Journal of Addictive Diseases
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t792306884

Prenatal Drug Exposure: Infant and Toddler Outcomes

Emmalee S. Bandstra[a]; Connie E. Morrow[a]; Elana Mansoor[a]; Veronica H. Accornero[a]
[a] Department of Pediatrics, University of Miami Miller School of Medicine, Miami, FL

Online publication date: 20 April 2010

To cite this Article Bandstra, Emmalee S. , Morrow, Connie E. , Mansoor, Elana and Accornero, Veronica H.(2010) 'Prenatal Drug Exposure: Infant and Toddler Outcomes', Journal of Addictive Diseases, 29: 2, 245 — 258
To link to this Article: DOI: 10.1080/10550881003684871
URL: http://dx.doi.org/10.1080/10550881003684871

Journal of Addictive Diseases, 29:245–258, 2010

ISSN: 1055-0887 print / 1545-0848 online
DOI: 10.1080/10550881003684871

Routledge
Taylor & Francis Group

Prenatal Drug Exposure: Infant and Toddler Outcomes

Emmalee S. Bandstra, MD
Connie E. Morrow, PhD
Elana Mansoor, PsyD
Veronica H. Accornero, PhD

ABSTRACT. This manuscript provides an overview of the current scientific literature on the impact of maternal drug use, specifically opioids and cocaine, during pregnancy on the acute and long-term outcomes of infants and toddlers from birth through age 3 years. Emphasis with regard to opioids is placed on heroin and opioid substitutes used to treat opioid addiction, including methadone, which has long been regarded as the standard of care in pregnancy, and buprenorphine, which is increasingly being investigated and prescribed as an alternative to methadone. Controlled studies comparing methadone at high and low doses, as well as those comparing methadone with buprenorphine, are highlighted and the diagnosis and management of neonatal abstinence syndrome is discussed. Over the past two decades, attention of the scientific and lay communities has also been focused on the potential adverse effects of cocaine and crack cocaine, especially during the height of the cocaine epidemic in the United States. Herein, the findings are summarized from prospective studies comparing cocaine-exposed with non-cocaine-exposed infants and toddlers with respect to anthropometric growth, infant neurobehavior, visual and auditory function, and cognitive, motor, and language development. The potentially stigmatizing label of the so-called "crack baby" preceded the evidence now accumulating from well-designed prospective investigations that have revealed less severe sequelae in the majority of prenatally exposed infants than originally anticipated. In contrast to opioids, which may produce neonatal abstinence syndrome and infant neurobehavioral deficits, prenatal cocaine exposure appears to be associated with what has been described as statistically significant but subtle decrements in neurobehavioral, cognitive, and language function, especially when viewed in the context of other exposures and the caregiving environment which may mediate or moderate the effects. Whether these early findings may herald more significant learning and behavioral problems during school-age and adolescence when the child is inevitably confronted with increasing social and academic challenges is the subject of ongoing longitudinal research.

KEYWORDS. Heroin, methadone, buprenorphine, cocaine, pregnancy, infant

INTRODUCTION

Substance abuse among women of childbearing age remains a significant concern in the United States and internationally. According to the 2006-2007 combined National Survey of Drug Use and Health (NSDUH), 5.2% of pregnant and 9.7% of nonpregnant women

Emmalee S. Bandstra, Connie E. Morrow, Elana Mansoor, and Veronica H. Accornero are affiliated with the University of Miami Miller School of Medicine, Department of Pediatrics, Miami, FL.

Address correspondence to: Emmalee S. Bandstra, MD, University of Miami Miller School of Medicine, Departments of Pediatrics and Obstetrics and Gynecology, Division of Neonatal Medicine, P.O. Box 016960 (R-131), Miami, FL 33101 (E-mail: ebandstr@med.miami.edu).

Supported by NIH (Grants R01 DA 006556; P50 DA 025484; K01 DA 16720); State of Florida Healthy Start Program; Health Foundation of South Florida; Maribel Lauber, Ed.S., for her editorial assistance

between 15 and 44 years reported past-month illicit drug use.[1] The current report focuses on the infancy and toddler outcomes of in utero exposure to two major illicit drugs of abuse: cocaine and opioids. Because mothers who abuse these and other illicit drugs also frequently use varying combinations of alcohol, tobacco, and other drugs, polysubstance use is a salient part of any discussion of the scientific evidence for adverse effects of in utero exposure to drugs of abuse.

Large percentages of both pregnant and nonpregnant women report past-month alcohol consumption and tobacco smoking, despite ubiquitous health warnings. An estimated 11.6% of pregnant women and 53.2% of nonpregnant women aged 15 to 44 years reported current alcohol comsumption.[1] In utero exposure to alcohol, although legal, is extremely hazardous.[2] Fetal alcohol syndrome (FAS) is the leading identifiable, nonhereditary cause of mental retardation in the Western world.[3] The hallmarks are growth retardation, distinctive mid-facial anomalies, and mental retardation associated with central nervous system (CNS) deficits.[4] Fetal alcohol spectrum disorder (FASD) is the umbrella term for FAS, partial FAS, alcohol-related birth defects, and alcohol-related neurodevelopmental disorders.[5] Among women aged 15 to 44 years, 16.4% of pregnant and 28.4% of nonpregnant women reported past month cigarette use.[1] Tobacco smoking by pregnant women has also been implicated in animal and human studies in the pathophysiology of fetal growth restriction and newborn neurobehavioral deficits.[6,7] Furthermore, passive exposure of pregnant women to second-hand tobacco smoke is potentially deleterious to fetal and infant development.[8–10]

OPIOIDS (HEROIN, METHADONE, AND BUPRENORPHINE)

There is no substantive evidence from either preclinical or clinical studies that maternal opioid abuse during pregnancy causes congenital malformations. However, detrimental fetal effects of heroin exposure in terms of prematurity and intrauterine growth restriction have long been recognized.[11,12] Infants exposed to heroin have decreased birth weight, length, and head circumference compared to non-exposed infants; infants born to methadone-maintained mothers have higher birth weights than those born to heroin-dependent mothers not maintained on methadone.[13] Kandall observed that methadone maintenance improves neonatal growth parameters compared to heroin-exposed infants, but this may be partially explained by improved prenatal care and other medical and psychosocial factors.[14]

