

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Prenatal Substance Abuse: Short- and Long-term Effects on the Exposed Fetus

Marylou Behnke, Vincent C. Smith, COMMITTEE ON SUBSTANCE ABUSE and
COMMITTEE ON FETUS AND NEWBORN

Pediatrics 2013;131:e1009; originally published online February 25, 2013;
DOI: 10.1542/peds.2012-3931

The online version of this article, along with updated information and services, is
located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/131/3/e1009.full.html>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2013 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™





TECHNICAL REPORT

Prenatal Substance Abuse: Short- and Long-term Effects on the Exposed Fetus

Marylou Behnke, MD, Vincent C. Smith, MD, COMMITTEE ON SUBSTANCE ABUSE, and COMMITTEE ON FETUS AND NEWBORN

KEY WORDS

prenatal drug exposure, alcohol, nicotine, marijuana, cocaine, methamphetamine, growth and development

ABBREVIATIONS

AAP—American Academy of Pediatrics

THC—tetrahydrocannabinol

This document is copyrighted and is property of the American Academy of Pediatrics and its Board of Directors. All authors have filed conflict of interest statements with the American Academy of Pediatrics. Any conflicts have been resolved through a process approved by the Board of Directors. The American Academy of Pediatrics has neither solicited nor accepted any commercial involvement in the development of the content of this publication.

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

All technical reports from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

www.pediatrics.org/cgi/doi/10.1542/peds.2012-3931

doi:10.1542/peds.2012-3931

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2013 by the American Academy of Pediatrics

abstract

FREE

Prenatal substance abuse continues to be a significant problem in this country and poses important health risks for the developing fetus. The primary care pediatrician's role in addressing prenatal substance exposure includes prevention, identification of exposure, recognition of medical issues for the exposed newborn infant, protection of the infant, and follow-up of the exposed infant. This report will provide information for the most common drugs involved in prenatal exposure: nicotine, alcohol, marijuana, opiates, cocaine, and methamphetamine. *Pediatrics* 2013;131:e1009–e1024

Substance abuse has been a worldwide problem at all levels of society since ancient times. Attention has been directed toward the use of legal and illegal substances by pregnant women over the past several decades. Almost all drugs are known to cross the placenta and have some effect on the fetus. The effects on the human fetus of prenatal cigarette use have been identified and studied since the 1960s,¹ the effects of alcohol and opiate use have been studied since the 1970s,^{2–4} and the effects a variety of other illicit drugs have been studied since the 1980s.^{5–7} This report reviews data regarding the prevalence of exposure and available technologies for identifying exposure as well as current information regarding short- and long-term outcomes of exposed infants, with the aim of facilitating pediatricians in fulfilling their role in the promotion and maintenance of infant and child health.

PREVALENCE

Prevalence estimates for prenatal substance use vary widely and have been difficult to establish. Differences are likely attributable to such things as the use of different sampling methods and drug-detection methods, screening women in different settings, and obtaining data at different points in time. For example, prevalence will vary depending on whether history or testing of biological specimens is used; whether the biological specimen is hair, urine, or meconium; and whether the specimens are merely screened for drugs or screened and confirmed with additional testing. There also will be differences depending on whether the sample being investigated is a community sample or a targeted sample, such as women who are in drug treatment or are incarcerated. Lastly, prevalence must be interpreted in light of the fact

that the use of specific drugs waxes and wanes over time nationwide as the popularity of certain substances changes.

Although a variety of prevalence studies have been conducted over the past 2 decades, there is 1 national survey that regularly provides information on trends in substance abuse among pregnant women. The National Survey on Drug Use and Health (formerly called the National Household Survey on Drug Abuse), sponsored by the Substance Abuse and Mental Health Services Administration (<http://www.oas.samhsa.gov/nhsda.htm>), is an annual survey providing national and state level information on the use of alcohol, tobacco, and illicit drugs in a sample of more than 67 000 noninstitutionalized people older than 12 years. Data are combined into 2-year epochs and include reported drug use for pregnant women between the ages of 15 and 44 years. Current illegal drug use among pregnant women remained relatively stable from 2007–2008 (5.1%) to 2009–2010 (4.4%). These average prevalence rates are significantly lower than reported current illicit drug use rates for nonpregnant women (10.9%). Importantly, the rate of current drug use among the youngest and possibly the most vulnerable pregnant women was highest (16.2% for 15- to 17-year-olds, compared with 7.4% among 18- to 25-year-olds and 1.9% among 26- to 44-year-olds). Table 1 summarizes these data along with information regarding current alcohol use, binge drinking,

