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NEURODEVELOPMENTAL EFFECTS OF COCAINE

Lynn Singer, PhD, Robert Arendt, PhD, and Sonia Minnes, MA

Department of Pediatrics, Case Western Reserve University School of Medicine (LS, RA); and Center for the Advancement of Mothers and Children, Rainbow Babies and Childrens Hospital (SM), Cleveland, Ohio

Abstract

The United States has recently been compelled to acknowledge and to cope with an alarming increase in incidence of drug exposure in newborns owing to a new *cocaine epidemic*. Perhaps because of the sudden onset of national recognition of the problem, the lack of a firm knowledge base regarding the mechanisms of the effects of cocaine on child development, and the sheer magnitude of the problem in urban areas of the United States, the issue of cocaine exposure in children has been characterized by medical, legal, and social policy controversies. This article focuses on elucidating what is and what is not known about cocaine's neurodevelopmental effects and aims to inform perinatologists about the complex issues associated with understanding and caring for the cocaine-exposed newborn.

INCIDENCE

There is widespread agreement that cocaine, especially in its "crack," or smoked, form, has become a pervasive presence in newborn nurseries and neonatal intensive care units in urban areas nationwide. Studies indicate that 10% to 15% of major urban newborn births are affected by maternal cocaine use.^{20,54} The National Association for Perinatal Addiction Research and Education (NAPARE) has estimated that over 100,000 infants annually are born with drug exposure. Data from one teaching hospital indicated a 15-fold increase in prenatal cocaine exposure in a 12-year period compared with previously obtained data.¹⁰⁰ Incidence rates may be higher within lower socioeconomic status and minority groups, however. In Ohio, for example, at a major university's obstetrics hospital, cocaine exposure affected 20% of minority, indigent newborns and from 25% to 30% of all very low birth weight (VLBW) births in 1990 (Robert Kleigman, MD, personal communication, June 1992).

CLINICS IN PERINATOLOGY

Because there has been no evidence that incidence rates are decreasing, the large numbers of infants and families affected will have medical and social ramifications for at least a generation. In addition to potential direct toxic effects on fetal and later child health and development, the cocaine epidemic has resulted in significantly increased neonatal health care and social costs. One study⁸⁵ has estimated that about \$500 million in additional health

care costs in 1990 stemmed from increased neonatal hospital costs and longer lengths of stay for cocaine-exposed neonates. The magnitude of this immediate health care burden, apart from long-term potential for negative sequelae in infants, warrants the integration of effective drug treatment strategies for pregnant women and early screening of drug-exposed infants into existing medical care and social support systems.

PHARMACOLOGY AND OBSTETRIC COMPLICATIONS

A powerful stimulant that produces a strong euphoric effect for most users, cocaine has become the drug of choice for increasing numbers of women of child-bearing age.¹ Its extensive use has been attributed to a confluence of factors. These factors include the faster, more intense, and less expensive “high” of the smoked, free-base form, *crack-cocaine*⁷⁵ and its appeal to women over other illicit drugs, such as heroin, that are injected.

Cocaine’s medical and psychologic effects on adults have been well documented.^{28,41} Cocaine acts as a stimulant in the central nervous system and an inhibitor of nerve conduction in the peripheral nervous system. The principal pharmacologic actions of cocaine on adults include (1) inhibiting active reuptake of catecholamine and serotonin related to the reinforcing euphoric effect of cocaine, decreased appetite, and decreased need for sleep; (2) cardiovascular toxicities, including vasoconstriction and tachycardia; and (3) blocking of nerve conduction by preventing transient inflow of sodium ions, producing a local anesthetic effect.²⁸ Cocaine affects primarily cardiovascular, respiratory, and central nervous systems. Tachycardia and hypertension are initial cardiac effects of cocaine. Acute myocardial infarcts and arrhythmias have been described in young adult cocaine users.⁷ Neurologic complications can include seizures, headaches, hyperpyrexia, and brief loss of consciousness.

Although formerly cocaine was considered a nonaddictive drug, its physiologic and psychologic dependency-inducing qualities are now recognized.⁵² Increased access to the drug and modes of use that augment absorption, such as “smoking” or intravenous administration, appear to induce compulsive use. Cocaine’s euphoric effects are usually prolonged, or its withdrawal “crash” cushioned, through the concomitant use of other drugs, typically alcohol, marijuana, and heroin. Studies show that the majority of women who use cocaine during pregnancy are “poly-drug” users.^{95,111} Thus cocaine-exposed infants are also more likely to be exposed to these other drugs during gestation than infants whose mothers did not use cocaine.

Some adverse pregnancy complications of maternal cocaine use have been consistently documented, especially placental abruption.^{10,15,71} Premature rupture of membranes and spontaneous abortions in cocaine-using pregnant women have also been noted, but findings across studies are inconsistent.⁹⁷ Poor nutrition during pregnancy, potentially affecting fetal growth, is also common with chronic cocaine use, owing to the anorectic effects of cocaine.³⁷ Drug use in women is associated with increased incidence of infectious diseases, especially sexually transmitted diseases (STDs) and human immunodeficiency viruses (HIVs). In a survey of cocaine-using women, Fullilove et al⁵⁰ reported 55% had a history of STD. Although most STDs can be treated effectively in neonates if discovered early, 20% to

40% of infants prenatally exposed to the acquired immunodeficiency syndrome (AIDS) virus will contract the disease.⁶⁵ Approximately 80% of all HIV infections in children in the United States and European countries are acquired perinatally.⁸²

SCREENING FOR DRUG EXPOSURE

Identification of cocaine use is most often based on maternal drug interview, urine toxicology screen, or both. An investigation of marijuana and cocaine use on fetal growth¹¹² highlighted the importance of using biologic markers in combination with self-reports to identify drug use during pregnancy. Because cocaine is metabolized and cleared from an adult woman in 3 to 6 days, however, the most commonly used marker, urine screening, has serious limitations.⁷⁷

Several other biologic markers, including meconium, amniotic fluid, and newborn dried blood specimen, have been investigated. Meconium testing has the advantage of detecting cocaine exposure from as early as the first trimester.⁸¹ Recent reports comparing different methods of cocaine exposure suggest that meconium testing is superior to urine, but these reports also emphasize the need to combine biologic screens with clinical interviews.^{5,105}

Neither urine nor meconium assessment provides a way of assessing maternal pattern of use. One other experimental method of detecting cocaine use, hair analysis, may prove useful in answering questions about maternal pattern of drug use during pregnancy. The question still remains whether a woman used small amounts of cocaine on a regular basis during her pregnancy or used large amounts in binges. Such information is currently obtainable only through clinical interview. Interviews can be highly unreliable owing to the denial common in women who use drugs and alcohol. A large prospective study⁴⁸ found that 24% of pregnant women who used cocaine would have been undetected if urine assays were not performed. Simultaneously 47% of women who had negative urine assays admitted cocaine use during clinical interview.

Because maternal prenatal or newborn screening for cocaine is not done universally, identification and treatment of cocaine-using women and their infants are riddled with controversy. Controversy stems from a number of factors, including racial and social class variation in preference for differing illegal drugs; a probable racial and social class bias in detecting maternal drug use in public versus private care hospitals; and racial, social class, and drug-related differences in referral to social service and legal systems.