The National Institutes of Health Consensus Panel considers methadone the standard of care for pregnant opioid-addicted women, but the most desirable dosing schedule continues to be debated. In the early 1990s, the Center for Substance Abuse Treatment Consensus Panel recommended that methadone dosing be individually determined to prevent withdrawal in the mother.[15] Some investigators advocate a low methadone dosing regimen to reduce or eliminate neonatal abstinence syndrome (NAS), whereas others argue that lower doses may lead to maternal withdrawal, craving, and supplemental use of illicit drugs, thus increasing fetal risk. Dashe et al. reported a significant relationship between maternal methadone dose and neonatal abstinence scores, need for pharmacologic intervention, and duration of hospital stay in affected infants.[16] In contrast, Berghalla et al. retrospectively reviewed 21 published investigations on maternal methadone dosage and concluded that maternal methadone dose, comparing <80 mg with ≥ 80 mg daily, does not correlate with neonatal withdrawal.[17]

In 1996, buprenorphine was introduced in France as an opioid substitute and, as discussed in this supplement's accompanying article on the topic, maternal buprenorphine therapy is being prescribed and investigated internationally in the hopes of improving treatment and decreasing maternal and neonatal side effects of methadone maintenance. The logic behind this assumption is that buprenorphine has mixed agonist and antagonist properties with high receptor affinity and low intrinsic activity, resulting in fewer or no autonomic signs and symptoms of opioid withdrawal following abrupt discontinuation in adults. In a review by Johnson et al. of 21 published studies, including 309

infants from 15 cohorts exposed in utero to buprenorphine, 62% of the infants had NAS and 48% of those required therapy.[18] The investigators concluded that buprenorphine-associated NAS is "similar to or less than" that resulting from methadone. Regardless of treatment regimen, pregnant women and their fetuses undergoing opioid substitution therapy should be closely monitored by an addiction specialist and an obstetrician experienced in such care and supported by a multidisciplinary team. Furthermore, because NAS is so common among infants born to mothers using either illicit opiates or prescribed opioid substitutes, physicians and nurses should be well-trained to recognize and adequately treat withdrawal signs. NAS usually relates to withdrawal from opioids such as heroin or methadone, but other narcotics, benzodiazepines, barbiturates, and even alcohol can induce similar signs. The onset of NAS is generally within 2 to 3 days of birth, but may occur as late as 1 month postnatal age. Clinically, NAS presents in 60% to 80% of infants exposed to heroin or methadone and includes varying combinations of CNS, gastrointestinal, metabolic, and autonomic system disturbances. Seizures due to NAS are easily controlled with anticonvulsants and subsequent follow-up of affected infants at 1 year has been shown to be comparable to that of opioid-exposed infants with no seizures.[19] Neurobehavioral effects among infants with prenatal opiate exposure include excessive sucking, hypertonia, high pitched cry, difficulty being consoled, irritability, and jitteriness.[20,21] Central and autonomic nervous system effects were of greater magnitude among opiate-exposed infants compared to those with cocaine exposure[21] and infants exposed to both appear to exhibit the loudest and highest pitched cries.[20]

Supportive care for NAS, regardless of severity, includes provision of a quiet, dimly lit environment and avoidance of noxious stimuli.[22] Loose swaddling may also be an effective adjunct in the supportive care of NAS, but it should be accomplished with appropriate adherence to supine positioning as recommended in the latest American Academy of Pediatrics Task Force on Sudden Infant Death Syndrome's Policy Statement.[23] Treatment of NAS depends on the severity of withdrawal signs as noted clinically or more appropriately as recommended by standardized assessments administered serially at 3 to 4 hour intervals following first appearance of NAS signs to guide initiation and titration of pharmacologic substitutes. There are two popular scoring tools for NAS, the Lipsitz Scale (11 signs each rated from 0 to 3)[24] and the more detailed Finnegan Neonatal Abstinence Score (9 CNS signs, 8 metabolic/vasomotor/respiratory signs, and 4 gastrointestinal signs with variable sign-dependent rating scales),[25] which requires a trained observer. Both scales are more appropriate for full-term infants because the clinical presentation of opioid-exposed premature infants may be influenced by CNS immaturity.

The American Academy of Pediatrics has published guidelines for treating NAS when indicated using opioid substitution therapy. Morphine in the form of diluted tincture of opium (DTO) is preferred over paregoric due to concerns about additives.[26] Practices vary widely and some clinicians advocate morphine or methadone instead of DTO as pharmacotherapy for opiate-induced NAS, thereby avoiding unwanted alcoholic extracts of various alkaloids in the opium tincture.

Phenobarbital is recommended as an adjunctive therapy, usually for anticonvulsant activity, in NAS due to opiates and as a primary treatment for NAS due to sedatives or hypnotics. Although further studies are needed, a preliminary prospective controlled trial of DTO plus phenobarbital compared to DTO alone in a small number of opiate-exposed infants with NAS showed promise in terms of decreased severity of withdrawal accompanied by shorter and less costly hospital stays.[27]

Limited reports on the long-term effects of prenatal opioid exposure on postnatal growth and neurodevelopment are available. Methodological limitations in study design, including small sample sizes, poorly defined comparison groups, and difficulty controlling for important environmental variables, make available results difficult to interpret. Moreover, difficulties associated with the studied population, namely high attrition rates and the lifestyle variability that characterizes the drug abuse culture, have further contributed to the paucity

of the literature.[28] Nevertheless, available information suggests that infants prenatally exposed to opiates are at an increased risk for neurodevelopmental impairment.[28,29] Furthermore, the home environment plays a significant modulating role in the developmental outcomes of exposed children,[28–30] although the magnitude of this effect remains unclear.

COCAINE

Many published prenatal cocaine studies from the 1980s and early 1990s included case reports and relatively small series. These methodologically limited studies evoked considerable media attention toward the plight of so-called "cocaine" or "crack" babies with devastating conditions such as congenital anomalies of the brain and other organs, CNS hemorrhage and infarction, and sudden infant death syndrome. Subsequently, several large well-designed prospective studies and meta-analyses have not confirmed these associations.[31–33]

Anthropometric Growth

Maternal cocaine abuse has been shown to be associated with significantly decreased infant birth weight, length, and head circumference, even in covariate-adjusted models accounting for prenatal exposure to other substances.[32,34] The mechanism whereby cocaine diminishes fetal growth is hypothesized to be through vasoconstriction of uterine and placental blood flow as well as direct adverse effects on fetal metabolism and fat deposition. Controlling for gestational age, nutritional indicators such as maternal weight gain, and prenatal exposure to other drugs, cocaine-associated effects on birth growth parameters[34] and lean body mass[34,35] prevail. In both animal and human studies, the magnitude of in utero cocaine-associated fetal growth decrements appear to depend on dose and gestational timing.[36–38]

