Growth, Development, and Behavior in Early Childhood Following Prenatal Cocaine Exposure

A Systematic Review

Deborah A. Frank, MD
Marilyn Augustyn, MD
Wanda Grant Knight, PhD
Tripler Pell, MSc
Barry Zuckerman, MD

Context Despite recent studies that failed to show catastrophic effects of prenatal cocaine exposure, popular attitudes and public policies still reflect the belief that cocaine is a uniquely dangerous teratogen.

Objective To critically review outcomes in early childhood after prenatal cocaine exposure in 5 domains: physical growth; cognition; language skills; motor skills; and behavior, attention, affect, and neurophysiology.

Data Sources Search of MEDLINE and *Psychological Abstracts* from 1984 to October 2000.

Study Selection Studies selected for detailed review (1) were published in a peer-reviewed English-language journal; (2) included a comparison group; (3) recruited samples prospectively in the perinatal period; (4) used masked assessment; and (5) did not include a substantial proportion of subjects exposed in utero to opiates, amphetamines, phencyclidine, or maternal human immunodeficiency virus infection.

Data Extraction Thirty-six of 74 articles met criteria and were reviewed by 3 authors. Disagreements were resolved by consensus.

Data Synthesis After controlling for confounders, there was no consistent negative association between prenatal cocaine exposure and physical growth, developmental test scores, or receptive or expressive language. Less optimal motor scores have been found up to age 7 months but not thereafter, and may reflect heavy tobacco exposure. No independent cocaine effects have been shown on standardized parent and teacher reports of child behavior scored by accepted criteria. Experimental paradigms and novel statistical manipulations of standard instruments suggest an association between prenatal cocaine exposure and decreased attentiveness and emotional expressivity, as well as differences on neurophysiologic and attentional/affective findings.

Conclusions Among children aged 6 years or younger, there is no convincing evidence that prenatal cocaine exposure is associated with developmental toxic effects that are different in severity, scope, or kind from the sequelae of multiple other risk factors. Many findings once thought to be specific effects of in utero cocaine exposure are correlated with other factors, including prenatal exposure to tobacco, marijuana, or alcohol, and the quality of the child's environment. Further replication is required of preliminary neurologic findings.

JAMA. 2001;285:1613-1625 www.jama.com

Recently, the US Supreme Court considered *Ferguson et al v City of Charleston*, a Fourth Amendment case (unreasonable search and seizure).[1] This case addresses a policy of the Medical University of South Carolina whereby health professionals, in cooperation with the local prosecutor, selectively screened the urine of medically indigent obstetric patients for cocaine metabolites.[1-3] Medical personnel reported positive results to the police, who would then come to the hospital to arrest prenatal and postpartum patients for possession of an illegal drug, delivery of drugs to a minor, or child abuse.[3,4] In the popular press, *People* magazine reported on C.R.A.C.K. (Children Requiring a Caring Kommunity), a controversial charity that raises money to give mothers with a history of illegal drug use financial incentives to accept long-acting contraception, or, in most cases, sterilization.[5] This charity and the policies at issue in *Ferguson v City of Charleston* reflect popular belief that women who use cocaine while pregnant inflict severe, persistent, and unusual impairments on their unborn children, recently described by a newspaper columnist as "blighted by a chemical assault in the womb."[6]

See also p 1626.

Public expectations of "blighted" children fuel controversial punitive poli-

Author Affiliations: Boston University School of Medicine (Drs Frank, Augustyn, Grant Knight, and Zuckerman and Ms Pell) and Boston University School of Public Health (Drs Frank and Zuckerman), Boston, Mass.
Corresponding Author and Reprints: Deborah A. Frank, MD, Boston Medical Center, Growth and Development Programs, 820 Harrison Ave, FGH Bldg, Third Floor, Boston, MA 02118-2393 (e-mail: dafrank@bu.edu).

cies directed toward addicted mothers.[7] Since 1985, more than 200 women in 30 states have faced criminal prosecution for using cocaine and other psychoactive substances during pregnancy.[7] Scholars and professional organizations have condemned efforts to sterilize or criminally prosecute addicted mothers as ethically and legally flawed, racially discriminatory, and an impediment to providing appropriate medical care to these women and their children.[3,4,7-9]

Recent reviews[10-15] and articles[16-18] show that most initial predictions of catastrophic effects of prenatal cocaine exposure upon newborns were exaggerated. After controlling for confounders, the most consistent effects of prenatal cocaine exposure are small but statistically significant decrements in 1 or more parameters of fetal growth for gestational age[12,13] and less optimal neonatal state regulation and motor performance.[10,11,14] Clinically silent findings on neonatal cranial ultrasounds following prenatal exposure have been found in some studies,[10,16] but not others.[17] Prenatal cocaine exposure without concurrent opiate exposure has not been shown to be an independent risk factor for sudden infant death syndrome.[15,18]

Despite the neonatal data, beliefs about cocaine's teratogenicity impose a stigma on cocaine-exposed infants[19,20] and children at school age.[21] Teachers fear that "crack kids" will be too developmentally delayed or disruptive to be taught in traditional classrooms.[22]

Given the current public concern, health professionals need a critical synthesis of studies of postneonatal outcomes of children exposed to cocaine in utero in 5 domains: (1) physical growth; (2) cognition; (3)language skills; (4) motor skills; and (5) behavior, attention, affect, and neurophysiology.

METHODS

Data Sources

MEDLINE and *Psychological Abstracts* were searched for all human studies published in English from 1984 until October 2000 that included the words *cocaine*, *crack/cocaine*, *crack*, *pregnancy*, *prenatal exposure*, *delayed effects*, *children*, and *related disorders*. Even if cited in MEDLINE, abstracts or nonreviewed proceedings of scientific meetings[23] were excluded. Seventy-four published articles were identified.[24-97]

Study Selection

We first applied selection criteria used by others[98]: all selected studies presented original research published in a refereed English-language journal, used human subjects, and used a control or comparison group. Detailed review was then restricted to studies that also met 3 criteria: (1) samples were prospectively recruited; (2) examiners of the children were masked to their cocaine exposure status; and (3) the cocaine-exposed cohort did not include a substantial proportion of children also exposed in utero to opiates, amphetamines, or phencyclidine, or whose mothers were known to be infected with the human immunodeficiency virus (HIV).

Justification of Selection Criteria

Studies were classified as prospectively recruited if the samples of cocaine-exposed and unexposed mother-infant dyads were identified and enrolled either during pregnancy or immediately after birth. Prospective recruitment obviates recall bias, when caregivers of a child who has experienced an adverse outcome are likely to recall prenatal exposure in greater detail, and selection bias, when caregivers are more likely to enroll children with already suspected developmental impairments. Such biases in retrospective samples can produce an overestimate of the risk of negative developmental outcomes.[99]

In behavioral research, examiners' bias may unconsciously distort measurement of developmental/behavioral outcomes.[99-101] Investigators have shown that evaluators were more likely to code children's videotaped behavior as abnormal if the children were labeled as "crack kids" than if they were not.[19,20]

Lower developmental test scores in infancy and less adaptive behavior at school age have been linked to prenatal opiate exposure.[102] In samples where most cocaine-exposed children are also opiate-exposed, the independent effect of cocaine on outcome cannot be clearly delineated. For the same reason, samples where cocaine exposure was largely confounded with exposure to methamphetamines or phencyclidine were also excluded. Exposure to HIV in utero is correlated with poor developmental outcome not only among infected infants, but also among those who seroreverted.[103] If most cocaine-exposed children in a sample are also offspring of HIV-infected mothers, it cannot be determined whether effects are due to cocaine or HIV exposure.

Procedures

Two developmental/behavioral pediatricians (D.A.F., M.A.) and a neuropsychologist (W.G.K.) reviewed all articles. After excluding 38 articles according to the above criteria, the same 3 authors abstracted the data from the remaining 36 articles in detail. If a single article covered outcomes in more than 1 domain (eg, cognitive test scores and behavior), each domain was addressed separately. If there was uncertainty, contact was made with the corresponding author of the article to clarify interpretation of data. Disagreements were resolved by consensus.

Of the excluded studies, 20* failed to mask investigators to children's cocaine exposure status. Seven[24,27,28,36,39,40,53] had no control group. Twenty-six† did not use prospective recruitment for some or all of their subjects. Thirteen‡ primarily recruited children with in utero exposure to opiates, methamphetamines, or phencyclidine. Two[32,44] reported samples predominantly composed of children of HIV-positive mothers.