The few anonymous screening studies of maternal drug use in pregnancy that have been reported all indicate a markedly similar rate (10% to 20%) of illegal drug use in poor, minority, and white middle-class groups.^{20,58,112} White, private-care women, however, tend to use marijuana, whereas minority, lower social class women tend to use cocaine.

Criteria for doing a toxicology screen vary greatly from hospital to hospital and from physician to physician. Commonly used criteria include infant withdrawal symptoms, lack of prenatal care, a family history of child neglect or abuse, and a history of maternal drug use. Few if any private care hospitals screen for maternal drug use. Even in large public hospitals, screening is rarely universal and affects primarily on poor or minority women who

use cocaine. As detection of neonatal cocaine exposure in some states initiates referral to legal or social service agencies for investigation of child abuse or neglect,¹⁰⁸ potential racial and social class biases and ethical implications become evident. In the only study to investigate the consequences of detection, Chasnoff et al²⁰ found that minority women in a statewide surveillance in Florida were more likely to be referred to the Department of Human Services (DHS) for drug use than were white, private-care mothers also identified as using an illicit drug during pregnancy.

Because detection of cocaine use in pregnant women can result in such adverse legal consequences as investigation for child abuse, loss of child custody, and even maternal incarceration, the importance of hospital screening and social policies that are equitable and protect all children at risk cannot be underestimated. Social policies involving cocaine contrast sharply with policies implemented around other drugs. If protection of the fetus and subsequent infant development is of concern, a substantial research base has already established the significant adverse developmental effects of prenatal exposure to alcohol, a legal, more widely abused drug with documented teratogenic effects^{26,99} but that social and legal institutional policies have largely ignored.

TERATOGENIC EFFECTS OF COCAINE

Whether cocaine is a teratogen remains an issue of some controversy. Early models of fetal cocaine exposure were predominately based on the effects of cocaine on the adult central nervous system. Cocaine's low molecular weight and high water and lipid solubility allow it to cross the placenta and the fetal blood-brain barrier readily and enter the fetal central nervous system.⁸⁸ Regarding the time of exposure, it is important to emphasize that cocaine can affect the unborn infant not only during embryologic differentiation and development that occurs during the first trimester of pregnancy, but also throughout gestation.⁶¹

The strongest support for the hypothesis that cocaine is a teratogen comes from experimental animal studies that match a pattern of congenital defects found in drug-exposed animals to those observed among infants born to mothers who used the drug during pregnancy.¹⁰⁹ Several animal studies suggest that cocaine may have a direct teratogenic effect on a fetus. Data presented indicted that 10.5-day-old Sprague-Dawley rat embryos cultured for 48 hours in different concentrations of cocaine exhibited growth in a concentration-dependent manner.³⁵ In another study, neonatal rats were administered cocaine cerebral glucose, and their subsequent metabolic patterns were examined.³³ When the animals reached adulthood, metabolic activity in the females, but not the males, exhibited significant increases. The cerebral structures in which the activity was found included many of the same as those excited in adult rats by acute administration of cocaine. These data suggest that cocaine exposure during gestation may constitute a risk factor leading to long-term alterations in brain functioning and perhaps later intellectual functioning.

Vascular Effects

The mechanism of reproductive toxicity with strongest theoretic and empiric support in human infants is maternal vasoconstriction. Cocaine has been shown to constrict uterine blood flow and to decrease fetal oxygenation in pregnant ewes.^{74,107} Early human studies

have suggested a link between cocaine use in pregnancy and increased congenital anomalies, particularly limb defects^{59,106} and cardiac, cranial, and genitourinary system malformations.^{10,16,21,69} Such sequelae are consistent with fetal vascular disruption. A review of the evidence to date concluded that disruptive vascular defects are most likely powerful consequences of in utero cocaine exposure.^{59,61} Two large prospective studies, however, have not resolved this issue. In one, a higher, but not significant, incidence of three minor congenital anomalies were found in newborns of cocaine users versus nonusers.¹¹² In another study, controlling for confounding factors of maternal age, smoking, alcohol, and other drug use, cocaine-exposed infants were found to have more genitourinary anomalies than a comparison sample.²¹

The cerebral blood flow velocity of 20 full-term, newborn, cocaine-exposed infants and 18 nonexposed infants was studied on the first 2 days after birth.¹⁰⁴ Increased mean arterial blood pressure and cerebral blood flow velocity on the first day of life suggested the existence of a hemodynamic effect that puts cocaine-exposed infants at increased risk for intracranial hemorrhage.

In an interesting pilot study with implications for long-term development, cardiovascular effects of prenatal cocaine exposure in a small group of newborns were compared with a group of normal controls.⁴⁰ Results from a complete echocardiographic study indicated that the left ventricular (LV) posterior wall and septum were significantly thicker in the exposed group. In addition, the exposed group had significantly larger LV mass, suggestive of the LV hypertrophy found in adult cocaine users.

Neurologic Abnormalities

Cranial ultrasound was used³⁰ to detect the presence of central nervous system injury in 74 generally healthy, term neonates exposed to cocaine, methamphetamine, or cocaine and a narcotic. The incidence of cranial abnormalities was significantly greater in the drug-exposed infants compared with a group of well infants. Lesions in the drug-exposed infants included intraventricular hemorrhage, echo-densities, and cavitory lesions focused in the basal ganglion, frontal lobes, and posterior fossa. Echodensities and echolucencies in the frontal lobe and basal ganglia may result in morphologic alterations that affect specific functions such as affect or information processing. Recently a large-scale study of infants in Boston, however, failed to replicate these findings.⁴⁷

Although striking, findings of congenital neurologic abnormalities have been limited to a few cases. It is unclear whether local hemorrhages, leading to infarcts and limb reduction defects, are directly responsible or whether vasoconstriction-produced anoxia results in a generalized inhibition of growth and differentiation in the developing embryo and fetus. In any case, if similar to other teratogens, prenatal cocaine exposure can potentially produce a continuum of anomalies—from mortality to possible noncranial congenital abnormalities, to more subtle forms of morbidity and behavioral deficits—depending on the extent of diminished blood flow as well as the time during gestation when the insult occurs.

It appears that cocaine is a relatively weak teratogen that produces toxicity to both the mother and the fetus. What remains uncertain are the implications of findings from animal

studies for the development of human infants. Animal studies, although more controlled, must be considered with great caution when applied to understanding of human development. Although it is possible to develop models that reconstruct fetal cocaine exposure, animal studies have not addressed the interaction of the numerous postnatal environmental factors that also influence developmental outcome. Unfortunately, animal research as well as some earlier studies with human infants failed to take postnatal factors into account. This led to exaggerated perceptions concerning the negative impact of prenatal cocaine exposure.

Effects of Cocaine on Birth Outcomes

Because several reviews of birth outcomes in cocaine-exposed infants^{77,94,97} have already been written, we only summarize the most consistent findings. The most noncontroversial finding regarding in utero cocaine exposure involves impaired somatic growth and decreased head circumference. Infant gestational age, birth weight, head circumference, and length were decreased and the rate of low birth weight increased in the majority of studies of the offspring of cocaine-using women.^{10,22,51,57,67,70,71,80,83,89,112} Studies have found depressed neonatal fat stores and lower lean body mass in cocaine-exposed infants after controlling for maternal weight/height and pregnancy weight gain.⁴⁶ Maternal cocaine use was also independently associated with reduced head circumference in a large, prospective survey in Boston.¹¹² This finding was particularly compelling because all mothers received prenatal care. It seems clear that maternal cocaine use is related to lower infant birth weight and decreased head circumference. The mechanisms, however, by which maternal cocaine use mediates fetal growth have not yet been determined.