Studies have yielded mixed results regarding the long-term effects of prenatal cocaine exposure on postnatal growth. These inconsistencies could be partly attributed to differences in cohort size and characteristics, differences in measurement of exposure, and the degree of statistical control for potential confounders and moderating characteristics.[39] A systematic review conducted by Frank et al. concluded that after controlling for level of exposure to other drugs, there is no consistent effect on physical growth, including weight, length, or head circumference, among children 6 years or younger.[40] Shankaran et al. evaluated neonatal size at birth and subsequent growth in prenatally exposed children and found that significant differences in weight, length, and head circumference at birth disappeared for weight and head circumference by age 2 years and for height by age 3 years.[41] Conversely, Covington et al. found that even after controlling for potential covariates, prenatal cocaine exposure was associated with height and weight deficits at age 7 years, particularly for children born to mothers older than 30 years.[42] Similarly, a recent study by Richardson et al. using a longitudinal growth-curve analysis found that children exposed to cocaine during the first trimester grew at a slower rate through 10 years of age compared to unexposed children.[43]

Infant Neurobehavior, Visual and Auditory Function

Numerous studies have documented subtle neonatal neurobehavioral effects associated with prenatal cocaine exposure, although findings have lacked coherence. The most frequently used assessment has been the Brazelton Neonatal Behavioral Assessment Scale (BNBAS), which includes the domains of orientation, habituation, state regulation, autonomic stability, reflexes, tone, motor performance, irritability, alertness, and excitability. Eyler et al. concluded that although subtle cocaine-associated deficits in neurobehavioral functioning were evident across a range of neonatal studies published between 1991 and 1998, there was no consistent pattern of domain-specific findings.[44] Subsequently, larger cohort studies of in utero cocaine exposure have reported subtle impairments in one or more BNBAS neurobehavioral clusters,[45–47] but with considerable variation regarding timing and level of exposure, severity of dysfunction, and specific domains affected.[44,46,47] Morrow et al. found a modest cocaine-associated adverse impact across all

neurobehavioral domains except for the reflex cluster score.[46] These findings were partially mediated by fetal growth and appeared dose-dependent. In another large study, Behnke et al. revealed a significant direct effect of prenatal cocaine exposure on the BNBAS qualifier items, but not on the cluster scores.[47] Several investigators reported no significant cocaine-associated findings on the BNBAS at birth[48–51] but did show cocaine-associated greater autonomic instability and abnormal reflexes,[50] impaired motor functions,[48] and dose-dependent difficulties with state regulation and excitability[51] at 2 to 4 weeks postpartum.

Controlled studies have found neurobehavioral deficits among infants exposed to cocaine or opiates using other neurological and physiological assessments.[20,21,32,52,53] For example, cocaine-exposed infants exhibited less arousal, poorer behavior regulation, and higher excitability at 1 month of age than non-exposed infants on the NICU Network Neurobehavioral Scale.[20] Studies have also reported mild cocaine-associated central and autonomic system dysfunction as evidenced by increased irritability, jitteriness, tremors, and hypertonia.[21,32] Using a modified still-face paradigm, Bendersky and Lewis demonstrated significant deficits in arousal modulation among 4-month-old infants with heavy in utero cocaine exposure.[52] Cocaine-exposed infants have also been shown to display abnormal cry characteristics, including high pitched cries and fewer cry utterances, excessive sucking, and sleep alterations.[21,44,54,55] A dose-dependent effect was found, with heavy cocaine exposure resulting in an increased number of cry utterances and short cries, suggestive of an over-aroused (excitable) pattern of neurobehavioral functioning.[20,54]

Studies evaluating the impact of prenatal cocaine exposure on infant cardiac and respiratory systems have shown dose-related alterations in infant regulation. Heavy exposure was associated with the highest increase in heart rate and the greatest decrease in respiratory sinus arrhythmia.[53] In another study, infants with cocaine exposure were found to have lower vagal tone and less heart rate variability at birth, suggestive of decreased autonomic control of the heart.[56] In utero exposure to cocaine may result in ocular/visual problems such as impaired visual attention and tracking,[44] optic nerve hypoplasia, delayed visual maturation, eyelid edema, nystagmus, and strabismus.[36] Research on auditory brainstem responses has evidenced abnormalities in the peripheral auditory system including varying degrees of hearing impairment and slowed brainstem transmission of sensory information among infants prenatally exposed to cocaine[36,57,58] and/or opiates.[57,58]

As may be seen in an emergent field of study, early reports are often characterized by small sample sizes and other methodological issues, resulting in inconsistent findings and lack of generalizability. Later studies addressing methodological issues of concern have begun to document modest cocaine-associated decrements in overall neurobehavioral function rather than a specific pattern of neurobehavioral deficits. In addition, factors such as polydrug use, demographic and environmental influences, caregiving and family issues, and physical and psychological disorders all have the potential to result in inconsistent findings if inadequately controlled.[59] It is also possible that variations across studies are a reflection of cohort-specific differences in neurobehavioral outcomes among infants with prenatal cocaine exposure. To date, a preponderance of the evidence shows subtle impairments in neurobehavioral outcomes due to prenatal cocaine or opiate exposure. The impact of these deficits on later functioning is unclear. Therefore, it is imperative that future studies consider the influence of mediating and moderating variables on the neurodevelopmental trajectories of children with prenatal cocaine, opiate, or polysubstance exposure.

Cognitive and Motor Development

Numerous published studies varying in methodological rigor have evaluated the effects of prenatal cocaine exposure on infant cognitive and motor development. A review of published studies between 1992 and 2000, including only peer-reviewed reports of prospectively enrolled birth cohorts that used examiners blind to exposure status, found that five of the nine studies reviewed reported no cocaine-related

effect on mental or physical development, most often assessed by the Bayley Scales of Infant Development (BSID).[40] The remaining four studies reported only subtle cocaine-related effects that did not maintain significance with multivariate statistical control or were evident only within subgroup or cross-sectional analyses. The review concluded that the effects of prenatal cocaine exposure on cognitive development during infancy were not readily discernable from effects due to other contextual factors including prematurity, assessment age, and other prenatal drug exposures.[40] Subsequently, larger prospective cohort studies have suggested a more complex picture in which the teratogenic effects of prenatal cocaine exposure are subtle and most evident when considering factors such as mediating pathways and severity of exposure. Five recent studies have documented cocaine-related effects on the BSID Mental Development Index (MDI) (Table 1). Two studies documented cocaine-related lower MDI scores as well as dose-dependent effects on development, findings not attenuated with statistical control of covariates.[60,61] Very low birth weight (<1,500 g) has also been linked to increased risk for cognitive impairment in prenatally cocaine-exposed infants, with one study reporting a 10-point difference in mean MDI scores at age 3 for preterm cocaine-exposed children.[62] Other studies have shown more subtle cocaine-related adverse effects on MDI in longitudinal models including mediating influences, such as birth weight and gestational age, head circumference, and other prenatal drug exposures.[47,63] An almost equal number of recent prospective studies have reported no cocaine-related effects on MDI after covariate adjustment,[64–67] suggesting that prenatal cocaine exposure is a marker for subtle performance decrements in MDI that attenuate with control for other variables such as low birth weight, HIV exposure, disruptions in maternal care, lower socioeconomic status, and maternal vocabulary scores.[67]