Data Extraction

The conceptual framework for data extraction was provided by recent theoretical advances in human behavioral teratology[104,105] delineating the implications of various methods of characteriz-

*References 24, 27, 30, 31, 33-37, 41, 42, 48, 49, 52, 53, 55-57, 60, 61.
†References 24-27, 29, 30, 33-38, 40-44, 46-49, 51, 54, 58, 59, 61.
‡References 28, 30, 32, 34, 41, 42, 49, 50, 54, 55-57, 59.

ing exposure to possible toxicants and of controlling for potential confounders. Many cocaine-exposed newborns are clinically indistinguishable from their unexposed peers,[18,106] so identification of exposed infants depends on maternal report or measurement of cocaine metabolites in biological matrices. Dose response is a critical issue in the study of all potential teratogens[105] but is difficult to ascertain for cocaine in human studies. Recently, infants' meconium and maternal hair have emerged as useful biological markers for estimating the dose of prenatal cocaine exposure.[97,107-111] However, at the time most cohorts available for study in the postneonatal period were recruited, assays of urine from mother or infant for benzoylecognine were the only biological indicators readily available. Urine assays do not reflect cumulative fetal drug exposure. Thus, researchers who address dose response rely on maternal interviews to classify levels of prenatal cocaine exposure, usually classifying 2 or more days a week during pregnancy as "heavier use."[63,66,85] For this review, we classified levels of prenatal cocaine exposure as heavier/lighter or as exposed/unexposed.

Even when their mothers do not use opiates, amphetamines, or phencyclidine, most cocaine-exposed infants are also exposed in utero to varying combinations of tobacco, alcohol, and marijuana.[112] The heaviest prenatal cocaine users are often the heaviest users of these other substances.[109] If prenatal exposure to tobacco, alcohol, and marijuana is not analytically controlled, their effects on neurodevelopment[74,84,113] may be misattributed to cocaine. If these substances are statistically controlled for without regard to the level of use, residual confounding may occur because of overaggregation of light and heavy exposure.[104,114] For this review, we considered whether prenatal tobacco, alcohol, and marijuana exposure are reported or not, are controlled analytically as dichotomous variables (exposed/not exposed), or are statistically controlled in a dose-related manner. However, statistical control in a dose-controlled manner offers the greatest assurance that effects of heavy tobacco, marijuana, or alcohol exposure will not be spuriously attributed to cocaine.

Interpreting cocaine effects is further complicated because the samples studied are, with a few exceptions,[77,90,93,97] drawn from economically disadvantaged, medically at-risk populations, whose characteristics are associated with high developmental risk without any psychoactive substance exposure. The number of environmental and medical variables, the accuracy of their measurement, and their distribution within the sample may influence the estimation of cocaine effects.[104]

The data were derived from 17 independent cohorts from 14 cities. Some cohorts were the subject of multiple articles, either at different ages or with differing analyses of the same data from a single age. Mutually exclusive samples were identified by author and city. For each article, a number of parameters were coded, including number of cocaine unexposed and exposed subjects and the number at varying levels of cocaine exposure if such data were available; how pregnancy exposure to tobacco, alcohol, and marijuana was addressed analytically and whether this exposure was significantly related to outcomes; what other covariates were matched, used as selection criteria, or controlled for statistically; which of these covariates influenced outcomes; and what, if any, statistically significant ($P<.05$, 2-tailed unless otherwise specified) cocaine effects were identified. Of the included articles, 4 do not report attrition.[66,77,78,87] In the others, sample retention from birth to the oldest age reported for the cohort ranges from 39%[70] to 94%.[62] Of these, 14 articles* from 11 cohorts document the characteristics of those retained compared with those lost to follow-up.

RESULTS

Physical Growth

If level of exposure to other substances is not controlled, prenatal cocaine exposure appears to be associated in 2 cohorts with postneonatal decrements in weight or occipitofrontal head circumference,[64,70,78,79] but not in another[89] (TABLE 1). However, in 2 cohorts that did control for dose of prenatal exposure to tobacco and alcohol[84,93] no negative cocaine effect was noted on the children's weight, length, or head circumference. In 1 cohort, full-term unexposed children were longer than exposed or unexposed preterm children and their exposed full-term counterparts.[71]

Standardized Cognitive Assessment

There is little impact of prenatal cocaine exposure on children's scores on nationally normed assessments of cognitive development (TABLE 2). Findings of cocaine effects depend on contextual factors, such as the child's history of prematurity, age at time of assessment, and the effects of prenatal exposure to other substances. Of the 9 studies evaluating prenatal cocaine effects on developmental test scores in infants, 5 found no effect,[71,77,79,85,89] including 1 that classified infants according to level of prenatal exposure to cocaine, tobacco, and alcohol.[85] Chasnoff et al[70] found that the 6-month-old infants whose mothers used cocaine, alcohol, and marijuana attained mean scores lower than infants of controls, but identical to those of infants whose mothers had used alcohol/marijuana without cocaine, suggesting no incremental impact of cocaine use. Mayes et al[91] reported bivariate association of lower psychomotor scores at 3 months with prenatal cocaine exposure, but not after statistical control for potential confounders. Alessandri et al[63] found no main effects of level of prenatal cocaine exposure on test scores at 8 or 18 months, but on post hoc comparisons children with the highest level of cocaine exposure in pregnancy (2 or more days a week) obtained significantly lower mental development scores at age 18 months than unexposed infants.

In very low-birth-weight infants, Singer et al[96] reported a negative association between prenatal cocaine exposure and developmental scores at 16 months corrected age, but in utero ex-

*References 64, 65, 67, 73, 74, 81, 83, 85, 89, 91-93, 96, 97.

posure to other psychoactive substances was not analytically controlled.

Six reports from 4 cohorts evaluated the association of prenatal cocaine exposure with cognitive test scores in children between the ages of 3 and 6 years.[64,78,82,83,89,93] Two articles presented results in a single cohort of 3-year-olds. In one, Azuma and Chasnoff[64] reported that children whose mothers only used alcohol and marijuana during pregnancy achieved mean IQ scores that were identical to those of children whose mothers had also used cocaine. In a second report of post hoc comparisons from the same cohort, Griffith et al[78] found that children exposed to cocaine in addition to other substances scored significantly lower than unexposed controls on a verbal reasoning scale of the IQ test. However, these scores were not lower than the scores of children who had been exposed to the other substances but not cocaine and were not statistically controlled for tobacco exposure. Another study found no cocaine effect on IQ.[89] In the cohort studied by Hurt et al[82,83] there was no impact of prenatal cocaine exposure on children's cognitive test scores at 48 months. In the oldest prospectively recruited cohort studied to date, Richardson et al[93] found no effect of prenatal cocaine exposure on any IQ scales at age 6 years, including verbal reasoning, and no association with children's academic skills.

The literature on prenatal exposure to cocaine has not shown consistent effects on cognitive or psychomotor development. However, 7 studies show that environmental factors such as caregiver (biological mothers vs kinship care or foster parents),[79,89] whether or not that caregiver received case management or home visiting services,[78,89] quality of the home environment,[63,64,78,83] and maternal IQ[77] were statistically significant correlates of test scores.

Language Skills

Three studies of toddlers[69,81,89] showed no association between prenatal cocaine exposure and receptive or expressive language scores on standardized measures (TABLE 3). Using a naturalistic language sample, Bland-Stewart et al[69] found that cocaine-exposed children produced different semantic categories than matched unexposed children. However, there were too few subjects to permit confounder control.

Motor Skills

Of 6 studies, 3 from 2 cohorts found less optimal motor scores in the first 7 months of life following prenatal cocaine exposure (TABLE 4).[75,76,97] No prospective study has identified a cocaine effect on motor development after age 7 months.[75,76,89] Dempsey et al[74] found mothers' prenatal tobacco use (quantified by urine assays of cotinine rather than by self-report), but not cocaine use (quantified by benzoylecognine levels in meconium), was the major predictor of abnormalities in infant muscle tone at 6 weeks. No other prospective study of motor outcome[75,76,79,89,97] following cocaine exposure used biological markers to measure tobacco exposure. It is not yet clear whether previously reported positive associations between prenatal cocaine exposure and less optimal early motor development may be a misattribution of tobacco effects.