Increased rates of preterm birth have also frequently been noted.^{15,24,57,69,71,95,112} Almost all studies of the development of cocaine-exposed infants, however, have focused on full-term infants. One exception is that of Zuckerman et al¹¹³ in which cocaine-exposed preterm newborns were surprisingly found to have a lower incidence of respiratory distress syndrome than matched controls.

Another controversy concerns the relationship between prenatal cocaine exposure and sudden infant death syndrome (SIDS). An early study involving a small convenience sample of cocaine-exposed infants¹⁴ reported an incidence rate of 15% (10 out of 66). A review of more recent, better controlled studies⁸ argued that although the risk of SIDS among cocaine-exposed infants is difficult to determine accurately, the rate is probably between 5.4 and 12.7 per 1000. Although this rate can be regarded as elevated, the authors concluded that home apnea monitoring is not routinely indicated because the risk is not substantial.

NEUROBEHAVIORAL EFFECTS

Neonatal Behavioral Studies

Concern has been raised as to whether, independent of immediate postnatal medical sequelae, cocaine may act as a behavioral teratogen: i.e., vulnerability to drug toxicity can occur beyond the perinatal period with long-term functional deficits resulting from fetal exposure. Initially, cocaine was assumed to produce withdrawal effects similar to those found in heroin-exposed newborns, as evidenced by clinical descriptions of tremulousness,

sleep irregularities, and crying abnormalities in cocaine-exposed newborns. Studies evaluating newborn behavior using heroin-derived abstinence scales,⁴⁴ however, yielded inconsistent findings in cocaine-exposed infants. To date, further attempts to document abnormalities in newborn behavior related to cocaine exposure have yielded inconsistent and controversial findings. Initial and subsequent studies have highlighted behavioral abnormalities in cocaine-exposed infants in the neonatal period.¹⁴ Many of the studies note behavioral differences similar to those also observed in alcohol-exposed or marijuana-exposed neonates. These sequelae include poor sucking, tremors, and poor habituation responses.¹⁰⁰ Because the majority of cocaine-exposed infants are also exposed to other illicit drugs, the question has been raised as to whether observed abnormalities may be the sequelae of alcohol, marijuana, or tobacco exposure rather than cocaine.

There are now seven published studies investigating the neurobehavioral sequelae of cocaine-exposed newborns in the first month of life using the *Brazelton Neonatal Behavioral Assessment Scale* (BNBAS).^{15,17,27,34,78,87,108} The BNBAS, the most widely used neonatal behavioral assessment, groups individual item scores into six behavioral clusters⁶⁶: habituation, orientation, motor performance, range of state, state regulation, and autonomic regulation. These clusters are conceptualized to describe autonomic, motor, state, and social attention systems that influence the infant's capabilities and limits in contributing to the caregiving environment.

All seven investigators administered the Brazelton within 1 to 7 days after birth on term, healthy infants but with widely divergent findings. Two separate studies of cocaine-exposed and comparison infants^{15,17} found depressed interactive behavior; impaired responses to environmental stimuli; and deficits of orientation, motor, and state regulation in cocaine-exposed cohorts. In a matched, stratified design,³⁴ cocaine-exposed infants were less likely than a nonexposed comparison group to show adaptive habituation to repeated stimulation in the first week of life. In contrast, four other studies,^{27,78,87,108} some with larger sample sizes and some of which controlled testing bias by ensuring examiners were *blinded* to drug status, found no significant deficits in cocaine-exposed infants on BNBAS dimensions in the early neonatal period.

It is difficult to draw specific conclusions from these neonatal studies for a number of reasons. Although all used the BNBAS as a measure of infant behavioral functioning, the populations sampled varied markedly. Mothers varied as to whether or not they were enrolled in drug treatment programs versus whether they were from urban or rural communities, and whether they were light versus heavy users. They also differed in level of prenatal care; extent of use of other drugs, especially alcohol and tobacco; and mode of use (smoked versus snorted). Smoked cocaine results in a significant increase in potency of the drug compared with snorted cocaine; thus differentiation of mode of use is important. Studies also differed as to whether or not urine samples were available for comparison groups, and sample sizes ranged from inadequate to large. For studies in which comparison groups did not have urine samples, null results could have stemmed from the undetected presence of cocaine exposure in the comparison sample. Only one study reported on the use of obstetric medications in cocaine versus noncocaine-using women. This study found cocaine users to be more likely to receive anesthesia during delivery.⁸⁷ Because obstetric

medication or anesthesia could be expected to influence infant behavioral performance within the first 3 days of life, their confounding effects need to be evaluated in studies of infants undertaken immediately postpartum.

Three of the investigators also readministered the BNBAS within a month's follow-up after birth, presumably when effects of other drugs would not influence test results. One study¹⁰⁸ found no differences between groups at the later assessment, whereas two^{27,78} found differences at follow-up. Cocaine-exposed infants in these two studies had increased abnormal reflexes²⁷ and deficits in motor function at 1 month.⁷⁸ In a study with a sample adequate to control for other drug use, neonatal complications, and tester factors, cocaine was found to have independent effects on infant motor behavior, state regulation, and abnormal reflexes at 28 days.²⁷ Despite these differences, none of the studies reported that the behavior of cocaine-exposed infants was clinically aberrant. Also, by 1 month of age, the environmental impact of living with a drug-using caregiver may have already exerted a negative effect on infant behavior.

Another difficulty limiting interpretation of these studies is the use of the BNBAS as the sole indicator of behavioral functioning. The BNBAS, similar to other neonatal and infant assessments, is limited in its predictive ability. Brazelton has recommended that the BNBAS *not* be used as a one-time-only assessment, as has been the case for all the studies published, but that outcomes be based on infant recovery curves taken from multiple assessments. Additionally, the BNBAS has been shown to be highly susceptible to examiner effects,³¹ which were not uniformly evaluated in these studies.

In another newborn study, the effects of fetal cocaine exposure on cry characteristics were examined in 80 cocaine-exposed and 80 comparison infants.⁶⁷ Abnormalities in crying have been reported in clinical observations of cocaine-exposed newborns.⁶⁸ Acoustic cry characteristics have been shown to be related to biologic insults, including low birth weight, marijuana exposure, and intrauterine growth retardation in several studies.⁶⁸ Cocaine exposure related to abnormal newborn acoustic cry characteristics through two pathways, reflecting both excitable and biologically depressed characteristics.⁶⁷ Findings suggested that these behavioral characteristics were due to direct toxic effects of cocaine for the excitable dimension and to indirect effects through low birth weight for the underaroused syndrome. As with all studies of neonatal measures, alterations in cry characteristics could represent persistent effects of the drug on the developing newborn system, relatively transient effects owing to the presence of cocaine in the infant, or confounding factors such as obstetric medication.