Typical motor development, assessed by the BSID Psychomotor Development Index (PDI), has shown little teratogenic sensitivity to prenatal cocaine exposure. In the above-cited 2001 review, only two studies found significant cocaine-related effects on PDI.[40] Our current review of more recent studies reveals a similar picture, with only one study showing a direct cocaine-related effect on PDI scores in longitudinal analyses spanning 12 through 36 months.[61] However, several studies have reported PDI findings specific to timing and degree of exposure. In one study, lower PDI scores were predicted by second trimester self-reported cocaine use,[66] and in another, there was a significant relationship between low birth weight and lower PDI scores in children with heavier cocaine exposure.[64] In a recent longitudinal analysis of global motor development from 1 to 18 months, motor skills for infants with cocaine exposure were lower on average overall, but this finding was most evident at the 1 and 4 month age points with recovery to normal motor function by 18 months.[68]

LANGUAGE DEVELOPMENT

A growing body of research suggests that prenatal cocaine exposure may impact early language development, increasing the risk for language delays in early childhood. In a longitudinal analysis through age 3 years, Morrow et al. reported that children with prenatal cocaine exposure had lower total language scores than non-cocaine-exposed children, with results partially mediated through fetal growth.[69] In the same cohort, increasing level of prenatal cocaine exposure was associated with increased decrements in expressive language functioning at age 3 years.[70] Singer et al. also noted that expressive language skills were more adversely affected in very low birth weight prenatally cocaine-exposed toddlers at age 3 years[62] and reported that heavily cocaine-exposed infants showed lower auditory comprehension and total language on the Preschool Language Scale-3 (PLS-3) than those with lighter or no cocaine exposure.[71] Prenatally cocaine-exposed children aged 14 to 50 months scored lower on the Sequenced Inventory of Communicative Development-Revised (SICD-R) total score but were not different from non-cocaine-exposed children on the Peabody Picture Vocabulary Test, primarily a measure of receptive vocabulary.[72] In a contrasting study, no group differences on the SICD-R were found at age 30

TABLE 1. Infant and Toddler Studies Reporting on Prenatal Cocaine Exposure (PCE) and Child Mental and Motor Development (2001 to Present)

Study	Sample Size and Exposure Groups	Measures[a]	Child Age	Controlled for Other Drug Use	Cocaine-Related Mental and Motor Development Findings
Richardson et al. (2008)[66]	61 PCE 1st trimester; 28 PCE all trimesters; 144 non-PCE	BSID	1 year	Yes; when significant, retained in regression models	PCE was not a significant predictor of MDI scores; 2nd trimester PCE was associated with significantly lower PDI.
Brown et al. (2004)[65]	83 PCE; 63 non-drug; (234 birth cohort; 62% retention)	BSID	2 years	N/A due to negative findings in uncontrolled models	No PCE-related group differences on MDI or PDI. PCE children had higher MDI when in nonparental vs. parental care.
Lewis et al. (2004)[61]	147 PCE; 89 non-PCE; (361 birth cohort; 65% retention)	BSID	12, 18, 24, and 36 months	Yes	Direct cocaine-related effects on MDI and PDI in longitudinal models, and at 12 and 24 months for MDI and 24 months for PDI in cross-sectional models; dose-response PCE-associated effects on MDI and PDI.
Messinger et al. (2004)[67]	522 PCE; 705 non-PCE; 98 opiate; 1,129 non-opiate	BSID-II	1, 2, and 3 years	Yes	MDI scores were lower by 1.6 points in PCE vs. non-PCE groups in uncontrolled models, but were not significantly different after covariate adjustment. Group differences in birth weight did not mediate the effect. No PCE-related group differences were noted for PDI.
Mayes et al. (2003)[63]	265 PCE; 66 non-PCE; 129 non-drug (460 birth cohort; retention across visits 69% to 87%)	BSID-II	3, 6, 12, 18, 24, and 36 months	Not as covariates but in the context of grouping	MDI scores were lower in PCE vs. nonPCE groups across all assessment ages; the PCE-related effect was entirely mediated through birth weight and gestational age. PDI declined in all 3 groups over time; PCE children showed a nonsignificant trend toward a greater decrease than children in the other groups.

Continued on next page

TABLE 1 (Continued)

Study	Sample Size and Exposure Groups	Measures[a]	Child Age	Controlled for Other Drug Use	Cocaine-Related Mental and Motor Development Findings
Behnke et al. (2002)[47]	Birth cohort: 154 PCE; 154 non-PCE	BNBAS; BSID	Birth, 1 and 6 months	Yes	Direct PCE-related effects at birth and 6 months on a "Development" latent construct which included the MDI and PDI in SEM longitudinal modeling; indirect effects at birth, 1 month and 6 months mediated by prenatal alcohol and tobacco exposure and birth head circumference.
Frank et al. (2002)[64]	75 PCE/light; 38 PCE/heavy; 90 non-PCE; (252 birth cohort; 81% retention)	BSID	6, 12, and 24 months	Yes	No PCE-related main effect for level of cocaine exposure on MDI or PDI scores; heavily PCE children who received early intervention had higher MDI scores than all other groups; for children with heavier cocaine exposure, low birth weight was related to lower PDI scores.
Singer et al. (2002)[60]	Birth cohort: 218 PCE; 197 non-PCE; retention: 6 months = 339 (84%); 12 months = 364 (90%); 2 years = 379 (94%)	BSID	6 and 12 months, 2 years (corrected age)	Yes	Direct PCE-related effect on MDI (6-point mean group difference at 2 years); PCE children were twice as likely to have significant developmental delay. MDI was related to higher cocaine metabolites in meconium and higher maternal self-report of amount and frequency of cocaine use during pregnancy. PDI scores were unrelated to PCE.
Singer et al. (2001)[62]	31 PCE VLBW[b]; 38 non-PCE VLBW; 76% of 41 PCE and 93% of 41 non-PCE had BSID data at age 3	BSID	3 years	Not reported	Direct PCE-related effect on MDI (10-point mean difference) and PDI scores (13-point mean difference). A higher percentage of PCE children (46%) vs. non-PCE (16%) scored in the delayed range.