and cigarette use by pregnant and nonpregnant women. An additional important finding from this survey was that the rate of cigarette smoking for those 15 to 17 years of age actually was higher for pregnant women than for nonpregnant women (22.7% vs 13.4%, respectively). This report details many sociodemographic variables related to drug use in the American population, and the reader is referred to the Substance Abuse and Mental Health Services Administration Web site for the full report (<http://www.oas.samhsa.gov/nhsda.htm>).

IDENTIFICATION OF PRENATAL EXPOSURE

Two basic methods are used to identify drug users: self-report or biological specimens. Although no single approach can accurately determine the presence or amount of drug used during pregnancy, it is more likely that fetal exposure will be identified if a biological specimen is collected along with a structured interview.⁸

Self-reported history is an inexpensive and practical method for identifying prenatal drug exposure and is the only method available in which information can be obtained regarding the timing of the drug use during pregnancy and the amount used. Unfortunately, self-report suffers from problems with the veracity of the informant and recall accuracy.^{9,10} Histories obtained by trusted, nonjudgmental individuals or via computerized survey forms; questions referring back to the previous trimester or prepregnancy usage, not current use; and pregnancy calendars used to assist recollection each improve the accuracy of the information obtained.^{11–13}

Several biological specimens can be used to screen for drug exposure. Each specimen has its own individual variations with regard to the window of detection, the specific drug metabolites

used for identification, methods of adulteration of the sample, and analytical techniques, thus altering the sensitivity and specificity for each drug of interest. The most common analytical method used for screening biological specimens is an immunoassay designed to screen out drug-free samples. Threshold values generally are set high to minimize false-positive test results but may be too high to detect low-dose or remote exposure. Because immunoassay is a relatively nonspecific test, positive results require confirmation by using gas chromatography/mass spectrometry. In addition, confirmation of the presence of a drug is not always associated with drug abuse. Alternative explanations include passive exposure to the drug, ingestion of other products contaminated with the drug, or use of prescription medications that either contain the drug or are metabolized to the drug.¹⁴ Thus, careful patient histories remain essential to the process of identification.

The 3 most commonly used specimens to establish drug exposure during the prenatal and perinatal period are urine, meconium, and hair; however, none is accepted as a “gold standard.” Urine has been the most frequently tested biological specimen because of its ease of collection. Urine testing identifies only recent drug use, because threshold levels of drug metabolites generally can be detected in urine only for several days. A notable exception to this is marijuana, the metabolites of which can be excreted for as long as 10 days in the urine of regular users¹⁵ or up to 30 days in chronic, heavy users. Urine is a good medium as well for the detection of nicotine, opiate, cocaine, and amphetamine exposure.^{16,17}

Meconium is also easy to collect noninvasively. It is hypothesized that drugs accumulate in meconium throughout pregnancy, and thus, meconium is

TABLE 1 Comparison of Drug Use Among Women 15 to 44 Years of Age by Pregnancy Status: 2009–2010

	Pregnant Women, %	Nonpregnant Women, %
Illicit drug use	4.4	10.9
Alcohol use	10.8	54.7
Binge drinking	3.7	24.6
Cigarette use	16.3	26.7

thought to reflect exposure during the second and third trimester of pregnancy when meconium forms. However, use of meconium to determine the timing or extent of exposure during pregnancy is controversial¹⁸ because of a lack of studies regarding the effects of the timing and quantity of the postpartum specimen collection as well as the effects of urine or transitional stool contamination of the meconium samples.¹⁹ Meconium has been used for the detection of nicotine, alcohol, marijuana, opiate, cocaine, and amphetamine exposure.^{16,20}