Behavior, Attention, Affect, and Neurophysiology

Heterogeneous techniques used to evaluate behavior, attention, affect, and neurophysiology following prenatal cocaine exposure are not readily comparable across studies (TABLE 5). In the first year of life, visual habituation (an

Table 1. Physical Growth*

Study	No.	Cocaine Effect	Outcome Measures	Assessment Ages	Tobacco Use
Azuma and Chasnoff,[64] 1993	92 + 25 poly 45 –	Both cocaine and polydrug exposed groups had lower OFC	Weight, height, OFC	3 years	R
Chasnoff et al,[70] 1992	106 + 45 poly 81 –	Both cocaine and polydrug exposed had lower OFC than unexposed at all ages measured	Weight, height, OFC	3, 6, 12, 18, and 24 months	R
Coles et al,[71] 1999	25 preterm + 32 full term + 22 preterm – 26 full term –	Full-term negatives longer; otherwise, no cocaine effect	Weight, length, OFC	8 weeks corrected for prematurity	R
Hurt et al,[79] 1995	101 + 118 –	Cocaine associated with lower weight and OFC at all ages	Weight, OFC	6, 12, 18, 24, and 30 months	R
Jacobson et al,[84] 1994	86H 48L 330 –	Cocaine exposure associated with faster postnatal weight gain in first 13 months, no effect on length or OFC	Weight, length, OFC	6.5 and 13 months	DC Correlated with faster postnatal weight gain
Kilbride et al,[89] 2000	111 + 41 –	No cocaine effect	Weight, length, OFC	2, 12, 24, 36 months	C
Richardson et al,[93] 1996	28 + 523 –	No cocaine effect	Weight, height, OFC	6 years	DC

*Across tables, abbreviations are explained at first mention only. Plus (+) indicates exposed to cocaine; poly, exposed to multiple drugs; minus (–), not exposed to cocaine; OFC, occipitofrontal head circumference; R, reported; C, controlled; IVH, intraventricular hemorrhage; H, heavier; L, lighter; DC, dose controlled; and NICU, neonatal intensive care unit.

indicator of recognition memory and learning) was negatively associated with higher levels of cocaine exposure in 1 cohort[85] but not in 3 others.[63,88,91] No cocaine effect was found on toddler play[80] or on observations of behavioral style during an infant motor assessment.[68] Problem-solving abilities did not differ between cocaine-exposed and unexposed preschoolers.[67]

Differences in affective expression have been correlated with prenatal exposure to cocaine in 4 studies from 3 cohorts of infants younger than age 2 years. Alessandri et al[62] found that 4- to 8-month-old cocaine-exposed children showed less arousal, interest, joy, or sadness during the learning task. In the same cohort, Bendersky and Lewis[66] reported no differences in maternal behaviors, but less joy and more negativity among 4-month-old infants with heavy cocaine exposure following a perturbation of the face-to-face interaction between mother and infant. Roumell et al[94] reported a bivariate association between prenatal cocaine exposure and decreased facial emotion after immunization, uncontrolled for other prenatal exposures. In studies of face-to-face interaction between mothers and infants, Mayes et al[92] found heavy prenatal cocaine use correlated with less optimal maternal behavior and with decreased readiness for interaction among infants at age 6 months but not 3 months.

Diverse techniques have been used to assess neurophysiology in cocaine-exposed and unexposed infants aged 13 months and younger. Cocaine-exposed infants showed lower basal cortisol levels, but normal cortisol increase in response to the stress of venipuncture and no difference in amount of observed crying.[86] On electroencephalographic sleep studies at 12 months, cocaine-exposed children did not differ from unexposed children in sleep architecture, but infants whose mothers continued to use cocaine into the third trimester showed subtle reductions in spectral energies.[95] In 2 reports from a single cohort, assessments of heart and respiratory response to auditory, visual, and social stimulation at age 8 weeks found that cocaine-exposed children showed increased heart rate to social stimulation and a higher baseline respiratory rate, but were not more dysregulated in arousal modulation or observed behavioral state.[65,71] Full-term cocaine-exposed infants showed better arousal modulation than their unexposed counterparts.[65]

Prenatal cocaine exposure, independent of exposure to alcohol, has not been found to be associated with levels of behavioral disturbances detectable by standard scoring of epidemiologic and clinical report measures by parents and teachers.[64,72,73,77,78,87,93] However, 2 studies in 1 cohort (1 study using a study-specific measure[72] and the other[73] using a new and as-yet unreplicated method of scoring the Teacher Report Form of the Child Behavior Problem Checklist[115]) found less-optimal scores among cocaine-exposed children. Another research group[90,93] found, after covariate control, an association between prenatal cocaine exposure and increased errors of omission, but not commission, on a continuous performance task.

COMMENT

Before summarizing our findings, we must acknowledge the limitations of our approach. Studies that meet our methodologic criteria may still lead to overestimation or underestimation of cocaine's impact. Prospective studies may yield biased results if there is differential attrition.[99] Less dysfunctional caregivers may be more likely to sustain study participation, creating differential retention of children with more

Alcohol Use	Marijuana Use	Selection/Matching Criteria	Controlled Variables	Other Effects
C Analyzed as single category		All drug users in prenatal care by 15 weeks and in drug treatment		
C Analyzed as single category		All drug users in prenatal care by 15 weeks and in drug treatment	Sex, gestational age	
R	R	Maternal age ≥19, English speaking, singleton or first-born twin, no O_2 >28 days, no seizures, no grade III or IV IVH, not breastfed		
R	R	Medicaid, all >34 weeks' gestation		
DC Correlated with both shorter stature and slower postnatal weight gain if mother aged >30	DC	All black, low socioeconomic status, at least 2 prenatal visits, >32 weeks' gestation	Maternal age, welfare, education, parity, prepregnancy weight, birth weight, height, breastfed, prenatal visits, infant age, sex, gestational age	Breastfeeding associated with faster postpartum growth
C	R	All from same ZIP code, 36 weeks' gestation, no NICU care, women referred for drug treatment excluded	Placement, gestational age, maternal age and education, OFC at birth, birth weight	
DC	DC	All in prenatal care by 5 months of pregnancy	Age, sex, height, ethnicity, current drug/alcohol use	

favorable outcomes. Alternatively, caregivers of children with obvious impairments may be more willing to return for repeated assessments, leading to an overestimation of risk for poor outcomes.

Reliance on interviews alone to classify exposure, which was the state of the art when the cohorts reported here were recruited, entails unavoidable imprecision.[14] In the absence of cumulative biological markers some cocaine-exposed children may have been misclassified as unexposed. Conversely, women who do admit cocaine use in interviews tend to be heavier users than those who deny use but whose use is detected by hair assays.[111] Generalization from atypical cases at the highest levels of exposure will lead to overestimation of the impact of prenatal cocaine exposure in the broader population of users. However, if a sample contains very few infants heavily exposed to cocaine,[77,93] possible effects of heavier use may be statistically "diluted" by overaggregation of various levels of exposure into a single category.[114]

Table 2. Standardized Cognitive Assessments*

Study	No.	Cocaine Effect	Outcome Measures	Assessment Ages	Tobacco Use
Alessandri et al,[63] 1998	15H 19L 78 –	No cocaine dose effect on PDI, no cocaine main effect on MDI, but interaction of heavy cocaine with age associated with lower MDI	BSID-II	8 and 18 months	DC
Azuma and Chasnoff,[64] 1993	92 + 25 poly 45 –	No cocaine effect	SBIS	3 years	R
Chasnoff et al,[70] 1992	106 + 45 poly 81 –	Cocaine exposed not different from other drugs, but lower on MDI and PDI at 6 months than unexposed	BSID	3, 6, 12, 18, and 24 months	R
Coles et al,[71] 1999	25 preterm + 32 full-term + 22 preterm – 26 full-term –	No cocaine effect	BSID	8 weeks corrected for prematurity	R
Graham et al,[77] 1992	30 + 20 poly 30 –	No cocaine effect	BSID	19.7 months	R
Griffith et al,[78] 1994	93 + 24 poly 25 –	Cocaine-exposed lower than controls on verbal reasoning	SBIS	3 years	R
Hurt et al,[79] 1995	101 + 118 –	No cocaine effect	BSID	6, 12, 18, 24, and 30 months	C
Hurt et al,[82] 1997	71 + 78 –	No cocaine effect	WPPSI-R	4 years	C Negative association with performance IQ
Hurt et al,[83] 1998	72 + 78 –	Neither prenatal nor concurrent maternal cocaine use associated with full-scale IQ ≤90	WPPSI-R	4 years	C
Jacobson et al,[85] 1996	86H 48L 330 –	No cocaine effect	BSID	13 months	DC
Kilbride et al,[89] 2000	111+ 41 –	No cocaine effect	BSID, SBIS	6, 12, and 24 months (BSID); 36 months (SBIS)	C
Mayes et al,[91] 1995	61 + 47 –	Cocaine univariately associated with PDI, but not after multivariate control	BSID	3 months	C
Richardson et al,[93] 1996	28 + 523 –	No cocaine effect	SBIS, WRAT-R	6 years	DC
Singer et al,[96] 1994	41 + 41 –	Lower MDI and PDI among cocaine exposed	BSID	16 months corrected for prematurity	R

*PDI indicates Psychomotor Development Index; MDI, Mental Development Index; BSID-II, Bayley Scales of Infant Development, 2nd ed; SBIS, Stanford Binet Intelligence Scale; HSQ, Home Screening Questionnaire; CBCL, Child Behavior Checklist; BSID, Bayley Scales of Infant Development; WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence-Revised; HOME, Home Observation for Measurement of the Environment; PCIS, Parent Caregiver Involvement Scale; OCS, Obstetrical Complication Scale; WRAT-R, Wide Range Achievement Test-Revised; AFDC, Aid for Families of Dependent Children; BPD, bronchopulmonary dysplasia; and VLBW, very low birth weight.

Four studies with positive[69,75,76,94] and 1 with negative[68] findings have small sample sizes and must be interpreted with particular caution since they may overestimate cocaine effects due to the impact of a few outliers or underestimate effects because of insufficient power or sampling variation.