PCE = prenatally cocaine-exposed with other drugs; non-PCE = no cocaine exposure but possible exposure to other drugs (usually alcohol, tobacco, and/or marijuana); BSID = Bayley Scales of Infant Development; PDI = Psychomotor Development Index; non-drug = no known drug exposure; MDI = Mental Development Index; BSID-II = Bayley Scales of Infant Development, 2nd edition; BNBAS = Brazelton Neonatal Behavioral Assessment Scale.

[a]All included studies used measures administered by trained examiners blinded to exposure status.

[b]VLBW = very low birth weight (less than 1500 gm).

months, but prenatally cocaine-exposed children were more restricted and delayed in semantic representations in language samples.[73] In studies using coding of language samples during play, qualitative cocaine-associated deficits in the use of complex language[74] and discourse pragmatics and syntax structure[75] were discerned in children with prenatal cocaine exposure.

Potential mechanisms for prenatal cocaine exposure's effect on language function include disruptions in attention processing due to direct impact on the monoaminergic neurotransmitter systems during fetal development, impaired parent-child dyadic interchanges critical to language development, and impoverished caregiving environments often associated with parental drug use and poverty.[74] Because language development during early childhood is clearly determined by many interacting genetic and environmental influences, from a clinical perspective, viewing prenatal cocaine exposure through the lens of cumulative risk may help to identify affected children in need of remediation. In addition, the study of language development in prenatally cocaine-exposed children into later school age and adolescence will be necessary to elucidate pathways linking language functioning to other critical childhood outcomes, including social, academic, and behavioral outcomes.[76]

Behavioral Teratology: Interpreting Prenatal Drug Effects in Infants and Toddlers

Traditional behavioral teratology models espoused by Vorhees and others incorporate the gradient of effects a toxin may have, extending from morphological abnormalities to functional and behavioral impairments, and acknowledge the role of genetics and the environment in the expression of a teratologic effect.[77,78] Much of the research studying the effects of prenatal substance exposure has been conceptualized from a teratologic approach that acknowledges that the effects of a toxin may not be evident at birth, but may arise later in development as functional and behavioral capacities develop. As noted by Fried, traditional models of behavioral teratology are based primarily on animal research in which control of the postnatal environment is optimized.[79] However, infants and children develop within the context of complex social and environmental conditions that also influence functional and behavioral capacities, making it difficult to ascertain a drug-specific teratogenic effect on developmental processes.[79] In addition, the environment may directly impact the expression or degree of a toxin's effect. For example, the influence of prenatal cocaine exposure on behavioral regulation in children may be exacerbated by stressful environmental conditions or disruptive caregiving environments that have been associated with ongoing parental drug use.[80,81]

Research in the area of developmental psychopathology has long established the importance of responsive parenting to optimal development during infancy and the toddler years. Children with prenatal substance exposure are at increased risk for premature birth, low birth weight, impairments in state regulation and arousal modulation and, especially with opioid exposure, withdrawal symptoms.[82] Infants exposed prenatally to drugs have often been described as irritable, lethargic, unresponsive, and/or easily overstimulated; these characteristics may impede healthy dyadic interchanges and have the potential to impair the quality of mother-child interactions.[83–85] In the case of prenatal cocaine exposure, deficits in infant attention may result in maternal difficulty sustaining interactions with their infant.[84,86,87] In addition, infants exposed to both opiates and cocaine have been found to exhibit higher levels of arousal, and their mothers have been found to be less sensitive and stimulating and more likely to disengage and terminate feeding sessions.[82] Continued cocaine use following delivery among mothers with comorbid depression or anxiety has also been related to greater maternal insensitivity and negative parenting behaviors during feeding interactions.[88] Similarly, mother-child interactions during play sessions were most impaired among children with both prenatal cocaine exposure and ongoing maternal cocaine use.[89] It is important to recognize that multiple factors may moderate or mediate the effects of prenatal substance exposure on the caregiving attachment relationship and, ultimately,

FIGURE 1. Comprehensive prevention and intervention services for substance-abusing mothers and their infants.

infant development. For example, mothers who use cocaine during pregnancy often abuse other substances, such as alcohol, marijuana, and nicotine, and typically reside in high-risk environments characterized by low-income neighborhoods, poverty, poor nutrition, ongoing caregiver substance use, family instability and homelessness, and limited social support.[83,85,88,90] Illicit substance use during pregnancy combined with these contextual risk factors may exacerbate maternal stress, compromise parenting quality, and negatively impact the caregiving relationship and infant development.

The current manuscript provides an overview of the scientific literature regarding the effects of prenatal opioids and cocaine use on infant and toddler growth and development. Both drugs have the potential to cause significant growth deficits at birth and through the toddler years. In contrast to opioids, which may produce severe NAS and infant neurobehavioral deficits, prenatal cocaine exposure appears to be associated with what has been described as subtle decrements in neurobehavioral, cognitive, and language function. However, even subtle deficits can be extremely costly when they result in significantly higher proportions of children ultimately requiring services for language delays or learning disabilities.[91] Furthermore, these early findings may herald even more significant learning and behavioral problems as the academic and social challenges of the school and community environment create additional stress during early school-age and adolescence. The next article by Lester et al. describes the post-toddler age outcomes of prenatally drug-exposed children. These children, their families, and society in general would be well-served by providing appropriate prevention and intervention services to address the unique needs of substance-abusing pregnant women and their developing offspring. Figure 1 depicts a prevention and intervention model for substance-using mothers and their infants that has inspired the

development of various initiatives supported by multiple streams of federal, state, county, and private foundation funding over the past two decades in our Perinatal Chemical Addiction Research and Education Program at the University of Miami Miller School of Medicine. Given the complexities of the environmental context of maternal drug use and the myriad of factors that affect risk and resiliency of their infants and toddlers, we and others[92] are convinced that prevention-intervention programs achieve the most success when maternal and child services are well-integrated and delivered with strong family support, including care coordination to reduce the family's barriers to accessing available services.