Hair is easy to collect, although some people decline this sampling method because of cosmetic concerns and societal taboos. Drugs become trapped within the hair and, thus, can reflect drug use over a long period of time. Unfortunately, using hair to determine timing and quantity of exposure also is controversial. In addition, environmental contamination, natural hair colors and textures, cosmetic hair processing, and volume of the hair sample available all affect the rational interpretation of the results.^{21–24} Hair is useful for the detection of nicotine, opiate, cocaine, and amphetamine exposure.^{16,25}

Other biological specimens have been studied for use in the detection of in utero drug exposure but are not commonly used in the clinical setting. These include such specimens as cord blood, human milk, amniotic fluid, and umbilical cord tissue.^{8,19,26} In the case of umbilical cord tissue, drug class-specific immunoassays for amphetamines, opiates, cocaine, and cannabinoids appear to be as reliable as meconium testing, with the additional benefit of availability of the tissue at the time of birth.²⁷

Beginning in the early 1980s, states began to enact legislation in response to the increasingly popular use of “crack” cocaine in our society. Such

laws required the reporting of women who used drugs during pregnancy to the legal system through states’ child abuse statutes. In 2003, the Keeping Children and Families Safe Act (Public Law 108-36) was passed by Congress, requiring physicians to notify their state child protective services agency of any infant identified as affected by illegal substances at birth or experiencing drug withdrawal. Currently, issues of whether to use biological specimens to screen for drug abuse; whether to screen the mother, her infant, or both; and which women and infants to screen are issues complicated by legal, ethical, social, and scientific concerns. Each of these concerns must be taken into account as obstetricians, neonatologists, and pediatricians work to develop protocols for identifying prenatal drug exposure. For example, there is no biological specimen that, when obtained randomly, identifies prenatal drug use with 100% accuracy; hence, a negative drug screening result does not ensure that the pregnancy was drug free. Targeted screening of high-risk women is problematic, because it can be biased toward women of racial or ethnic minorities and those who are economically disadvantaged or socially disenfranchised. Universal screening of pregnant women is impractical and not cost-effective.^{28–30} Finally, testing of biological specimens when the maternal history is positive for drug use increases medical costs and does not necessarily provide information that guides the medical care of the infant.³¹

MECHANISMS OF ACTION OF DRUGS ON THE FETUS

Drugs can affect the fetus in multiple ways. Early in gestation, during the embryonic stage, drugs can have significant teratogenic effects. However, during the fetal period, after

major structural development is complete, drugs have more subtle effects, including abnormal growth and/or maturation, alterations in neurotransmitters and their receptors, and brain organization. These are considered to be the direct effects of drugs. However, drugs also can exert a pharmacologic effect on the mother and, thus, indirectly affect the fetus. For example, nicotine acts on nicotinic cholinergic receptors within the mesolimbic pathway, and neuropathways activated by alcohol enhance inhibitory γ -aminobutyric acid (GABA) receptors and reduce glutamate receptor activity. Drugs of abuse mimic naturally occurring neurotransmitters, such that marijuana acts as anandamides, opiates act as endorphins, and cocaine and stimulants act within the mesolimbic dopaminergic pathways to increase dopamine and serotonin within the synapses.³² Other indirect effects of drugs of abuse on the fetus include altered delivery of substrate to the fetus for nutritional purposes, either because of placental insufficiency or altered maternal health behaviors attributable to the mother’s addiction. These altered behaviors, which include poor nutrition, decreased access/compliance with health care, increased exposure to violence, and increased risk of mental illness and infection, may place the fetus at risk.³³

Nicotine concentrations are higher in the fetal compartment (placenta, amniotic fluid, fetal serum) compared with maternal serum concentrations.^{34–36} Nicotine is only 1 of more than 4000 compounds to which the fetus is exposed through maternal smoking. Of these, ~30 compounds have been associated with adverse health outcomes. Although the exact mechanisms by which nicotine produces adverse fetal effects are unknown, it is likely that hypoxia, undernourishment of

the fetus, and direct vasoconstrictor effects on the placental and umbilical vessels all play a role.^{37,38} Nicotine also has been shown to have significant deleterious effects on brain development, including alterations in brain metabolism and neurotransmitter systems and abnormal brain development.^{39–43} Additional toxicity from compounds in smoke, such as cyanide and cadmium, contribute to toxicity.^{44–48}