Although a higher incidence of prematurity has been noted in many cocaine-exposed cohorts, there are few data available on the behavioral functioning of preterm, cocaine-exposed infants. Two areas of functioning have thus far been examined in a small group of 21 relatively healthy, preterm, cocaine-exposed infants who ranged from 31 to 37 weeks' gestational age.⁶² As in full-term studies, cocaine-exposed infants were smaller in growth parameters than comparison infants and had a higher proportion of motor problems. Cocaine-exposed infants showed abnormalities in arousal and attention mechanisms, through preferences for visual stimulation, and on measures of basal Cortisol levels.⁷²

Sensory Motor Development

In light of the clear effect of cocaine on the motor activity of adults^{41,53} and animals,^{6,33,39,60,110} it is surprising that sensory motor development in infants exposed to cocaine has not received more attention. One reason may be the poor record of conventional measures of neonatal and infant development in predicting later cognitive and behavioral functioning based on sensorimotor abilities. Regardless of the difficulties in prediction, however, emergence of voluntary and skilled control of manipulation, locomotion, and posture in response to environmental demands is one of the earliest indications of normal developmental progress. Conversely, delays in the organization of early movement, and the coordination of motor activity with sensory stimulation, are often the first indications of later cognitive deficits.

A few published studies have investigated cocaine exposure and motor development in human infants with inconsistent findings. As noted previously, two studies used the BNBAS to investigate the effects of cocaine exposure on neonatal motor behavior^{28,78} and found poorer performance.

In a study beyond the neonatal period,⁹⁰ a group of 15 full-term cocaine-exposed infants were compared with a control group of 50 full-term infants at 4 months of age. The cocaine infants evidenced significantly more risk for motor dysfunction on the *Movement Assessment of Infants*.¹³ A breakdown of the total score revealed significant differences in muscle tone, reflex, and volitional movements. Rather than using only measures that strictly assess differences between cocaine-exposed and drug-free infants in motor milestones, the authors recommended using measures that are sensitive to qualitative differences.

One recent study produced an unforeseen result.³ Cocaine-exposed infants had higher scores on a global measure of motor skills than a nonexposed comparison group. The authors suggested that the better performance was primarily in gross motor development and may be related to increased muscle tone. No data are yet available to replicate this finding or to support the position that cocaine-exposed infants have persistent, increased muscle tone.

Long-Term Follow-Up Studies

Because prenatal cocaine exposure has only recently become a major concern, longitudinal studies are relatively few. Although the development of drug-exposed infants beyond the neonatal period has major implications for health, education, and social services, it also raises many difficult scientific issues.

In one of the few published, follow-up studies of prenatally drug-exposed infants, standardized scores from the *Bayley Scales of Infant Development* were reported on a group of cocaine-exposed children.¹⁹ The Mental portion of the Bayley Scales assesses sensory-perceptual acuity, visual and auditory discrimination, and verbal ability. The Psychomotor portion provides a measure of gross and fine motor abilities and coordination.

At 2 years of age, cocaine-exposed children did not differ on the scales from a nonexposed comparison group. Cocaine and other drug-exposed infants did, however, show an increased

proportion of infants with Mental and Psychomotor Index Scores greater than 2 SD below average on the scales.

The same study also reported that the mean head size, a correlate of brain growth, of the drug-exposed infants was smaller at birth and remained smaller through 2 years of age compared with the control infants. When all groups were combined, there was a significant correlation between head size and developmental score. The authors noted that postnatal head growth may be an important biologic marker in predicting development of prenatally drug-exposed children.

A recent follow-up report on the same subjects¹⁸ suggested that differences in head growth were still evident at 3 years. Although mean score at 3 years of age of the drug-exposed children was within the normal range, the children were more likely to be perceived by their mothers as displaying behavior problems. The 3-year-old, drug-exposed children also scored significantly lower on verbal and reasoning tasks.

A preliminary report from another ongoing study found that the mean scores of cocaine-exposed infant groups were below those of a nonexposed comparison group on the *Bayley Mental Scale*, but not on the *Motor Development Scale*, at 6 and 12 months of age.⁹² Additionally, when compared with the nonexposed infants, a disproportionate number of cocaine-exposed infants had scores below average on the Mental Scale. Differences were still present after accounting for group differences in gestational age.

Other investigators¹⁰¹ have assessed visual recognition memory in 36 healthy, full-term infants prenatally exposed to drugs with the *Fagan Test of Infant Intelligence* (FTII) at 67 and 92 weeks' conceptional age. The FTII is an alternative infant assessment measure based on differential visual fixation to novel over familiar pictures.³⁸ The infants were born to mothers who used several drugs, frequently in combination, including amphetamines, marijuana, and opiates. The most frequently reported drug, used by 78% of the mothers, was cocaine. Mean scores on the FTII differed significantly between groups, with the drug-exposed infants scoring lower. These findings support the hypothesis that infants exposed to cocaine may be at risk for later subtle cognitive abnormalities. Methodologic limitations of the study, however, make any conclusions speculative. Particularly troublesome is the lack of information regarding gestational age of the participants. As previously mentioned, cocaine-exposed infants are often premature, and prematurity is related to a variety of developmental problems.

Because of the many birth outcome variables involved, including prematurity, intrauterine growth retardation, and possible neurologic abnormalities, the lack of a clear understanding of cocaine's contribution to these medical conditions makes establishing an identifiable pattern of cocaine exposure, such as fetal cocaine syndrome, unlikely in the near future. However, just as most children exposed to alcohol during gestation do not develop fetal alcohol syndrome (FAS) but may experience a continuum of developmental difficulties, the recently hypothesized relationship between fetal cocaine exposure and infant medical risk suggests the potential for diverse long-term behavioral problems. Therefore, although it is important to determine the specific effects of prenatal cocaine exposure, it may be equally

important to treat birth outcomes as biologic markers of a vulnerability to a harmful environment.

We have argued that the findings from animal studies and the consistent findings of intrauterine growth retardation in humans suggest significant negative sequelae of fetal cocaine exposure.⁹⁴ Currently available studies of neurobehavioral outcome in cocaine-exposed infants are still inconclusive regarding the nature, extent, and persistence of negative effects of fetal cocaine exposure. This is due largely to the lack of population-based studies, small and biased samples studied, and extremely high attrition rates in even short-term follow-up studies. It is apparent that, contrary to early media reports, some cocaine-exposed infants, under certain conditions such as prenatal maternal drug treatment and intensive infant intervention, function within normal developmental limits within the first 3 years of life.

Owing to social policy implications, outcome studies of in utero cocaine exposure have become controversial. It has been argued that, regardless of validity, concern about long-term development has resulted in hasty judgments of the extent and persistence of effects brought on by prenatal cocaine exposure.⁷³ Environment, it is noted, plays a significant role in the development of at-risk infants, and currently available scientific evidence is too fragmented and contradictory to draw specific conclusions about cocaine's independent effects on child behavior.

CAREGIVING INFLUENCES ON INFANT DEVELOPMENT

Maternal Cocaine Use in the Postnatal Period

Continued maternal cocaine use during the postnatal period is important to consider because it may compromise parenting and expose the child to other risk factors affecting neurodevelopment. Maternal preoccupation with obtaining cocaine and the possibility of increased psychologic symptoms in cocaine-using women may adversely affect the mother-child interaction and general caretaking/parenting behavior. Unfortunately, many barriers to successful drug treatment exist for the drug-dependent mother.⁴³ Among these barriers are insufficient and inadequate services to meet the needs of pregnant women and mothers, long intervals between desired treatment and scheduled treatment, and lack of adequate care for children while the mother is receiving treatment. Additionally, most traditional drug treatment programs were designed for white, middle-class, male populations and may not generalize to other populations.⁹⁵ A consequence of these significant barriers to treatment is that many drug-exposed infants are raised by mothers who continue to use drugs.