REFERENCES

1. Substance Abuse and Mental Health Services Administration. Results from the 2007 National Survey on Drug Use and Health: national findings. NSDUH Series H-34. Rockville, MD: Office of Applied Studies, 2008.
2. Bandstra ES, Accornero VH. Infants of substance-abusing mothers. In: Martin RJ, Fanaroff AA, Walsh MC (eds). Fanaroff and Martin's neonatal-perinatal medicine: diseases of the fetus and newborn. Philadelphia, PA: Mosby Elsevier Press; 2006:733–57.
3. Abel EL, Sokol RJ. Fetal Alcohol Syndrome is now leading cause of mental-retardation. Lancet 1986; 2:1222.
4. Sulik K, Johnston M, Webb M. Fetal alcohol syndrome: embryogenesis in a mouse model. Science 1981; 214:936–938.
5. Committee to Study Fetal Alcohol Syndrome. Fetal Alcohol Syndrome: diagnosis, epidemiology, prevention, and treatment. Washington, DC: National Academy Press, 1996.
6. Slotkin TA. Fetal nicotine or cocaine exposure: which one is worse? J Pharmacol Exp Ther 1998; 285:931–45.
7. Law KL, Stroud LR, LaGasse LL, Niaura R, Liu J, Lester BM. Smoking during pregnancy and newborn neurobehavior. Pediatrics 2003; 111:1318–23.
8. American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. Pediatrics 1989; 84:924–36.
9. Jaddoe V, Troe E, Hofman A, Mackenbach J, Moll H, Steegers E, Witteman J. Active and passive maternal smoking during pregnancy and the risks of low birthweight and preterm birth: the Generation R Study. Paediatr Perinat Epidemiol 2008; 22:162–71.
10. American Academy of Pediatrics Committee on Substance Abuse. Tobacco's toll: implications for the pediatrician. Pediatrics 2001; 107:794–8.
11. Fricker HS, Segal S. Narcotic addiction, pregnancy, and the newborn. Am J Dis Child 1978; 132:360–6.
12. Zelson C, Rubio E, Wasserman E. Neonatal narcotic addiction: 10 year observation. Pediatrics 1971; 48:178–89.
13. Kaltenbach K. Effects of in-utero opiate exposure: new paradigms for old questions. Drug Alcohol Depend 1994; 36:83–7.
14. Kandall SR, Albin S, Lowinson J, Berle B, Eidelman AL, Gartner LM. Differential effects of maternal heroin and methadone use on birth weight. Pediatrics 1976; 58: 681–5.
15. Center for Substance Abuse Treatment Consensus Panel. Pregnant, substance-using women [DHHS Publication No. (SMA) 02–3677]. Treatment Improvement Protocol (TIP) Series #2. Rockville, MD: Substance Abuse and Mental Health Services Administration, 1993.
16. Dashe JS, Sheffield JS, Olscher DA, Todd SJ, Jackson GL, Wendel GD. Relationship between maternal methadone dosage and neonatal withdrawal. Obstet Gynecol 2002; 100:1244–9.
17. Berghella V, Lim PJ, Hill MK, Cherpes J, Chennat J, Kaltenbach K. Maternal methadone dose and neonatal withdrawal. Am J Obstet Gynecol 2003; 189(2):312–7.
18. Johnson RE, Jones HE, Fischer G. Use of buprenorphine in pregnancy: patient management and effects on the neonate. Drug Alcohol Depend 2003; 70:S87–S101.
19. Doberczak TM, Shanzer S, Cutler R, Senie RT, Loucopoulos JA, Kandall SR. One-year follow-up of infants with abstinence-associated seizures. Arch Neurol 1988; 45:649–53.
20. Lester BM, Tronick EZ, LaGasse L, Seifer R, Bauer CR, Shankaran S, Bada HS, Wright LL, Smeriglio VL, Lu J, Finnegan LP, Maza PL. The maternal lifestyle study: effects of substance exposure during pregnancy on neurodevelopmental outcome in 1-month-old infants. Pediatrics 2002; 110:1182–92.
21. Das A, Poole WK, Bada HS. A repeated measures approach for simultaneous modeling of multiple neurobehavioral outcomes in newborns exposed to cocaine in utero. Am J Epidemiol 2004; 159:891–9.
22. Kandall SR. Treatment strategies for drug-exposed neonates. Clin Perinatol 1999; 26:231–43.
23. The American Academy of Pediatrics Task Force on Sudden Infant Death Syndrome. The changing concept of sudden infant death syndrome: diagnostic coding shifts, controversies regarding the sleeping environment, and new variables to consider in reducing risk. Pediatrics 2005; 116:1245–55.
24. Lipsitz PJ. Proposed narcotic withdrawal score for use with newborn-infants: pragmatic evaluation of its efficacy. Clin Pediatr 1975; 14:592–4.
25. Finnegan LP, Kaltenbach K. The assessment and management of neonatal abstinence syndrome. In: Hoekelman N, eds. Primary pediatric care. St. Louis, MO: C.V. Mosby Company, 1992:1367–78.

26. American Academy of Pediatrics Committee on Drugs. Neonatal drug withdrawal. Pediatrics 1998; 101:1079–88.

27. Coyle MG, Ferguson A, LaGasse L, Oh W, Lester B. Diluted tincture of opium (DTO) and phenobarbital versus DTO alone for neonatal opiate withdrawal in term infants. J Pediatr 2002; 140:561–4.

28. Hunt RW, Tzioumi D, Collins E, Jeffery HE. Adverse neurodevelopmental outcome of infants exposed to opiate in-utero. Early Hum Dev 2008; 84:29–35.

29. Ornoy A, Segal J, Bar-Hamburger R, Greenbaum C. Developmental outcome of school-age children born to mothers with heroin dependency: importance of environmental factors. Dev Med Child Neurol 2001; 43: 668–75.

30. Ornoy A, Michailevskaya V, Lukashov I, BarHamburger R, Harel S. The developmental outcome of children born to heroin-dependent mothers, raised at home or adopted. Child Abuse Negl 1996; 20:385–96.

31. Behnke M, Eyler FD, Garvan CW, Wobie K. The search for congenital malformations in newborns with fetal cocaine exposure. Pediatrics 2001; 107:E74.

32. Bauer CR, Langer JC, Shankaran S, Bada HS, Lester B, Wright LL, Krause-Steinrauf H, Smeriglio VL, Finnegan LP, Maza PL, Verter J. Acute neonatal effects of cocaine exposure during pregnancy. Arch Pediatr Adolesc Med 2005; 159:824–34.