While acknowledging these limitations, we conclude that after control for exposure to tobacco and alcohol, effects of prenatal cocaine on physical growth are not shown.[64,70,71,79,84,89,93] Researchers have not found a negative association of prenatal cocaine exposure, independent of environmental risk and exposure to other psychoactive substances, with developmental scores from infancy to age 6 years.* However, sufficient information is not available to elucidate whether there are specific cocaine effects on developmental scores in the context of prematurity.[96]

Prospective data in the language and motor domains are only available for

*References 63, 64, 70, 71, 77-79, 82, 83, 85, 89, 91, 93.

Alcohol Use	Marijuana Use	Selection/Matching Criteria	Controlled Variables	Other Effects
DC	DC	All with biological mothers	Environmental risk, neonatal medical risk, sex	Among lightly exposed, increased environmental risk associated with decreased MDI
C Analyzed as single category		All drug users in prenatal care by 15 weeks and in drug treatment	OFC, HSQ, perseverance, CBCL	Poor HSQ and poor perseverance associated with lower IQ
C Analyzed as single category		All drug users in prenatal care by 15 weeks and in drug treatment	Sex, OFC	Smaller OFC correlated with MDI at 12, 18, and 24 months, OFC at birth associated with PDI at 6 months and MDI at 24 months
R	R	Maternal age ≥19, English speaking, singleton or first-born twin, no O_2 >28 days, no seizures, no grade III or IV IVH, not breastfed		
R	C	Tobacco, marital status, obstetric history, ethnicity, self-referred to Mother Risk Counseling	Maternal IQ	Maternal IQ associated with MDI
C Analyzed as single category; associated with decreased abstract reasoning		All drug users in prenatal care by 15 weeks and in drug treatment	Caregiver, child's sex, OFC, CBCL, and Summative Attention Scale of SBIS	Drug-free environment associated with better scores on verbal reasoning among cocaine-exposed
C	C	Medicaid, all >34 weeks' gestation, cocaine use in at least 2 trimesters	Congenital syphilis, maternal age and education, foster care	Foster care associated with lower MDI at 18 months
C	C	Medicaid	Maternal age and education, gravidity, parity, prenatal care, sex, foster care	
C	C	Medicaid	HOME, PCIS, sex, child age, foster care, day care/Head Start attendance, parental education, gravidity, parity, prenatal care, current cocaine use	Higher HOME scores and better PCIS associated with full-scale IQs above 90
DC	R	All black, all received prenatal care	Maternal age, depression, prenatal visits, HOME, parity, examiner, sex, age at test, continued maternal drug use	
C	R	All from same ZIP code, 36 weeks' gestation, no NICU care, women referred for drug treatment excluded	Placement, gestational age, maternal age and education, OFC at birth, birth weight	Birth weight associated with MDI at 12 months; with case management, children cared for by biological mothers have higher SBIS verbal scores; children in care of relatives have highest overall scores
C	C	All with biological mothers	Maternal age and education, OCS, prenatal care, birth weight, birth length, and OFC at birth	
DC	DC	All in prenatal care by 5 months	Maternal ethnicity, IQ, current maternal alcohol/drug use, self-esteem, HSQ, child's grade	
R	R	All black, all receiving AFDC, severity of BPD, all VLBW	Chronological age at testing, IVH, foster placement	

children up to age 3 years.[69,74-76,78,79,81] No effects on standardized language measures have been shown. Less-optimal motor development before age 7 months but not thereafter has been found by some investigators[75,76,97] but not others.[74,79,89] Recent research suggests that motor findings attributed to cocaine may in fact reflect heavy prenatal tobacco exposure.[74]

Except for the work of 1 investigator,[72,73] prenatal cocaine exposure independent of exposure to alcohol has not yet been found to be associated with levels of behavioral disturbance that are readily detected by standard scoring of epidemiologic and clinical report measures from parents and teachers.[64,72,77,78,87,93] However, sophisticated experimental and physiological paradigms of uncertain clinical importance have detected possible effects of prenatal cocaine exposure. Of these, only the finding of decreased emotional expressiveness has been replicated in more than 1 study.[62,66,92,94]

The differences between our conclusions and those of others show how methodologic rigor influences understanding of prenatal cocaine exposure. For instance, a respected research group recently concluded from a meta-analysis of 6 studies that prenatal cocaine exposure is associated with decreased competence in expressive and receptive language.[98] However, 5 of these studies[29,37,43,46,51] were retrospective; 2 did not use masked assessors.[37,57] In 2 samples, the majority of cocaine-exposed children were also exposed to opiates and methamphetamines.[37,57] Furthermore, none of these studies analytically controlled for the possible effects of prenatal tobacco exposure, an established correlate of language impairment.[113] Nevertheless, newspaper articles used the conclusions of the meta-analysis to declare that "because of cocaine-related receptive language impairments," "crack babies" would cost taxpayers an additional $42 to $352 million per year in special education services.[116]

When prenatal cocaine and tobacco exposure are compared dispassionately, it becomes clear how sociopolitical forces shape discrepant interpretations of similar scientific data. The mechanisms of nicotine and cocaine effects on the developing brain are similar, involving vasoconstriction, hypoxia, and perturbations of neurotransmitter networks.[117] Prenatal tobacco exposure has been associated with in-

Table 3. Language Skills*

Study	No.	Cocaine Effect	Outcome Measures	Assessment Ages	Tobacco Use	Alcohol Use	Marijuana Use
Bland-Stewart et al,[69] 1998	11 + 11 –	Delays in early semantic development, no effect on SICD-R score	SICD-R language sample	24 months	NR	NR	NR
Hurt et al,[81] 1997	76 + 81 –	No cocaine effect	PLS	2.5 years	NR	NR	NR
Kilbride et al,[89] 2000	111 + 41 –	No cocaine effect	REEL, SICD-R	6, 12, 24 months (REEL), 36 months (SICD-R)	C	C	R

*SICD-R indicates Sequenced Inventory of Communicative Development-Revised; NR, not reported; PLS, preschool language; and REEL, Receptive Expressive Emergent Language Scale.

Table 4. Motor Skills

Study	No.	Cocaine Effect	Outcome Measures	Assessment Ages	Tobacco Use
Dempsey et al,[74] 2000	40 + 56 –	No cocaine effect	Neurologic examination	6 weeks	DC High doses associated with hypertonia
Fetters and Tronick,[75] 1996	28 + 22 –	Higher total risk on the MAI at 7 months, lower mean percentile on AIMS at 7 months	AIMS, MAI, PDMS	1, 4, 7, and 15 months	C
Fetters and Tronick,[76] 1998	28 + 22 –	No difference on PDMS, significant differences on prone and standing subscores of AIMS and primitive reflex score of MAI at 7 months	AIMS, MAI, PDMS	1, 4, 7, and 15 months	C
Hurt et al,[79] 1995	101 + 118 –	No cocaine effect	Tone and reflexes	6 and 12 months	C
Kilbride et al,[89] 2000	111 + 41 –	No cocaine effect	PDMS	6, 12, 24, and 36 months	C
Swanson et al,[97] 1999	48 + COC3 72 + COC12 186 –	Higher full-scale MAI total risk, COC3 associated with less optimal volitional movement than COC12, COC3 at higher risk for neuromotor dysfunction than unexposed but COC12 is not	MAI	4 months	DC

*MAI indicates Movement Assessment of Infants; AIMS, Alberta Infant Motor Scales; PDMS, Peabody Development Motor Scales; COC3, cocaine use in third trimester; and COC12, discontinued cocaine use before third trimester.

fant mortality,[118] moderate impairment of cognitive functioning,[119] and a range of behavioral problems (which, unlike those associated with cocaine exposure, are detectable on relatively insensitive epidemiologic measures).[120] It has been calculated that low birth weight attributable to maternal smoking annually costs $263 million (1995 dollars) in excess direct medical costs for neonatal care alone.[121] Despite increased health care costs imposed by their tobacco use, there are no sterilization campaigns for mothers who use tobacco. No pregnant women have been charged with child abuse for tobacco use in pregnancy. Teachers do not dread having a "tobacco kid" assigned to their class.