Mother-Infant Interaction

A caregiver's ability to respond through talking, eye contact, and tactile stimulation to the infant's behavioral cues is necessary for optimal intellectual and emotional infant development. Although it has been suggested that drug-dependent mothers are impaired in the ability to respond to their infants,^{29,36,49,91} the specific interactional behavior of cocaine-using mothers is still under investigation.

It has been suggested that maternal psychologic status and her interactions with infants may be impaired through drug intoxication or withdrawal.²³ A few studies have focused on psychologic or personality characteristics of cocaine-using mothers in relation to interactional style and caregiving. One study found decreased responsivity and lower social involvement of the cocaine-using mother to her infant's cues in the neonatal period.⁴⁵ Another examined the relationship of maternal psychopathology, evaluated by a personality inventory, to scores on the infant orientation subscale of the BNBAS.⁵⁶ It was found that the infant's orientation score at 1 month of age was significantly negatively correlated with clinically elevated maternal scores. The conclusion was that maternal psychologic distress in cocaine-using women affects interaction with her infant.

Maternal Psychologic Characteristics

Cocaine dependence has been associated with increases in psychopathology, such as depression, psychoticism, anxiety, and personality disorders,^{12,32,55,63,79} although a consistent pattern of symptoms has not emerged. Additionally, it is not clear whether psychologic distress precedes the onset, or is a result of, cocaine use.

Depression in cocaine-using women is a concern because maternal depression has been demonstrated to have adverse effects on infant development.⁴² Investigations of depression in cocaine-using mothers have produced inconsistent results. Although some studies^{108,111} have found a relationship between cocaine use and level of depression, other studies have not.^{76,96}

For example, Singer et al⁹⁶ recently surveyed cocaine-using postpartum mothers with a self-report, measuring depression and other symptoms of psychologic distress.⁹⁶ Symptoms of depression were no more prevalent in the cocaine-using sample than the control group. Cocaine-using mothers did report more symptoms of paranoid ideation, phobic anxiety, somatic complaints, and psychoticism compared with noncocaine-using women.

A group of cocaine-dependent and alcohol-dependent women receiving drug treatment were assessed for personality disorders according to DSM III-R criteria.⁸⁴ Significantly more cocaine-dependent women (75%) versus alcohol-dependent women (32%) met the criteria for personality disorder in this study. Specifically paranoid, borderline, and histrionic personality disorders were most prevalent for cocaine-dependent women.

In another study of cocaine-using mothers, treatment seekers were found to endorse more symptoms of anxiety and somatic complaints and were more likely to have reported suicidal ideation within the past 30 days than a similar group of cocaine-using mothers who were not currently seeking treatment.⁹⁸ Thus, the severity of maternal addiction may influence her psychologic symptom profile.

A review of recent studies investigating psychologic distress in cocaine-using mothers clearly indicates that psychologic distress is prevalent in cocaine-using women in many forms and likely affects parenting adversely. Probable reasons for the contradictory results among studies are confounding variables, such as severity of addiction, duration of use,

poly-drug use, and other stressful life events or environmental factors such as social supports.

Associated Maternal Risk Factors

Many factors associated with a drug-using lifestyle may affect an infant's development in the postnatal period. For example, increased risks associated with STD owing to greater sexual activity or through shared needles by drug-using women are passed on to her fetus in the perinatal period.

Physical or sexual abuse in substance-using women are other factors associated with a drug-using lifestyle. In a sample of drug-using, incarcerated women, 19% report having been severely beaten as children.⁸⁶ Other researchers^{43,64,102} report alarmingly high (up to 80%) incidence of early physical or sexual abuse among substance-abusing women. Drug use during pregnancy also appears to be associated with increased risk for maternal battering.² Pregnant victims of abuse were more likely to use alcohol, marijuana, and cocaine than nonvictims. Battered women in a public prenatal clinic more frequently self-admitted alcohol and cocaine use than women who were not battered.⁹

Presumably children of cocaine-using women are at risk from additional injury inflicted through battering prenatally, in addition to being witness to ongoing violence in the home or being potential victims of abuse themselves. Children who live in violent families are reported to have more behavior problems, more difficult temperaments, and more aggression than children from nonviolent families. Additionally, a woman using illicit drugs may expose herself and her children to the potential violence related to drug acquisition.

More passive forms of neglect and abuse have also been noted among cocaine-dependent mothers. The caregiver's limited financial resources are used for obtaining cocaine rather than family essentials. Although smokable cocaine in the form of "crack" is relatively inexpensive, the addictive nature of the drug often compels a mother to use money or other resources that she can sell for cash to purchase more and more of the drug. Often cocaine is purchased at the expense of supplies such as diapers, formula, or medication for her infant.⁴

A high incidence of failure to thrive in children of cocaine-using mothers also reflects a redirection of time, food, and energy in the cocaine-dependent mother.⁴ Failure to thrive is characterized by an infant's failure to grow along an established growth curve. It can result in serious medical and psychologic consequences, including electrolyte imbalances, seizures, cognitive delays, and apathy.^{11,93} Because infants exposed to cocaine tend to be of lower birth weight, they are at increased risk for falling off the expected growth curve.

The overall risk of neglect and abuse requiring out of home placement of cocaine-exposed infants is significant. In a national study of 10 hospitals, the United States General Accounting Office¹⁰³ found that approximately 30% of the 4000 surveyed drug-exposed infants born in 1989 were placed in foster care. The increased need for foster care placement indicates that parental abandonment, abuse, and neglect of children are associated with increases in maternal drug use.¹⁰³

Maternal Drug Use Patterns

In light of the fact that cocaine-using women are much more likely also to use other drugs, the relevance of studying the isolated effect of cocaine use comes into question. A recent survey of psychologic distress among cocaine-using mothers indicated that as a group, the best predictor of psychologic distress was the combined use of both cocaine and alcohol.⁹⁶ In addition to the interaction effect of cocaine and alcohol on psychologic distress in mothers, consideration of specific detrimental effects to the developing fetus has begun to be investigated in mammals. The interactive effect of alcohol and cocaine was found to affect birth weight, postnatal mortality, and delayed physical maturation more adversely in rats than the use of either drug alone.²⁵

The unique effects of specific combinations of drugs may produce a uniquely different outcome for a developing fetus. Additionally, maternal use of a combination of drugs may affect parenting behavior in a unique way. The explosive increase in the use of “crack” cocaine in pregnant women has placed an emphasis on the search for specific sequelae of its use on infant development. Because cocaine rarely seems to be used in isolation but is characteristically used in combination with other harmful drugs, it may be useful to expand research endeavors in this area.

SUMMARY

How and to what extent fetal cocaine exposure produces specific, negative, long-term effects on infant neurodevelopmental competence has not yet been determined. We have argued previously that results from animal studies, the findings of intrauterine growth retardation in human studies, and the markedly higher incidence of numerous associated risk factors in cocaine-exposed cohorts herald significant clinical risk to the developing infant.⁹⁴ Recognition of infant risk status should not imply condemnation of a group of children but, as with preterm infants, lead to aggressive, national, social, and scientific efforts to delineate and intervene with potential sequelae of drug exposure.