33. Behnke M, Davis EF, Conlon M, Wobie K, Stewart WN, Cumming W. Incidence and description of structural brain abnormalities in newborns exposed to cocaine. J Pediatr 1998; 132:291–4.

34. Bandstra ES, Morrow CE, Anthony JC, Churchill SS, Chitwood DD, Steele BM, Ofir AY, Xue L. Intrauterine growth of full-term infants: impact of prenatal cocaine exposure. Pediatrics 2001; 108:1309–19.

35. Frank DA, Bauchner H, Parker S, Huber AM, Kyei-Aboagye K, Cabral H, Zuckerman BS. Neonatal body proportionality and body composition after *in utero* exposure to cocaine and marijuana. J Pediatr 1990; 117:622–6.

36. Church MW, Crossland WJ, Holmes PA, Overbeck GW, Tilak JP. Effects of prenatal cocaine on hearing, vision, growth, and behavior. Ann N Y Acad Sci 1998; 846:12–28.

37. Eyler FD, Behnke M, Conlon M, Woods NS, Wobie K. Birth outcome from a prospective, matched study of prenatal crack/cocaine use: I. Interactive and dose effects on health and growth. Pediatrics 1998; 101:229–37.

38. Bateman DA, Chiriboga CA. Dose-response effect of cocaine on newborn head circumference. Pediatrics 2000; 106:e33.

39. Nordstrom-Klee B, Delaney-Black V, Covington C, Ager J, Sokol R. Growth from birth onwards of children prenatally exposed to drugs: a literature review. Neurotoxicol Teratol 2002; 24:481–8.

40. Frank DA, Augustyn M, Knight WG, Pell T, Zuckerman B. Growth, development, and behavior in early childhood following prenatal cocaine exposure: a systematic review. JAMA 2001; 285:1613–25.

41. Shankaran S, Lester B, Das A, Bauer CR, Bada H, LaGasse L, Higgins R. Impact of maternal substance use during pregnancy on childhood outcome. Semin Fetal Neonatal Med 2007; 12:143–50.

42. Covington CY, Nordstrom-Klee B, Ager J, Sokol R, Delaney-Black V. Birth to age 7 growth of children prenatally exposed to drugs: a prospective cohort study. Neurotoxicol Teratol 2002; 24:489–96.

43. Richardson GA, Goldschmidt L, Larkby C. Effects of prenatal cocaine exposure on growth: a longitudinal analysis. Pediatrics 2007; 120:1017–27.

44. Eyler FD, Behnke M. Early development of infants exposed to drugs prenatally. Clin Perinatol 1999; 26:107–50.

45. Singer LT, Arendt R, Minnes S, Farkas K, Salvator A. Neurobehavioral outcomes of cocaine-exposed infants. Neurotoxicol Teratol 2000; 22:653–66.

46. Morrow CE, Bandstra ES, Anthony JC, Ofir AY, Xue L, Reyes M. Influence of prenatal cocaine exposure on full-term infant neurobehavioral functioning. Neurotoxicol Teratol 2001; 23:533–44.

47. Behnke M, Eyler FD, Garvan CW, Wobie K, Hou W. Cocaine exposure and developmental outcome from birth to 6 months. Neurotoxicol Teratol 2002; 24:283–95.

48. Neuspiel DR, Hamel SC, Hochberg E, Greene J, Campbell D. Maternal cocaine use and infant behavior. Neurotoxicol Teratol 1991; 13:229–33.

49. Myers BJ, Dawson KS, Britt GC, Lodder DE, Meloy LD, Saunders MK, Meadows SL, Elswick RK. Prenatal cocaine exposure and infant performance on the Brazelton Neonatal Behavioral Assessment Scale. Subst Use Misuse 2003; 38:2065–96.

50. Coles CD, Platzman KA, Smith IE, James ME, Falek A. Effects of cocaine and alcohol use in pregnancy on neonatal growth and neurobehavioral status. Neurotoxicol Teratol 1992; 14:23–33.

51. Tronick EZ, Frank DA, Cabral H, Mirochnick M, Zuckerman BS. Late dose-response effects of prenatal cocaine exposure on newborn neurobehavioral performance. Pediatrics 1996; 98:76–83.

52. Bendersky M, Lewis M. Arousal modulation in cocaine-exposed infants. Dev Psychol 1998; 34:555–64.

53. Schuetze P, Eiden RD. The association between maternal cocaine use during pregnancy and physiological regulation in 4–to 8–week-old infants: an examination of possible mediators and moderators. J Pediatr Psychol 2006; 31:15–26.

54. Corwin MJ, Lester BM, Sepkoski C, McLaughlin S, Kayne H, Golub HL. Effects of in utero cocaine exposure on newborn acoustical cry characteristics. Pediatrics 1992; 89:1199–203.

55. Rotta NT, Cunha GB. [Prenatal exposure to cocaine: review of the neurobehavioral effects]. J Pediatr (Rio J) 2000; 76:179–84.

56. Mehta SK, Super DM, Connuck D, Kirchner HL, Salvator A, Singer L, Fradley LG, Kaufman ES. Autonomic

alterations in cocaine-exposed infants. Am Heart J 2002; 144:1109–15.

57. Lester BM, LaGasse L, Seifer R, Tronick EZ, Bauer CR, Shankaran S, Bada HS, Wright LW, Smeriglio VL, Liu J, Finnegan LP, Maza PL. The Maternal Lifestyle Study (MLS): effects of prenatal cocaine and/or opiate exposure on auditory brain response at one month. J Pediatr 2003; 142:279–85.

58. Tan-Laxa MA, Sison-Switala C, Rintelman W, Ostrea EM. Abnormal auditory brainstem response among infants with prenatal cocaine exposure. Pediatrics 2004; 113:357–60.

59. Lester BM, LaGasse LL, Freier K, Brunner SM. Studies of cocaine-exposed human infants. NIDA Res Monogr 1996; 164:175–210.

60. Singer LT, Arendt R, Minnes S, Farkas K, Salvator A, Kirchner HL, Kliegman R. Cognitive and motor outcomes of cocaine-exposed infants. JAMA 2002; 287:1952–60.

61. Lewis MW, Misra S, Johnson HL, Rosen TS. Neurological and developmental outcomes of prenatally cocaine-exposed offspring from 12 to 36 months. Am J Drug Alcohol Abuse 2004; 30:299–320.

62. Singer LT, Hawkins S, Huang J, Davillier M, Baley J. Developmental outcomes and environmental correlates of very low birthweight, cocaine-exposed infants. Early Hum Dev 2001; 64:91–103.