We have focused on cocaine as a suspected behavioral teratogen, since exaggerated views of its teratogenicity have provided the rationale for selectively targeting pregnant women who use cocaine for sanctions even more punitive than those imposed on women who use other illicit substances.[3,8,122] Our focus omits 2 important considerations beyond the scope of this review. First, even if cocaine were as hazardous to a child's development as some claim, established teratogenicity (eg, that of heavy alcohol use) does not justify policies that violate the usual canons of medical ethics and civil liberties.[3] Second, health providers should not ignore that cocaine use in pregnancy is often a marker for a mother-child dyad at risk for poor health and impaired caregiving due to factors ranging from infectious diseases to domestic violence. Addiction to any intoxicant may so impair parents that they abuse or neglect a child.[123] However, presumptive punitive sanctions imposed in pregnancy or at birth do not reduce these risks to the child. On the contrary, fear of prosecution may discourage pregnant and parenting women from seeking prenatal care and drug treatment,[8,124] which have been shown to optimize infant outcome.[125] Stigma and negative expectations generalized from mothers to their children may in themselves impede the children's academic progress.[101] Care of families affected by substance abuse should be comprehensive and not irrationally shaped by social prejudices that demonize some drugs and drug users and not others.[123]

Much is still unknown about the effects of prenatal cocaine exposure. Research on prenatal marijuana and tobacco exposure suggests that, even if no drug effects are found between the ages of 6 months and 6 years, the increasing cognitive demands and social expectations of school or puberty may unmask sequelae of exposure not previously identified.[126,127] Cumulative environmental risk and protective factors may also exacerbate or moderate negative cognitive and behavioral outcomes as children mature.[128] However, among children up to 6 years of age, there is no convincing evidence that prenatal cocaine exposure is associated with any

Selection/Matching Criteria	Controlled Variables	Other Effects
Age, sex, foster care, maternal age and education		
Medicaid		
All from same ZIP code, 36 weeks' gestation, no NICU care, women referred for drug treatment excluded	Placement, gestational age, maternal age and education, OFC at birth, birth weight	Case management of children cared for by biological mothers associated with higher SICD-R scores

Alcohol Use	Marijuana Use	Selection/Matching Criteria	Controlled Variables	Other Effects
C	C	Birth weight >2000 g, English speaking, maternal age >18, no NICU care	Ethnicity, adequacy of prenatal care, OFC, gestational age, homelessness	
C	R	Maternal education, maternal age >18, health insurance, ethnicity, birth weight >2000 g, no NICU care	Hobel score, cumulative risk index, child hospitalization and poor health, maternal education, ethnicity	
C	R	Maternal education, maternal age >18, health insurance, ethnicity, birth weight >2000 g, no NICU care		
C	C	Medicaid, all >34 weeks' gestation, cocaine use in at least 2 trimesters	Congenital syphilis, maternal age and education, foster care	
C	R	All from same ZIP code, 36 weeks' gestation, no NICU care, women referred for drug treatment excluded	Placement, gestational age, maternal age and education, OFC at birth, birth weight	
DC	DC	Maternal age >17, gestational age ≥37 weeks	Prenatal visits, infant sex and age, parity, ethnicity, maternal age and education, marital status, income	Prenatal care decreased association between cocaine exposure and primitive reflexes and volitional movement to nonsignificant

Table 5. Behavior, Attention, Affect, Neurophysiology*

Study	No.	Cocaine Effect	Outcome Measures	Assessment Ages	Tobacco Use
Alessandri et al,[62] 1993	36 + 36 –	Cocaine associated with fewer positive emotions, less arousal, and less instrumental responding	Instrumental responses and facial expressions during learning	4, 6, or 8 months	R
Alessandri et al,[63] 1998	37H 30L 169 –	No cocaine effect	Habituation	8 months	DC
Azuma and Chasnoff,[64] 1993	92+ 25 poly 45 –	No cocaine effect	CBCL externalizing scale	3 years	R
Bard et al,[65] 2000	27 preterm + 39 full-term + 23 preterm – 29 full-term –	None on behavioral state or heart rate; higher baseline respiratory rate and better arousal modulation in full-term infants, and poorer arousal modulation in preterm infants; preterm exposed are no more dysregulated than full-term unexposed	Arousal and arousal modulation in heart rate and respiratory rate	8 weeks corrected for prematurity	DC Associated with arousal modulation of heart rate
Bendersky and Lewis,[66] 1998	24H 17L 66 –	Heavily exposed showed less joy and more negative expressions during reengagement	Still face paradigm	4 months	DC
Betancourt et al,[67] 1999	7 + 81 –	No cocaine effect	Goodman Lockbox	3.5 and 4.5 years	C
Blanchard et al,[68] 1998	26 + 23 –	No cocaine effect	Qualitative behavioral ratings during motor testing	1, 4, and 7 months	C
Coles et al,[71] 1999	25 preterm + 32 full-term + 22 preterm – 26 full-term –	Increased heart rate to social stimulation	Heart rate response to auditory, visual, and social stimulation	8 weeks corrected for prematurity	C
Delaney-Black et al,[72] 1998	27 + 75 –	1-Tailed cocaine effect on problem behaviors and daydreaming, but no effect on Conners Scale total	Conners Teachers Rating Scale and Problem Behavior Scale	72-90 months (6-7.5 years)	C
Delaney-Black et al,[73] 2000	201 + 270 –	None with standard scoring method, but higher Externalizing-Internalizing Difference Score in cocaine exposed	Teacher Report Form of CBCL	6 years	DC
Graham et al,[77] 1992	30 + 20 marijuana 30 –	No cocaine effect	Vineland Social Maturity	18 months	R
Griffith et al,[78] 1994	93 + 24 poly 25 –	Similar to polydrug effects, but both show more aggressive and destructive behavior	CBCL	3 years	R
Hurt et al,[80] 1996	83 + 93 –	No cocaine effect	Free play	18 and 24 months	C
Jacobson et al,[85] 1996	86H 48L 330 –	Heavy cocaine exposure associated with poor visual memory on Fagan Test at 6 and 12 months and faster responsiveness on Visual Expectancy at 6 months	Fagan Test of Infant Intelligence; Visual Expectancy Paradigm	6 and 12 months	DC
Jacobson et al,[86] 1999	29 + 57 –	Cocaine exposed had lower basal cortisol prestress, but not poststress level	Cortisol levels before and after venipuncture	13 months	DC
Johnson et al,[87] 1999	53 + 37 –	No cocaine effect	CBCL	24 months	NR
Karmel et al,[88] 1996	46 + 147 – 162 – with CNS injury	No cocaine effect	Arousal modulated visual attention	4 months corrected for prematurity	NR
Leech et al,[90] 1999	26 + 582 –	Cocaine associated with increased errors of omission	CPT	6 years	DC Associated with more errors of omission
Mayes et al,[91] 1995	61 + 47 –	No effect on visual habituation, more cocaine-exposed too irritable to start procedure	Visual habituation	3 months	C
Mayes et al,[92] 1997	43 + 17 poly 21 –	Less readiness for interaction at 6 months	Face-to-face interaction	3 and 6 months	C
Richardson et al,[93] 1996	28 + 523 –	No cocaine effect	Teacher Report Form of CBCL	6 years	DC
Roumell et al,[94] 1997	14 + 16 –	Cocaine associated with less facial emotion	Facial expression coding after inoculation	18 months	R
Scher et al,[95] 2000	37 + 34 –	Third-trimester exposure associated with reduced spectral θ energies; no sleep effects	Quantitative EEG	Day 2, 1 year	DC Increased indeterminate sleep, increased arousal

*CNS indicates central nervous system; BAER, brainstem auditory evoked responses; CPT, Continuous Performance Test; EEG, electroencephalogram; and REM, rapid eye movement.