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References

1. Abelson H, Miller J. A decade of trends in cocaine use in the household population. National Institute of Health Monograph Series. 1985; 61:35–49.
2. Amaro H, Fried L, Cabral H, et al. Violence during pregnancy and substance abuse. Am J Public Health. 1990; 80:575–579. [PubMed: 2327535]
3. Anisfield E, Cunningham N. Project 0 to 2: A comprehensive intervention with cocaine-abusing women and their infants. Final Report to the National Center on Child Abuse and Neglect. in press.
4. Arendt R, Minnes S, Diffenbacher N, et al. Cocaine exposed infants and their mothers: An interdisciplinary model of service and research. The Child, Youth and Family Services Quarterly. 1991; 14:2–4.
5. Bandstra ES, Stelle BW, Dale DD, et al. Detection of in utero cocaine exposure: A comparative methodologic study. Pediatr Res. 1992; 31:58A.

6. Barr GA, Lithgow T. Pharmacology of reward: Enhancement of self-stimulation of D-amphetamine and cocaine in three and ten day old rats. *Brain Res.* 1986; 389:193–202. [PubMed: 3948007]
7. Bates C. Medical risks of cocaine use. *West J Med.* 1988; 148:440–444. [PubMed: 3291396]
8. Bauchner H, Zuckerman B. Cocaine, sudden infant death syndrome, and home monitoring. *J Pediatr.* 1990; 117:904–906. [PubMed: 2246688]
9. Berenson A, Stiglic N, Wilkinson G, et al. Drug abuse and other risk factor for physical abuse in pregnancy among white non-Hispanic, black, and Hispanic women. *Am J Obstet Gynecol.* 1991; 186:1491–1499. [PubMed: 2048595]
10. Bingol N, Fuchs M, Diaz V, et al. Teratogenicity of cocaine in humans. *J Pediatr.* 1987; 110:93–96. [PubMed: 3794893]
11. Bithoney, W.; Rathbun, J. Failure-to-thrive. In: Levine, M.; Cary, W.; Crocker, A., et al., editors. *Developmental and Behavioral Pediatrics*. Philadelphia: WB Saunders; 1983.
12. Campbell BK, Stark MJ. Psychopathology and personality characteristics in different forms of substance abuse. *Int J Addict.* 1990; 25:1467–1474. [PubMed: 2094684]
13. Chandler, LS.; Andrew, MS.; Swanson, MW. *Movement Assessment of Infants: A Manual*. Washington: Rolling Bay; 1980.
14. Chasnoff IJ, Burns KA, Burns WJ. Cocaine use in pregnancy: Perinatal morbidity and mortality. *Neurotoxicol Teratol.* 1987; 9:291–293. [PubMed: 3683346]
15. Chasnoff IJ, Burns WJ, Schnoll SH, et al. Cocaine use in pregnancy. *N Engl J Med.* 1985; 313:666–669. [PubMed: 4022059]
16. Chasnoff IJ, Chisum GM, Kaplan EW. Maternal cocaine use and genitourinary tract malformations. *Teratology.* 1988; 37:201–204. [PubMed: 3368874]
17. Chasnoff IJ, Griffith D, MacGregor S, et al. Temporal patterns of cocaine use in pregnancy. *JAMA.* 1989; 261:1741–1744. [PubMed: 2918671]
18. Chasnoff IJ, Griffith DR, Azuma S. Intrauterine cocaine/poly drug exposure: Three year outcome. *Pediatr Res.* 1992; 31:9A.
19. Chasnoff IJ, Griffith DR, Freier C, et al. Cocaine/poly drug use in pregnancy: Two year follow-up. *Pediatrics.* 1992; 89:284–289. [PubMed: 1370867]
20. Chasnoff IJ, Landress H, Barrett M. The prevalence of illicit drug or alcohol use during pregnancy and discrepancies in mandatory reporting in Pinellas County, Florida. *N Engl J Med.* 1990; 322:1202–1206. [PubMed: 2325711]
21. Chavez GF, Mulinare J, Cordero JF. Maternal cocaine use during early pregnancy as a risk factor for congenital urogenital anomalies. *JAMA.* 1989; 262:795–798. [PubMed: 2746835]
22. Cherukuri R, Minkoff H, Feldman J, et al. A cohort study of alkaloidal cocaine (“crack”) in pregnancy. *Obstet Gynecol.* 1989; 72:145–151.
23. Chethick L, Burns K, Burns W, et al. The assessment of early relationship dysfunction in cocaine-abusing mothers and their infants. *Infant Behavior and Development.* 1990; 13:312.
24. Chouteau M, Namerow PB, Leppert P. The effect of cocaine abuse on birthweight and gestational age. *Obstet Gynecol.* 1988; 72:351–354. [PubMed: 3405550]
25. Church MW, Holmes PA, Overbeck GW, et al. Interactive effects of prenatal alcohol and cocaine exposure on postnatal mortality, development and behavior in the long-evans rat. *Neurotoxicol Teratol.* 1991; 13:377–386. [PubMed: 1921917]
26. Clarren SK, Smith DW. The fetal alcohol syndrome. *N Engl J Med.* 1978; 298:1063–1067. [PubMed: 347295]
27. Coles CD, Platzman KA, Smith I, et al. Effects of cocaine, alcohol, and other drugs used in pregnancy on neonatal growth and neurobehavioral status. *Neurotoxicol Teratol.* 1991; 13:229–233. [PubMed: 2046640]
28. Cregler LL, Mark H. Medical complications of cocaine abuse. *N Engl J Med.* 1986; 315:1495–1500. [PubMed: 3537786]
29. Davis S. Chemical dependency in women: A description of its effect and outcome on adequate parenting. *J Subst Abuse Treat.* 1990; 7:225–232. [PubMed: 2290185]

