36 (0.06-2.31)	NA

Abbreviations: CI, confidence interval; CPS, child protective services; NA, not applicable.
*Discharge information was available for 714 exposed and 7421 nonexposed subjects.
†The category totals do not always add up owing to a small number of missing values not obtainable at the time of the hospital interview.
‡Model fit with only birth weight and cocaine exposure because of modeling limitations.

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49 times more likely to be involved with child protective services and 17 times more likely to be placed in foster care. Adoption was a seriously considered option for 6 times as many cocaine-abusing women. The manpower and fiscal impact of these social risks on society are significant.

Prenatal exposure to cocaine has a different face than had been previously emphasized. It does not result in obvious and marked fetal damage, but rather, as recent reports suggest, a more subtle impact has evolved.[47] Significant societal expenditures will continue to be required to address the social, environmental, and developmental issues of children born to mothers engaged in the drug abuser's lifestyle.

Cocaine use by women during pregnancy with resultant fetal exposure is preventable, but the degree of disability that may result from a particular exposure must be clarified to mobilize resources to respond effectively and efficiently. Long-term issues regarding the impact of cocaine exposure on cognition, learning, neurodevelopment, behavior, emotional stability, and potential infectious morbidity are important and clinically relevant. The Maternal Lifestyle Study is currently engaged in examining these late outcome issues as part of an 11-year follow-up.

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