Ethanol easily crosses the placenta into the fetus, with a significant concentration of the drug identified in the amniotic fluid as well as in maternal and fetal blood.^{49,50} A variety of mechanisms explaining the effects of alcohol on the fetus have been hypothesized. These include direct teratogenic effects during the embryonic and fetal stage of development as well as toxic effects of alcohol on the placenta, altered prostaglandin and protein synthesis, hormonal alterations, nutritional effects, altered neurotransmitter levels in the brain, altered brain morphology and neuronal development, and hypoxia (thought to be attributable to decreased placental blood flow and alterations in vascular tone in the umbilical vessels).^{51–69}

Although the main chemical compound in marijuana, δ -9-tetrahydrocannabinol (THC), crosses the placenta rapidly, its major metabolite, 11-nor-9-carboxy-THC, does not.⁷⁰ Unlike other drugs, the placenta appears to limit fetal exposure to marijuana, as fetal THC concentrations have been documented to be lower than maternal concentrations in studies of various animal species.^{15,70–72} The deleterious effects of marijuana on the fetus are thought to be attributable to complex pharmacologic actions on developing biological systems, altered uterine blood flow, and altered maternal health behaviors.^{73–75} Similar to other drugs, marijuana has been shown to alter brain neurotransmitters as well

as brain biochemistry, resulting in decreased protein, nucleic acid, and lipid synthesis.^{74,76–79} Marijuana can remain in the body for up to 30 days, thus prolonging fetal exposure. In addition, smoking marijuana produces as much as 5 times the amount of carbon monoxide as does cigarette smoking, perhaps altering fetal oxygenation.⁸⁰

In humans, opiates rapidly cross the placenta, with drug equilibration between the mother and the fetus.⁸¹ Opiates have been shown to decrease brain growth and cell development in animals, but studies of their effects on neurotransmitter levels and opioid receptors have produced mixed results.^{82–89}

Pharmacologic studies of cocaine in animal models using a variety of species have demonstrated that cocaine easily crosses both the placenta and the blood-brain barrier and can have significant teratogenic effects on the developing fetus, directly and indirectly.⁹⁰ Cocaine's teratogenic effects most likely result from interference with the neurotrophic roles of monoaminergic transmitters during brain development,^{91–94} which can significantly affect cortical neuronal development and may lead to morphologic abnormalities in several brain structures, including the frontal cingulate cortex.⁹⁴ It also appears that the development of areas of the brain that regulate attention and executive functioning are particularly vulnerable to cocaine. Thus, functions such as arousal, attention, and memory may be adversely affected by prenatal cocaine exposure.^{89,91,95–97} Furthermore, insults to the nervous system during neurogenesis, before homeostatic regulatory mechanisms are fully developed, differ from those on mature systems. Thus, cocaine exposure occurring during development of the nervous system might be expected to

result in permanent changes in brain structure and function, which can produce altered responsiveness to environmental or pharmacologic challenges later in life.⁹⁸

Methamphetamine is a member of a group of sympathomimetic drugs that stimulate the central nervous system. It readily passes through the placenta and the blood-brain barrier and can have significant effects on the fetus.^{99–101} After a single dose of methamphetamine to pregnant mice, levels of substance in the fetal brain were found to be similar to those found in human infants after prenatal methamphetamine exposure, with accumulation and distribution of the drug most likely dependent on the monoaminergic transport system. It is possible that the mechanism of action of methamphetamine is an interaction with and alteration of these neurotransmitter systems in the developing fetal brain¹⁰⁰ as well as alterations in brain morphogenesis.¹⁰²