63. Mayes LC, Cicchetti D, Acharyya S, Zhang H. Developmental trajectories of cocaine-and-other-drug-exposed and non-cocaine-exposed children. J Dev Behav Pediatr 2003; 24:323–35.

64. Frank DA, Jacobs RR, Beeghly M, Augustyn M, Bellinger D, Cabral H, Heeren T. Level of prenatal cocaine exposure and scores on the Bayley Scales of Infant Development: modifying effects of caregiver, early intervention, and birth weight. Pediatrics 2002; 110:1143–52.

65. Brown JV, Bakeman R, Coles CD, Platzman KA, Lynch ME. Prenatal cocaine exposure: a comparison of 2-year-old children in parental and nonparental care. Child Dev 2004; 75:1282–95.

66. Richardson GA, Goldschmidt L, Willford J. The effects of prenatal cocaine use on infant development. Neurotoxicol Teratol 2008; 30:96–106.

67. Messinger DS, Bauer CR, Das A, Seifer R, Lester BM, LaGasse LL, Wright LL, Shankaran S, Bada HS, Smeriglio VL, Langer JC, Beeghly M, Poole WK. The maternal lifestyle study: cognitive, motor, and behavioral outcomes of cocaine-exposed and opiate-exposed infants through three years of age. Pediatrics 2004; 113: 1677–85.

68. Miller-Loncar C, Lester BM, Seifer R, LaGasse LL, Bauer CR, Shankaran S, Bada HS, Wright LL, Smeriglio VL, Bigsby R, Liu J. Predictors of motor development in children prenatally exposed to cocaine. Neurotoxicol Teratol 2005; 27:213–20.

69. Morrow CE, Bandstra ES, Anthony JC, Ofir AY, Xue LH, Reyes MB. Influence of prenatal cocaine exposure on early language development: longitudinal findings from four months to three years of age. J Dev Behav Pediatr 2003; 24:39–50.

70. Morrow CE, Vogel AL, Anthony JC, Ofir AY, Dausa AT, Bandstra ES. Expressive and receptive language functioning in preschool children with prenatal cocaine exposure. J Pediatr Psychol 2004; 29:543–54.

71. Singer LT, Arendt R, Minnes S, Salvator A, Siegel AC, Lewis BA. Developing language skills of cocaine-exposed infants. Pediatrics 2001; 107:1057–64.

72. 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; 30:45–72.

73. Bland-Stewart LM, Seymour HN, Beeghly M, Frank DA. Semantic development of African-American children prenatally exposed to cocaine. Semin Speech Lang 1998; 19:167–86.

74. Malakoff ME, Mayes LC, Schottenfeld R, Howell S. Language production in 24-month-old inner-city children of cocaine-and-other-drug-using mothers. J Appl Dev Psychol 1999; 20:159-80.

75. Mentis M, Lundgren K. Effects of prenatal exposure to cocaine and associated risk factors on language development. J Speech Hear Res 1995; 38:1303–18.

76. Bandstra ES, Morrow CE, Vogel AL, Accornero VH, Ofir AY, Anthony JC. Language development in children exposed to cocaine *in utero*: a longitudinal perspective. Ital J Pediatr 2003; 29:31–8.

77. Vorhees CV, Butcher RE. Behavioral teratology. In: Snell K, ed. Developmental toxicology. New York: Praeger Press, 1982:249–98.

78. Vorhees CV. Concepts in teratology and developmental toxicology derived from animal research. Ann N Y Acad Sci 1989; 562:31–41.

79. Fried PA. Conceptual issues in behavioral teratology and their application in determining long-term sequelae of prenatal marihuana exposure. J Child Psychol Psychiatry 2002; 43:81–102.

80. Mayes LC. A behavioral teratogenic model of the impact of prenatal cocaine exposure on arousal regulatory systems. Neurotoxicol Teratol 2002; 24:385–95.

81. Mayes LC, Grillon C, Granger R, Schottenfeld RS. Regulation of arousal and attention in preschool children exposed to cocaine prenatally. Ann N Y Acad Sci 1998; 846:126–43.

82. LaGasse LL, Messinger D, Lester BM, Seifer R, Tronick EZ, Bauer CR, Shankaran S, Bada HS, Wright LL, Smeriglio VL, Finnegan LP, Maza PL, Liu J. Prenatal drug exposure and maternal and infant feeding behaviour. Arch Dis Child 2003; 88:F391–9.

83. Johnson MO. Mother-infant interaction and maternal substance use/abuse: an integrative review of research

literature in the 1990s. Online J Knowl Synth Nurs 2001; 8.

84. Mayes LC, Feldman R, Granger RH, Haynes OM, Bornstein MH, Schottenfeld R. 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.

85. Freier K. In utero drug exposure and maternal-infant interaction: the complexities of the dyad and their environment. Infant Ment Health J 1994; 15:176–88.

86. Bandstra ES, Morrow CE, Anthony JC, Accornero VH, Fried PA. Longitudinal investigation of task persistence and sustained attention in children with prenatal cocaine exposure. Neurotoxicol Teratol 2001; 23:545–59.

87. Accornero VH, Amado AJ, Morrow CE, Xue LH, Anthony JC, Bandstra ES. Impact of prenatal cocaine exposure on attention and response inhibition as assessed by continuous performance tests. J Dev Behav Pediatr 2007; 28:195–205.

88. Eiden RD, Stevens A, Schuetze P, Dombkowski LE. A conceptual model for maternal behavior among polydrug cocaine-using mothers: the role of postnatal cocaine use and maternal depression. Psychol Addict Behav 2006; 20:1–10.

89. Johnson AL, Bandstra ES, Morrow CE, Accornero VH, Xue L, Anthony JC. Maternal cocaine use: estimated effects on mother-child play interactions in the preschool period. J Dev Behav Pediatr 2002; 23:191–202.

90. Espinosa M, Beckwith L, Howard J, Tyler R, Swanson K. Maternal psychopathology and attachment in toddlers of heavy cocaine-using mothers. Inf Men Health J 2001; 22:316–33.

91. Lester BM, LaGasse LL, Seifer R. Cocaine exposure and children: the meaning of subtle effects. Science 1998; 282:633–4.

92. Finnegan LP, Hagan T, Kaltenbach K. Opiod dependence: scientific foundations for clinical practice, pregnancy and substance abuse: perspectives and directions. Proceedings of the New York Academy of Medicine 1991; 67:223–9.