30. Dixon SD, Bejar R. Echoencephalographic findings in neonates associated with maternal cocaine and methamphetamine use: Incidence and clinical correlates. *J Pediatr.* 1989; 115:770–778. [PubMed: 2681639]
31. DiPietro J, Larson S. Examiner effects in the administration of the NBAS: The illusion of reliability. *Infant Behavior and Development.* 1989; 12:119–124.
32. Dougherty RJ, Lesswing NJ. Inpatient cocaine abusers: An analysis of psychological and demographic variables. *J Subst Abuse Treat.* 1989; 6:45–47. [PubMed: 2709473]
33. Dow-Edwards DL, Freed L, Milhorst TH. Stimulation of brain metabolism by perinatal cocaine exposure. *Dev Brain Res.* 1988; 42:137–141.
34. Eisen L, Field T, Bandstra E, et al. Perinatal cocaine effects on neonatal stress behavior and performance on the Brazelton scale. *Pediatrics.* 1991; 88:477–480. [PubMed: 1881726]
35. El-Bizri H, Guest I, Varma DR. Effects of cocaine on rat embryo development in vivo and in cultures. *Pediatr Res.* 1991; 29:187–190. [PubMed: 2014157]
36. Emmelkamp PM, Heeres H. Drug addiction and parental rearing style: A controlled study. *Int J Addict.* 1988; 23:207–216. [PubMed: 3366496]
37. Evans A, Gillogley K. Drug use in pregnancy: Obstetric perspectives. *Clin Perinatol.* 1991; 18:23–31. [PubMed: 2040116]
38. Fagan JF, Shepherd PA. The Fagan test of infant intelligence: Training manual. Cleveland, Ohio, Infantest Corp. 1989
39. Falk JL, Ma G, Lau CE. Chronic oral cocaine self-administration: Pharmacokinetics and effects on spontaneous and discriminative motor functions. *J Pharmacol Exp Ther.* 1991; 257:457–465. [PubMed: 2020003]
40. Fallah-Najmbadi H, Zahka KG, Eisenberg IR, et al. Prenatal exposure to cocaine induces increased ventricular mass in the newborn. *Pediatr Res.* 1992; 31:233A.
41. Farrar HC, Kearns GL. Cocaine: Clinical pharmacology and toxicology. *J Pediatr.* 1989; 115:665–675. [PubMed: 2681634]
42. Field T. Early interaction between infants and their post-partum depressed mothers. *Infant Behavior and Development.* 1984; 7:527–532.
43. Finnegan LP. Perinatal substance abuse: Comments and Perspectives. *Semin Perinatol.* 1991; 15:331–339. [PubMed: 1948145]
44. Finnegan, LP. *Current Therapy in Neonatal and Perinatal Medicine.* Ontario, Canada: BC Decker; 1984. Neonatal abstinence.
45. Fitzgerald E, Kaltenback K, Finnegan L. Patterns of interactions among drug dependent women and their infants. *Pediatr Res.* 1990; 25:10A.
46. Frank D, Bauchner H, Parker S, et al. Neonatal body proportionality and body composition after in utero exposure to cocaine. *J Pediatr.* 1990; 117:622–626. [PubMed: 2213392]
47. Frank D, McCarten K, Cabral H, et al. Cranial ultrasounds in term newborns: Failure to replicate excess abnormalities in cocaine exposed. *Pediatr Res.* 1992; 31:247A. [PubMed: 1373233]
48. Frank D, Zuckerman BS, Amaro H, et al. Cocaine use during pregnancy: Prevalence and correlates. *Pediatrics.* 1988; 82:888–895. [PubMed: 3186380]
49. Freier MC, Griffith DR, Chasnoff IJ. In utero drug exposure: Developmental follow-up and maternal-infant interaction. *Semin Perinatol.* 1991; 15:310–316. [PubMed: 1948142]
50. Fullilove RE, Fullilove MT, Bowser BP, et al. Risk of sexually transmitted disease among black adolescent crack users in Oakland and San Francisco, Calif. *JAMA.* 1990; 263:851–855. [PubMed: 2296147]
51. Fulroth RF, Phillips B, Durant DJ. Perinatal outcome of infants exposed to cocaine and/or heroin in utero. *Am J Dis Child.* 1989; 143:905–910. [PubMed: 2756964]
52. Gawin FH. Cocaine Addiction: Psychology and Neurophysiology. *Science.* 1991; 251:1580–1586. [PubMed: 2011738]
53. Gawin FH, Ellinwood T. Cocaine and other stimulants. *N Engl J Med.* 1988; 318:1173–1182. [PubMed: 3283549]

54. Gillogley K, Evans A, Hansen R, et al. The perinatal impact of cocaine, amphetamine, and opiate use detected by universal intrapartum screening. *Am J Obstet Gynecol.* 1990; 163:1535–1542. [PubMed: 2240103]
55. Griffin ML, Weiss RS, Mirin SM, et al. A comparison of male and female cocaine abusers. *Arch Gen Psychiatry.* 1989; 46:122–126. [PubMed: 2913971]
56. Griffith DR, Chasnoff IJ, Freier MC. Effects of maternal psychopathology on the neurobehavioral development of cocaine exposed infants. *Pediatr Res.* 1989; 25:3A.
57. Hadeed AJ, Siegel SR. Maternal cocaine use during pregnancy: Effects on the newborn infant. *Pediatrics.* 1989; 84:205–210. [PubMed: 2748245]
58. Hagopian E, Darby M, Patti L, et al. The prevalence of antepartum substance abuse. *Pediatr Res.* 1990; 25:207A.
59. Hoyme HE, Jones KL, Dixon SD, et al. Prenatal cocaine exposure and fetal vascular disruption. *Pediatrics.* 1990; 85:743–747. [PubMed: 2330234]
60. Hutchings DE, Fico TA, Dow-Edwards DL. Prenatal cocaine: Maternal toxicity, fetal effects, and locomotor activity in rat offspring. *Neurotoxicol Teratol.* 1989; 11:65–69. [PubMed: 2725443]
61. Jones KL. Developmental pathogenesis of defects associated with prenatal cocaine exposure: Fetal vascular disruption. *Clin Perinatol.* 1991; 18:139–146. [PubMed: 2040114]
62. Karmel B.; Gardner J.; Magnano C. NIDA Research Monograph, Problems of Drug Dependence, Proceedings of the 52nd Annual Scientific Meetings. Richmond: Virginia; 1990. Neurofunctional consequences of in utero cocaine exposure.
63. Kleinman PH, Miller AB, Millman RB, et al. Psychopathology among cocaine abusers entering treatment. *J Nerv Ment Dis.* 1990; 178:442–447. [PubMed: 2366058]
64. Ladwig GB, Andersen MD. Substance abuse in women: Relationship between chemical dependency of women and past reports of physical and/or sexual abuse. *Int J Addict.* 1989; 24:739–754. [PubMed: 2606585]
65. Lambert J. Maternal and perinatal issues regarding HTV infection. *Pediatr Ann.* 1990; 19:468. [PubMed: 2216549]
66. Lester BM, Als H, Brazelton TB. Regional obstetric anesthesia and newborn behavior: A reanalysis toward synergistic effects. *Child Dev.* 1982; 53:687–692. [PubMed: 7094677]
67. Lester BM, Corwin MJ, Sepkoski C, et al. Neurobehavioral syndromes in cocaine exposed newborn infants. *Child Dev.* 1991; 62:695–705.
68. Lester BM, Dreher M. Effects of marijuana use during pregnancy on newborn cry. *Child Dev.* 1989; 60:765–771. [PubMed: 2758874]
69. Little BB, Snell LM, Klein VR, et al. Cocaine abuse during pregnancy: Maternal and fetal implications. *Obstet Gynecol.* 1989; 73:157–160. [PubMed: 2911419]
70. Livesay S, Erlich S, Finnegan LP. Cocaine and pregnancy: Maternal and infant outcome. *Pediatr Res.* 1987; 21:238A. [PubMed: 3562122]
71. MacGregor S, Keith L, Bachicha J, et al. Cocaine use during pregnancy: Correlation between prenatal care and perinatal outcome. *Obstet Gynecol.* 1989; 74:882–885. [PubMed: 2586952]
72. Magnano C, Gardner J, Karmel B. Differences in salivary cortisol levels in cocaine-exposed and non-cocaine-exposed NICU infants. *Dev Psychobiol.* 1992; 25:93–103. [PubMed: 1577206]
73. Mayes LC, Granger RH, Bornstein MH, et al. The problems of prenatal cocaine exposure. *JAMA.* 1992; 267:406–408. [PubMed: 1727966]
74. Moore TR, Sorg J, Miller L, et al. Hemodynamic effects of intravenous cocaine on the pregnant ewe and fetus. *Am J Obstet Gynecol.* 1986; 155:883–888. [PubMed: 3766645]
75. Neerhof MG, MacGregor SN, Retzky SS, et al. Cocaine use during pregnancy: Peripartum prevalence and perinatal outcome. *Am J Obstet Gynecol.* 1989; 161:633–638. [PubMed: 2782344]
76. Neuspiel DR, Hamel SC. Cocaine use and post partum psychiatric symptoms. *Psychol Rep.* 1992; 70:51–56. [PubMed: 1565744]
77. Neuspiel DR, Hamel SC. Cocaine and infant behavior. *J Dev Behav Pediatr.* 1991; 12:55–64. [PubMed: 2016404]
78. Neuspiel DR, Hamel SC, Hochberg E, et al. Maternal cocaine use and infant behavior. *Neurotoxicol Teratol.* 1991; 13:229–233. [PubMed: 2046640]