MEDICAL ISSUES IN THE NEWBORN PERIOD

Fetal Growth

Fetal tobacco exposure has been a known risk factor for low birth weight and intrauterine growth restriction for more than 50 years,¹⁰³ with decreasing birth weight shown to be related to the number of cigarettes smoked.^{104–107} Importantly, by 24 months of age, most studies no longer demonstrate an effect of fetal tobacco exposure on somatic growth parameters of prenatally exposed infants.^{108–114} Growth restriction is 1 of the hallmarks of prenatal alcohol exposure and must be present to establish a diagnosis of fetal alcohol syndrome.^{3,115} However, even moderate amounts of alcohol use during pregnancy is associated with a decrease in size at birth.^{116–119} In general, marijuana has

not been associated with fetal growth restriction, particularly after controlling for other prenatal drug exposures.^{109,120-122} Fetal growth effects are reported in studies of prenatal opiate exposure; however, confounding variables known to be associated with poor growth, such as multiple drug use and low socioeconomic status, were not well controlled in many of the studies.¹²³ Using data from the Maternal Lifestyle Study, Bada et al¹²⁴ reported lower birth weight in opiate-exposed newborn infants born at ≥ 33 weeks' gestation, independent of use of other drugs, prenatal care, or other medical risk factors. An independent effect of prenatal cocaine exposure on intrauterine growth has been the most consistent finding across studies of prenatally exposed infants.^{122,125-130} Early studies on prenatal methamphetamine exposure¹³¹ as well as recent studies¹³² reveal independent effects of the drug on fetal growth. However, the literature available is limited at this time. Several reviews on the effects of prenatal drug exposure on growth contain additional details.¹³³⁻¹³⁵

Congenital Anomalies

Nicotine has been associated with oral facial clefts in exposed newborn infants,¹³⁶⁻¹⁴⁰ although the data are relatively weak. There is a vast literature on the teratogenic effects of prenatal alcohol exposure after the first description of fetal alcohol syndrome in 1973.³ The American Academy of Pediatrics (AAP) policy statement "Fetal Alcohol Syndrome and Alcohol-Related Neurodevelopmental Disorders" contains more information.¹⁴¹ No clear teratogenic effect of marijuana or opiates is documented in exposed newborn infants.¹⁴² Original reports regarding cocaine teratogenicity have not been further documented.^{135,143} Studies of fetal methamphetamine exposure in humans are

limited. However, Little et al¹³¹ reported no increase in the frequency of major anomalies in a small sample of exposed infants when compared with non-exposed infants.

Withdrawal

No convincing studies are available that document a neonatal withdrawal syndrome for prenatal nicotine exposure. Although several authors describe abnormal newborn behavior of exposed infants immediately after delivery, the findings are more consistent with drug toxicity, which steadily improves over time,^{144,145} as opposed to an abstinence syndrome, in which clinical signs would escalate over time as the drug is metabolized and eliminated from the body. There is 1 report of withdrawal from prenatal alcohol exposure in infants with fetal alcohol syndrome born to mothers who drank heavily during pregnancy,¹⁴⁶ but withdrawal symptoms have not been reported in longitudinal studies available in the extant literature. Neonatal abstinence symptoms have not been observed in marijuana-exposed infants, although abnormal newborn behavior has been reported with some similarities to that associated with narcotic exposure.¹⁴⁷ An opiate withdrawal syndrome was first described by Finnegan et al¹⁴⁸ in 1975. Neonatal abstinence syndrome includes a combination of physiologic and neurobehavioral signs that include such things as sweating, irritability, increased muscle tone and activity, feeding problems, diarrhea, and seizures. Infants with neonatal abstinence syndrome often require prolonged hospitalization and treatment with medication. Methadone exposure has been associated with more severe withdrawal than has exposure to heroin.¹⁴⁹ Early reports regarding buprenorphine, a more recent alternative to methadone, suggest minimal to mild withdrawal in exposed

neonates. A large multicenter trial evaluating buprenorphine's effect on exposed infants documented decreased morphine dose, hospital length of stay, and length of treatment.¹⁵⁰⁻¹⁵² There has been no substantiation of early reports regarding cocaine withdrawal.¹⁵³ Currently, no prospective studies of withdrawal in methamphetamine-exposed infants are available. A retrospective study by Smith et al¹⁵⁴ reported withdrawal symptoms in 49% of their sample of 294 methamphetamine-exposed newborn infants. However, only 4% required pharmacologic intervention. The AAP clinical report on neonatal drug withdrawal contains in-depth information on neonatal drug withdrawal, including treatment options.¹⁵⁵