Alcohol Use	Marijuana Use	Selection/Matching Criteria	Controlled Variables	Other Effects
R	NR	Sex, birth order, maternal age, all with biological mothers, all receiving AFDC, all black, all with ≤high school	Beck Depression Inventory and Life Events Survey	
DC	DC	All with biological mothers		
C	C	All drug users in prenatal care by 15 weeks and in drug treatment		Smaller OFC associated with more externalizing behavior
DC	DC	Maternal age ≥19, English speaking, singleton or first-born twin, no O_2 >28 days, no seizures, no grade III or IV IVH, not breastfed	Quality of caregiving, maternal psychosocial resources, term status	Term status associated with higher arousal and with arousal modulation of respiratory rate and arousal of heart rate
DC	DC	All with biological mothers	Maternal vocalization, maternal sensitivity, Environmental Risk Score, Contingent Responsivity Score, neonatal medical complications	Maternal sensitivity associated with both joy and negative expression; neonatal medical risk and maternal vocalization associated with joy
C	C	Medicaid, all >34 weeks' gestation	Gestational age, birth weight, IQ, preschool experience	
C	C	Maternal education, maternal age >18, health insurance, ethnicity, birth weight >2000 g, no NICU care	Maternal age, parity	Child age associated with examiner's persistence and maternal parity with interruptions
C	C	Maternal age ≥19, English speaking, singleton or first-born twin, no O_2 >28 days, no seizures, no grade III or IV IVH, not breastfed	Caregiving potential, quality of caregiveing	Caregiving instability explained more variance than cocaine exposure, preterm drug-exposed had least optimal response
DC	NR	All black	Child's sex	
DC Associated with higher total score, increased attention problems, more delinquent behavior	C	All black, all with prenatal care, children with mental retardation excluded	Child's sex, custody changes, exposure to violence, current lead level, current caregiver drug use, socioeconomic status, marital status	Child's sex male, current lead level, exposure to violence, older age, custody change, caregiver marital status, and current caregiver drug use associated with less optimal scores
R	C	Marital status, obstetric history, ethnicity, self-referred to Mother Risk Counseling	Maternal IQ	
C Analyzed as single category, associated with aggression		All drug users in prenatal care by 15 weeks and in drug treatment	Child's sex, drug-free caregiver	
C	C	Medicaid	NICU admission, age at testing, foster care	
DC	R	All black, all received prenatal care	Maternal age, depression, prenatal visits, HOME, parity, examiner, infant's sex, age at test	
DC Related to higher basal cortisol, heavy exposure to poststress elevation	DC	All black, all received prenatal care	Milk, teething, pacifier, birth size, maternal verbal ability, age at test, postpartum drug use, ego maturity, caregiver depression	New teeth, maternal depression, AFDC associated with higher basal cortisol; age at visit, maternal verbal ability with poststress cortisol
NR	NR	All Hispanic or black	Ethnicity, maternal stress and social support, maternal depression, child's sex	Maternal stress and social support associated with total internalizing and externalizing behavior; depression with externalizing behavior problems
NR	NR	Cocaine-exposed had normal BAER and cranial ultrasounds	Arousal condition	CNS injury associated with neonatal pattern of attention
DC	DC Associated with more errors of commission, fewer of omission	All in prenatal care by 5 months	Ethnicity, child's sex, illnesses, hospitalizations, SBIS IQ, HSQ, maternal work status, life events, hostility, maternal age, male in household, current caregiver alcohol/drug use	Omission predicted by lower child SBIS IQ and age, and mother more hostile and not working; commission predicted by child's male sex, male in household, and lower SBIS IQ
C	C	All with biological mothers	Maternal age, education, OCS, prenatal care, birth weight, length, OFC	
C	C	All with biological mothers	Maternal age and education, infant's sex, OCS, infant size at birth	
DC	DC	All in prenatal care by 5 months	Ethnicity, child's IQ and grade, current maternal alcohol/drug use	
R	R	Hospital payment, maternal education, all black		
DC Decreased indeterminate sleep and δ energies, increased REM and spectral correlation	DC Increased arousal, decreased β energies	Full-term, Apgar score >5, mother in prenatal care by 5 months, no general anesthesia	Child's sex and age, ethnicity, number of hospitalizations, maternal age	

developmental toxicity different in severity, scope, or kind from the sequelae of many other risk factors. Many findings once thought to be specific effects of in utero cocaine exposure can be explained in whole or in part by other factors, including prenatal exposure to tobacco, marijuana, or alcohol* and the quality of the child's environment.†

*References 64, 65, 70, 74, 78, 84, 86, 90, 95
†References 63, 64, 66, 68, 71, 73, 77-79, 83, 84, 86, 87, 89, 90

Author Contributions: *Study concept and design:* Frank, Augustyn, Zuckerman.
Acquisition of data: Frank, Augustyn, Pell.
Analysis and interpretation of data: Frank, Augustyn, Grant Knight, Zuckerman.
Drafting of the manuscript: Frank, Grant Knight.
Critical revision of the manuscript for important intellectual content: Augustyn, Pell, Zuckerman.
Obtained funding: Frank.
Administrative, technical, or material support: Augustyn, Grant Knight, Pell, Zuckerman.
Study supervision: Frank, Zuckerman.
Funding/Support: This work was supported by grant DA 06532 from the National Institute of Drug Abuse (Dr Frank).
Acknowledgment: We thank Ruth Rose-Jacobs, ScD, David Bellinger, PhD, Howard Cabral, PhD, Tim Heeren, PhD, and Marjorie Beeghly, PhD, for their thoughtful comments. We also thank Ivana Hanson, BA, and Elizabeth Soares, BS, for their assistance in the preparation of the manuscript. We would particularly like to thank Lisa Blazejewski, MS, for her expert bibliographic and editorial assistance.

REFERENCES

1. Greenhouse L. Justices consider limits of the legal response to risky behavior by pregnant women. *New York Times*. October 5, 2000:A26.
2. Horger EO III, Brown SB, Condon CM. Cocaine in pregnancy. *J S C Med Assoc*. 1990;86:527-532.
3. Nelson J, Marshall MF. *Ethical and Legal Analyses of Three Coercive Policies Aimed at Substance Abuse by Pregnant Women*. Charleston, SC: The Robert Wood Johnson Foundation; 1998.
4. Paltrow LM. Pregnant drug users, fetal persons, and the threat to *Roe v Wade*. *Albany Law Rev*. 1999;62: 999-1055.
5. O'Neill AM, Carter K. Desperate measures. *People*. September 27, 1999:145-149.
6. Will GF. Paying addicts not to have kids is a good thing. *Baltimore Sun*. November 1, 1999:15A.
7. Paltrow LM, Cohen D, Carey CA. *Year 2000 Overview: Governmental Responses to Pregnant Women Who Use Alcohol or Other Drugs*. Philadelphia, Pa: National Advocates for Pregnant Women of the Women's Law Project; 2000.
8. Haack R. *Drug-Dependent Mothers and Their Children: Issues in Public Policy and Public Health*. New York, NY: Springer Publications; 1997.
9. American Public Health Association, South Carolina Medical Association, American College of Obstetricians and Gynecologists, et al. Brief Amici Curiae in support of the petitioners in *Ferguson v City of Charleston*. (SCT 2000).
10. Frank DA, Augustyn M, Zuckerman BS. Neonatal neurobehavioral and neuroanatomic correlates of prenatal cocaine exposure. In: Harvey JA, Kosofsky BE, eds. *Cocaine: Effects on the Developing Brain*. New York, NY: New York Academy of Sciences; 1998:40-50.