79. Newcomb MD, Bentler PM, Fahy B. Cocaine and psychopathology: Associations among young adults. *Int J Addict*. 1987; 22:1167–1188. [PubMed: 3436688]
80. Oro AS, Dixon SD. Perinatal cocaine and methamphetamine exposure: Maternal and neonatal correlates. *J Pediatr*. 1987; 111:571–578. [PubMed: 3655989]
81. Ostrea EM, Brady M, Parks P, et al. Drug screening of meconium in infants of drug-dependent mothers: An alternative to urine testing. *J Pediatr*. 1989; 115:474–477. [PubMed: 2769510]
82. Oxtoby, MJ. Perinatally acquired HIV infection. In: Pizzo, PA.; Wilfert, CM., editors. *Pediatric AIDS*. Baltimore: Williams & Wilkins; 1991. p. 3-21.
83. Petitti DA, Coleman C. Cocaine and the risk of low birthweight. *Am J Public Health*. 1990; 80:25–28. [PubMed: 2293798]
84. Pettinati H, Cabezas R, Jensen J, et al. Incidence of personality disorders in cocaine versus alcohol-dependent females: National Institutes of Health Monograph Series. 1990; 105:369–370.
85. Phibbs C, Bateman D, Schwartz R. The neonatal costs of maternal cocaine use. *JAMA*. 1991; 266:1521–1526. [PubMed: 1880883]
86. Regan DO, Ehrlich SM, Finnegan LP. Infants of drug addicts: At risk for child abuse, neglect and placement in foster care. *Neurotoxicol Teratol*. 1987; 9:315–319. [PubMed: 3683350]
87. Richardson G, Day N. Maternal and neonatal effects of moderate cocaine use during pregnancy. *Neurotoxicol Teratol*. 1991; 13:455–460. [PubMed: 1921925]
88. Roe D, Little B, Bawden R, et al. Metabolism of cocaine by human placentas: Implications for fetal exposure. *Am J Obstet Gynecol*. 1990; 163:715–718. [PubMed: 2403150]
89. Ryan L, Ehrlich S, Finnegan L. Cocaine abuse in pregnancy: Effects on the fetus and newborn. *Neurotoxicol Teratol*. 1987; 9:295–299. [PubMed: 3683347]
90. Schneider, JW. *Drugs, Alcohol, Pregnancy and Parenting*. The Netherlands: Dordrecht; 1988. Motor assessment and parent education beyond the newborn period; p. 115-125.
91. Siddiqi TA, Tsang RC. Babies of substance abusing mothers: An overview. *Pediatr Ann*. 1991; 20:527–530. [PubMed: 1945531]
92. Singer LT, Arendt R, Yamashita T, et al. Development of infants exposed in utero to cocaine. *Pediatr Res*. 1992; 31:260A.
93. Singer LT, Fagan J. Cognitive development in the failure-to-thrive infant: A three year longitudinal study. *J Pediatr Psychol*. 1984; 9:363–383. [PubMed: 6502402]
94. Singer LT, Garber R, Kliegman R. Neurobehavioral sequelae of fetal cocaine exposure. *J Pediatr*. 1991; 119:667–672. [PubMed: 1919905]
95. Singer LT, Song LY, Warshawsky E, et al. Maternal gravidity predicts prematurity in cocaine exposed infants. *Pediatr Res*. 1991; 29:266A.
96. Singer LT, Yamashita T, Arendt R, et al. Increased psychological distress in postpartum cocaine-using women. *Pediatr Res*. 1992; 31:260A.
97. Slutsker L. Risks associated with cocaine use during pregnancy. *Obstet Gynecol*. 1992; 79:778–789. [PubMed: 1565365]
98. Smith I, Moss-Wells S, Moeti R, et al. Characteristics of non-referred cocaine abusing mothers. National Institute of Drug Abuse Monograph Series. 1989; 95:330.
99. Streissguth AP, Barr HM, Sampson PD. Moderate prenatal alcohol exposure: Effects on child IQ and learning problems at age seven and one-half years. *Alcohol Clin Exp Res*. 1990; 14:622–669.
100. Streissguth AP, Grant TM, Barr HM, et al. Cocaine and the use of alcohol and other drugs during pregnancy. *Am J Obstet Gynecol*. 1991; 164:1239–1243. [PubMed: 2035565]
101. Struthers JM, Hansen RL. Visual recognition memory in drug-exposed infants. *Dev Behav Pediatr*. 1992; 13:108–111.
102. Tracy CE, Williams HC. Social Consequences of substance abuse among pregnant and parenting women. *Pediatr Ann*. 1991; 20:548–553. [PubMed: 1945534]
103. US General Accounting Office Report: Drug exposed infants: A generation at-risk. Washington, DC: 1990.
104. Van de Bor M, Walther FJ, Sims ME. Increased cerebral blood flow velocity in infants of mothers who abuse cocaine. *Pediatr*. 1990; 85:733–736.

105. Wagner C, Kwong T, Schultz J. Improved identification of infants at high risk for intrauterine cocaine exposure: Meconium is superior to urine. *Pediatr Res.* 1992; 31:228A. [PubMed: 1348576]
106. Webster WS, Brown-Woodman PDC. Cocaine as a cause of congenital malformations of vascular origin: Experimental evidence in the rat. *Teratology.* 1990; 41:689–697. [PubMed: 2353316]
107. Woods J, Plessinger M, Clark K. Effect of cocaine on uterine blood flow and fetal oxygenation. *JAMA.* 1987; 257:957–961. [PubMed: 3806879]
108. Woods N, Eyler F, Behnke M, et al. Cocaine use during pregnancy: Maternal depressive symptoms and infant neurobehavior over the first month. *Infant Behavior and Development.* 1992 in press.
109. Zimmerman EF. Substance abuse in pregnancy: Teratogenesis. *Pediatr Ann.* 1991; 20:541–547. [PubMed: 1945533]
110. Zubrycki EM, Giordano M, Sanberg PR. The effects of cocaine on multivariate locomotor behavior and defecation. *Behav Brain Res.* 1990; 36:155–159. [PubMed: 2302315]
111. Zuckerman B, Amaro H, Bauchner H, et al. Depressive symptoms during pregnancy: Relationship to poor health behaviors. *Am J Obstet Gynecol.* 1989; 160:1107–1111. [PubMed: 2729387]
112. Zuckerman B, Frank DA, Hingson R, et al. Effects of maternal marijuana and cocaine use on fetal growth. *N Engl J Med.* 1989; 320:762–768. [PubMed: 2784193]
113. Zuckerman B, Mynard E, Cabral H. A preliminary report of prenatal cocaine exposure and respiratory distress syndrome in premature infants. *Am J Dis Child.* 1991; 145:696–698. [PubMed: 2035498]