11. Held JR, Riggs ML, Dorman C. The effect of prenatal cocaine exposure on neurobehavioral outcome. *Neurotoxicol Teratol*. 1999;21:619-625.
12. Lutiger B, Graham K, Einarson TR, Koren G. Relationship between gestational cocaine use and pregnancy outcome. *Teratology*. 1991;44:405-414.
13. Holzman C, Paneth N. Maternal cocaine use during pregnancy and perinatal outcomes. *Epidemiol Rev*. 1994;16:315-334.
14. Frank DA, Augustyn M, Mirochnick M, Pell T, Zuckerman BS. Are there dose effects of prenatal cocaine exposure on children's bodies and brains? In: Fitzgerald HE, Lester BM, Zuckerman BS, eds. *Children of Addiction: Research, Health, and Public Policy Issues*. New York, NY: RoutledgeFalmer; 2000:1-28.
15. Fares I, McCulloch KM, Raju TN. Intrauterine cocaine exposure and the risk for sudden infant death syndrome. *J Perinatol*. 1997;17:179-182.
16. Frank DA, McCarten KM, Robson CD, et al. Level of in utero cocaine exposure and neonatal ultrasound findings. *Pediatrics*. 1999;104:1101-1105.
17. Behnke M, Davis Eyler F, Conlon M, et al. Incidence and description of structural brain abnormalities in newborns exposed to cocaine. *J Pediatr*. 1998; 132:291-294.
18. Ostrea EM, Ostrea AR, Simpson PM. Mortality within the first two years in infants exposed to cocaine, opiate, or cannabinoid during gestation. *Pediatrics*. 1997;100:79-83.
19. Woods NS, Eyler FD, Conlon M, et al. Pygmalion in the cradle: observer bias against cocaine-exposed infants. *J Dev Behav Pediatr*. 1998;19:283-285.
20. Thurman SK, Brobeil RA, Ducette JP. Prenatally exposed to cocaine: does the label matter? *J Early Interv*. 1994;18:119-130.
21. Rotzoll BW. Costs increase as crack babies mature. *Chicago Sun-Times*. April 23, 2000:12.
22. Elliott KT, Coker DR. Crack babies: here they come, ready or not. *J Instructional Psychol*. 1991;18:60-64.
23. Harvey JA, Kosofsky BE, eds. *Cocaine: Effects on the Developing Brain*. New York, NY: New York Academy of Sciences; 1998.
24. Angelilli M, Fischer H, Delaney-Black V, et al. History of in utero cocaine exposure in language-delayed children. *Clin Pediatr (Phila)*. 1994;33:514-516.
25. Arendt R, Singer L, Angelopoulos J, et al. Sensorimotor development in cocaine-exposed infants. *Infant Behav Dev*. 1998;21:627-640.
26. Arendt R, Angelopoulos J, Salvator A, Singer L. Motor development of cocaine-exposed children at age two years. *Pediatrics*. 1999;103:86-92.
27. Barone D. Changing perceptions: the literacy development of children prenatally exposed to crack or cocaine. *J Literacy Res*. 1997;20:183-219.
28. Belcher HME, Shapiro BK, Leppert M, et al. Sequential neuromotor examination in children with intrauterine cocaine/polydrug exposure. *Dev Med Child Neurol*. 1999;41:240-246.
29. Bender SL, Word CO, DiClemente RJ, et al. The developmental implications of prenatal and/or postnatal crack cocaine exposure in preschool children: a preliminary report. *J Dev Behav Pediatr*. 1995;16:418-424.
30. Blackwell P, Kirkhart K, Schmitt D, Kaiser M. Cocaine/polydrug-affected dyads: implications for infant cognitive development and mother-infant interaction during the first six postnatal months. *J Appl Dev Psychol*. 1998;19:235-248.
31. Chapman JK. Developmental outcomes in two groups of infants and toddlers: prenatally cocaine exposed and noncocaine exposed part 1. *Infant-Toddler Interv*. 2000;10:19-36.
32. Chiriboga CA, Vibbert M, Malouf R, et al. Neurological correlates of fetal cocaine exposure. *Pediatrics*. 1995;96:1070-1077.
33. Edmondson R, Smith TM. Temperament and behavior of infants prenatally exposed to drugs. *Infant Ment Health J*. 1994;15:368-379.
34. Espy KA, Kaufmann PM, Glisky ML. Neuropsychologic function in toddlers exposed to cocaine in utero. *Dev Neuropsychol*. 1999;15:447-460.
35. Franck EJ. Prenatally drug-exposed children in out-of-home care. *Child Welfare*. 1996;75:19-34.
36. Harsham J, Keller J, Disbrow D. Growth patterns of infants exposed to cocaine and other drugs in utero. *J Am Diet Assoc*. 1994;94:999-1007.
37. Hawley TL, Halle TG, Drasin RE, Thomas NG. Children of addicted mothers: effects of the "crack epidemic" on the caregiving environment and the development of preschoolers. *Am J Orthopsychiatry*. 1995; 65:364-379.
38. Heffelfinger A, Craft S, Shyken J. Visual attention in children with prenatal cocaine exposure. *J Int Neuropsychol Soc*. 1997;3:237-245.
39. Hofkosh D, Pringle JL, Wald HL, et al. Early interactions between drug involved mothers and infants. *Arch Pediatr Adolesc Med*. 1995;149:665-672.
40. Howard J, Beckwith L, Espinosa M, Tyler R. Development of infants born to cocaine-abusing women. *Neurotoxicol Teratol*. 1994;17:403-411.
41. Johnson JM, Seikel JA, Madison CL, Foose SM, Rinard KD. Standardized test performance of children with a history of prenatal exposure to multiple drugs/cocaine. *J Commun Disord*. 1997;30:45-73.
42. Madison CL, Johnson JM, Seikel JA, et al. Comparative study of the phonology of preschool children prenatally exposed to cocaine and multiple drugs and non-exposed children. *J Commun Disord*. 1998; 31:231-244.
43. Malakoff ME, Mayes LC, Schottenfeld RS. Language abilities of preschool-age children living with cocaine-using mothers. *Am J Addict*. 1994;3:346-354.
44. Mentis M, Lundgren K. Effects of prenatal exposure to cocaine and associated risk factors on language development. *J Speech Hear Res*. 1995;38: 1303-1318.
45. Morrison D, Villarreal S. Cognitive performance of prenatally drug-exposed infants. *Infant-Toddler Interv*. 1993;3:211-220.
46. Nulman I, Rovet J, Altmann D, et al. Neurodevelopment of adopted children exposed in utero to cocaine. *CMAJ*. 1994;151:1591-1597.
47. Phelps L, Wallace NV, Bontrager A. Risk factors in early child development: is prenatal cocaine/polydrug exposure a key variable? *Psychol Schools*. 1997;34: 245-252.
48. Phelps L, Cottone JW. Long-term developmental outcomes of prenatal cocaine exposure. *J Psychoeducational Assess*. 1999;17:343-353.
49. Rodning C, Beckwith L, Howard J. Characteristics of attachment organization and play organization in prenatally drug-exposed toddlers. *Dev Psychopathol*. 1990; 1:277-289.
50. Rodning C, Beckwith L, Howard J. Quality of attachment and home environments in children born prenatally exposed to PCP and cocaine. *Dev Psychopathol*. 1991;3:351-366.
51. Rotholz DA, Snyder P, Peters G. A behavioral comparison of preschool children at high and low risk from prenatal cocaine exposure. *Education Treatment Children*. 1995;18:1-18.
52. Schneider JW, Chasnoff IJ. Motor assessment of cocaine/polydrug exposed infants at age 4 months. *Neurotoxicol Teratol*. 1992;14:97-101.
53. Singer L, Arendt R, Farkas K, et al. Relationship of prenatal cocaine exposure and maternal postpartum psychological distress to child developmental outcome. *Dev Psychopathol*. 1997;9:473-489.
54. Stanger C, Higgins ST, Bickel WK, et al. Behavioral and emotional problems among children of cocaine and opiate dependent parents. *J Am Acad Child Adolesc Psychiatry*. 1999;38:421-428.
55. van Baar A, Flury P, Ultee CA. Behavior in first year after drug dependent pregnancy. *Arch Dis Child*. 1989; 64:241-245.
56. van Baar AL, Soepatmi S, Gunning WB, Akkerhuis GW. Development after prenatal exposure to cocaine, heroin, and methadone. *Acta Paediatr*. 1994; 404:40-46.
57. van Baar A, de Graaff BMT. Cognitive development

at preschool-age of infants of drug-dependent mothers. *Dev Med Child Neurol*. 1994;36:1063-1075.
58. van Beveren TT, Little BB, Spence MJ. Effects of prenatal cocaine exposure and postnatal environment on child development. *Am J Hum Biol*. 2000;12:417-428.
59. Wasserman GA, Kline JK, Bateman DA. Prenatal cocaine exposure and school age intelligence. *Drug Alcohol Depend*. 1998;50:203-210.
60. Weathers WT, Crane MM, Sauvain KJ, Blackhurst MS. Cocaine use in women from a defined population: prevalence at delivery and effects on growth in infants. *Pediatrics*. 1993;91:350-354.
61. Yolton KA, Bolig R. Psychosocial, behavioral, and developmental characteristics of toddlers prenatally exposed to cocaine. *Child Study J*. 1994;24:49-68.
62. Alessandri S, Sullivan MW, Imaizumi S, Lewis M. Learning and emotional responsivity in cocaine-exposed infants. *Dev Psychol*. 1993;29:989-997.
63. Alessandri SM, Bendersky M, Lewis M. Cognitive functioning in 8 to 18 month old drug-exposed infants. *Dev Psychol*. 1998;34:565-573.
64. Azuma S, Chasnoff I. Outcome of children prenatally exposed to cocaine and other drugs: a path analysis of three-year data. *Pediatrics*. 1993;92:396-402.
65. Bard KA, Coles CD, Platzman KA, Lynch ME. The effects of prenatal drug exposure, term status, and caregiving on arousal and arousal modulation of 8-week-old infants. *Dev Psychobiol*. 2000;36:194-212.
66. Bendersky M, Lewis M. Arousal modulation in cocaine-exposed infants. *Dev Psychol*. 1998;34:555-564.
67. Betancourt L, Fischer R, Giannetta J, et al. Problem-solving ability of inner-city children with and without in utero cocaine exposure. *J Dev Behav Pediatr*. 1999; 20:418-424.
68. Blanchard Y, Suess PE, Beeghly M. Effects of prenatal drug exposure on neurobehavioral functioning in young infants. *Phys Occup Ther Pediatr*. 1998;18: 19-37.
69. Bland-Stewart L, Seymour H, Beeghly M, Frank DA. Semantic development of African-American toddlers exposed to cocaine. *Semin Speech Lang*. 1998; 19:167-187.
70. Chasnoff IJ, Griffith DR, Freier C, Murray J. Cocaine/polydrug use in pregnancy. *Pediatrics*. 1992; 89:284-289.
71. Coles CD, Bard KA, Platzman KA, Lynch ME. Attentional response at eight weeks in prenatally drug-exposed and preterm infants. *Neurotoxicol Teratol*. 1999;21:527-537.
72. Delaney-Black V, Covington C, Templin T, et al. Prenatal cocaine exposure and child behavior. *Pediatrics*. 1998;102:945-950.
73. Delaney-Black V, Covington C, Templin T, et al. Teacher-assessed behavior of children prenatally exposed to cocaine. *Pediatrics*. 2000;106:782-791.
74. Dempsey DA, Hajnal BL, Partridge JC, et al. Tone abnormalities are associated with maternal cigarette smoking during pregnancy in in utero cocaine-exposed infants. *Pediatrics*. 2000;106:79-85.
75. Fetters L, Tronick EZ. Neuromotor development of cocaine exposed and control infants from birth to 15 months. *Pediatrics*. 1996;98:938-943.
76. Fetters L, Tronick EZ. Trajectories of motor development: polydrug exposed infants in the first fifteen months. *Phys Occup Ther Pediatr*. 1998;18:1-18.
77. Graham K, Feigenbaum A, Pastuszak A, et al. Pregnancy outcome and infant development following gestational cocaine use by social cocaine users in Toronto, Canada. *Clin Invest Med*. 1992;15:384-394.
78. Griffith DR, Chasnoff IJ, Azuma S. Three-year outcome of children exposed prenatally to drugs. *J Am Acad Child Adolesc Psychiatry*. 1994;33:20-27.
79. Hurt H, Brodsky NL, Betancourt L, et al. Cocaine-exposed children. *J Dev Behav Pediatr*. 1995;16:29-35.
80. Hurt H, Brodsky NL, Betancourt L, et al. Play behavior in toddlers with in utero cocaine exposure. *J Dev Behav Pediatr*. 1996;17:373-379.
81. Hurt H, Malmud E, Betancourt L, et al. A prospective evaluation of early language development in children with in utero cocaine exposure and in control subjects. *J Pediatr*. 1997;130:310-312.
82. Hurt H, Malmud E, Betancourt L, et al. Children with in utero cocaine exposure do not differ from control subjects on intelligence testing. *Arch Pediatr Adolesc Med*. 1997;151:1237-1241.
83. Hurt H, Malmud E, Braitman LE, et al. Inner-city achievers: who are they? *Arch Pediatr Adolesc Med*. 1998;152:993-997.
84. Jacobson JL, Jacobson SW, Sokol RJ. Effects of prenatal exposure to alcohol, smoking, and illicit drugs on postpartum somatic growth. *Alcohol Clin Exp Res*. 1994; 18:317-323.
85. Jacobson JL, Jacobson SW, Sokol RJ, et al. New evidence for neurobehavioral effects of in utero cocaine exposure. *J Pediatr*. 1996;129:581-590.
86. Jacobson SW, Bihun JT, Chiodo LM. Effects of prenatal alcohol and cocaine exposure on infant cortisol levels. *Dev Psychopathol*. 1999;11:195-208.
87. Johnson HL, Nusbaum BJ, Bejarano A, Rosen TS. An ecological approach to development in children with prenatal drug exposure. *Am J Orthopsychiatry*. 1999; 69:448-456.
88. Karmel BZ, Gardner JM, Freedland RL. Arousal modulated attention at four months as a function of intrauterine cocaine exposure. *J Pediatr Psychol*. 1996; 21:821-832.
89. Kilbride H, Castor C, Hoffman E, Fuger K. Thirty-six-month outcome of prenatal cocaine exposure for term or near-term infants. *J Dev Behav Pediatr*. 2000; 21:19-26.
90. Leech SL, Richardson GA, Goldschmidt L, Day NL. Prenatal substance exposure: effects on attention and impulsivity of six-year olds. *Neurotoxicol Teratol*. 1999; 21:109-118.
91. Mayes LC, Bornstein MH, Chawarska K, Granger RH. Information processing and developmental assessments in three-month-old infants exposed prenatally to cocaine. *Pediatrics*. 1995;95:539-545.
92. Mayes LC, Feldman R, Granger RH. The effects of polydrug use with and without cocaine on mother-infant interaction at 3 and 6 months. *Infant Behav Dev*. 1997;20:489-502.
93. Richardson GA, Conroy ML, Day NL. Prenatal cocaine exposure: effects on the development of school-age children. *Neurotoxicol Teratol*. 1996;18:627-634.
94. Roumell N, Abramson L, Delaney V, Willey R. Facial expressivity to acute pain in cocaine-exposed infants. *Infant Ment Health J*. 1997;18:274-281.
95. Scher MS, Richardson GA, Day NL. Effects of prenatal cocaine/crack and other drug exposure on electroencephalographic sleep studies at birth and one year. *Pediatrics*. 2000;105:39-48.
96. Singer LT, Yamashita TS, Hawkins S, et al. Increased incidence of intraventricular hemorrhage and developmental delay in cocaine-exposed, very low birth weight infants. *J Pediatr*. 1994;124:765-771.
97. Swanson MW, Streissguth AP, Sampson PD, Olson HC. Prenatal cocaine and neuromotor outcome at four months. *J Dev Behav Pediatr*. 1999;20:325-334.
98. Lester BM, LaGasse LL, Seifer R. Cocaine exposure and children. *Science*. 1998;282:633-634.
99. Schlesselman JJ, Stolley PD. Sources of bias. In: Schlesselman JJ, ed. *Case-Control Studies: Design, Conduct, Analysis*. New York, NY: Oxford University Press; 1982:124-143.
100. Rosenthal R. *Experimenter Effects in Behavioral Research*. New York, NY: Appleton; 1966.
101. Rosenthal R, Jacobson L. *Pygmalion in the Classroom: Teacher Expectation and Pupils' Intellectual Development*. New York, NY: Holt Rinehart & Winston Inc; 1968.
102. Hans S. Maternal opioid drug use and child development. In: Zagon I, Slotkin T, eds. *Maternal Substance Abuse and the Developing Nervous System*. Boston, Mass: Academic Press Inc; 1992:177-207.
103. Brazdziunas DM, Roizen NJ, Kohrman AF, Smith DK. Children of HIV-positive parents: implications for intervention. *Psychosoc Rehabil J*. 1994;17:145-149.
104. Bellinger D. Interpreting the literature on lead and child development. *Neurotoxicol Teratol*. 1995;17: 201-212.
105. Jacobson JL, Jacobson SW. Methodological considerations in behavioral toxicology in infants and children. *Dev Psychol*. 1996;32:390-403.
106. Ostrea EM, Brady MJ, Gause S, Raymundo AL, Stevens M. Drug screening of newborns by meconium analysis. *Pediatrics*. 1992;89:107-113.
107. Chiriboga CA, Brust JCM, Bateman D, Hauser WA. Dose-response effect of fetal cocaine exposure on newborn neurologic function. *Pediatrics*. 1999;103:79-85.
108. Delaney-Black V, Covington C, Ostrea E, et al. Prenatal cocaine and neonatal outcome. *Pediatrics*. 1996;98:735-740.
109. Tronick EZ, Frank DA, Cabral H, et al. Late dose-response effects of prenatal cocaine exposure on newborn neurobehavioral performance. *Pediatrics*. 1996; 98:76-83.
110. Mirochnick M, Frank DA, Cabral H, et al. Relation between meconium concentration of the cocaine metabolite benzoylecognine and fetal growth. *J Pediatr*. 1995;126:636-638.
111. Kuhn L, Kline M, Ng S, et al. Cocaine use during pregnancy and intrauterine growth retardation. *Am J Epidemiol*. 2000;152:112-119.
112. Frank DA, Zuckerman BS, Amaro H, et al. Cocaine use during pregnancy. *Pediatrics*. 1988;82:888-895.
113. Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 9- to 12-year-olds prenatally exposed to cigarettes and marijuana. *Neurotoxicol Teratol*. 1998;20:293-306.
114. Leon DA. Failed or misleading adjustment for confounding. *Lancet*. 1993;342:479-481.
115. Achenbach TM. *Manual for the Child Behavior Checklist/4-18 and 1991 Profile*. Burlington: University of Vermont; 1991.
116. Freyer FJ. Cocaine in the womb: it costs society plenty. *Providence Journal*. October 23, 1998:A-01.
117. Slotkin TA. Fetal nicotine or cocaine exposure: which one is worse? *J Pharmacol Exp Ther*. 1998;285: 931-945.
118. Werler MM. Teratogen update: smoking and reproductive outcomes. *Teratology*. 1997;55:382-388.
119. Lassen K, Oei TP. Effects of maternal cigarette smoking during pregnancy on long-term physical and cognitive parameters of child development. *Addict Behav*. 1998;23:635-653.
120. Weitzman M, Gortmaker S, Sobol A. Maternal smoking and behavior problems of children. *Pediatrics*. 1992;90:342-349.
121. Lightwood JM, Phibbs CS, Glantz SA. Short term health and economic benefits of smoking cessation: low birth weight. *Pediatrics*. 1999;104:1312-1320.
122. Gomez LE. *Misconceiving Mothers: Legislators, Prosecutors, and the Politics of Prenatal Drug Exposure*. Philadelphia, Pa: Temple University Press; 1997.
123. Adger HJ, Macdonald DI, Wenger S. Core competencies for involvement of health care providers in the care of children and adolescents in families affected by substance abuse. *Pediatrics*. 1999;103:1083-1084.
124. Murphy S, Rosenbaum M. *Pregnant Women on Drugs: Combating Stereotypes and Stigma*. New Brunswick, NJ: Rutgers University Press; 1999.
125. Racine A, Joyce T, Anderson R. The association between prenatal care and birth weight among women exposed to cocaine in New York City. *JAMA*. 1993; 270:1581-1586.
126. Fried PA, Watkinson B. Visuoperceptual functioning differs in 9- to 12-year-olds prenatally exposed to cigarettes and marihuana. *Neurotoxicol Teratol*. 2000;22:11-20.
127. Goldschmidt L, Day NL, Richardson GA. Effects of prenatal marijuana exposure on child behavior problems at age 10. *Neurotoxicol Teratol*. 2000; 22:325-336.
128. Huston A, McLoyd V, Cull C. Children and poverty: issues in contemporary research. *Child Dev*. 1991; 65:275-282.