Neurobehavior

Abnormalities of newborn neurobehavior, including impaired orientation and autonomic regulation¹⁵⁶ and abnormalities of muscle tone,^{144,147,157} have been identified in a number of prenatal nicotine exposure studies. Poor habituation and low levels of arousal along with motor abnormalities have been identified in women who drank alcohol heavily during their pregnancy.^{80,158} Prenatal marijuana exposure is associated with increased startles and tremors in the newborn.¹²⁰ Abnormal neurobehavior in opiate-exposed newborn infants is related to neonatal abstinence (see earlier section on Withdrawal). Using the Brazelton Newborn Behavioral Assessment Scale,¹⁵⁹ reported effects of prenatal cocaine exposure on infants have included irritability and lability of state, decreased behavioral and autonomic regulation, and poor alertness and orientation.¹⁶⁰ Recent data from the Infant Development, Environment, and Lifestyle multicenter study on the effects of prenatal methamphetamine exposure documented abnormal

neurobehavioral patterns in exposed newborn infants consisting of poor movement quality, decreased arousal, and increased stress.¹⁶¹

Breastfeeding

Few sources are available documenting the prevalence of drug use during breastfeeding. Lacking recent data, the 1988 National Maternal and Infant Health Survey (<http://www.cdc.gov/nchs/about/major/nmihs/abnmihs.htm>) revealed that the prevalence of drug use during pregnancy was comparable to the prevalence of use among women who breastfed their infants. Women who used various amounts of alcohol or marijuana and moderate amounts of cocaine during their pregnancy were not deterred from breastfeeding their infants. Thus, the pediatrician is faced with weighing the risks of exposing an infant to drugs during breastfeeding against the many known benefits of breastfeeding.¹⁶² For women who are abstinent at the time of delivery or who are participating in a supervised treatment program and choose to breastfeed, close postpartum follow-up of the mother and infant are essential.

For most street drugs, including marijuana, opiates, cocaine, and methamphetamine, the risks to the infant of ongoing, active use by the mother outweigh the benefits of breastfeeding, because most street drugs have been shown to have some effect on the breastfeeding infant.^{163–166} In addition, the dose of drug being used and the contaminants within the drug are unknown for most street drugs. Nicotine is secreted into human milk^{167,168} and has been associated with decreased milk production, decreased weight gain of the infant, and exposure of the infant to environmental tobacco smoke.^{169–171} Alcohol is concentrated in human milk. Heavy alcohol use has been shown to be associated with decreased milk

supply and neurobehavioral effects on the infant.^{172–174} However, for nicotine and alcohol, the benefits of breastfeeding in the face of limited use of these drugs outweigh the potential risks. Marijuana has an affinity for lipids and accumulates in human milk,¹⁷⁵ as can cocaine²⁶ and amphetamines.^{101,165} Although the AAP considers the use of marijuana, opiates, cocaine, and methamphetamine to be a contraindication to breastfeeding, supervised methadone use not only is considered to be compatible with breastfeeding, with no effect on the infant or on lactation, but also is a potential benefit in reducing the symptoms associated with neonatal abstinence syndrome. Several available reviews provide more detailed information with regard to breastfeeding and substance abuse.^{162,176} The reader is also referred to the AAP policy statement “Breastfeeding and the Use of Human Milk.”¹⁷⁷

LONG-TERM EFFECTS RELATED TO PRENATAL DRUG EXPOSURE

Growth

The effects of prenatal tobacco exposure on long-term growth are not clear-cut. Reports in the literature of effects on height and weight^{178–181} have not been substantiated by research teams able to control for other drug use in the sample.^{109,117,182,183} Recent studies, some of which include adolescents, have suggested that the effect on growth might be attributable to a disproportionate weight for height, such that prenatally exposed children were more likely to be obese as evidenced by a higher BMI, increased Ponderal index, and increased skinfold thickness.^{113,183,184} A robust and extensive literature is available documenting the effects of prenatal alcohol exposure on long-term growth. Although poor growth is 1 of the hallmarks of fetal alcohol

syndrome, it is the least sensitive of the diagnostic criteria.¹⁸⁵ No independent effect of prenatal marijuana exposure on growth has been documented throughout early childhood and adolescence.^{109,182,184} Long-term effects on growth have not been documented in the opiate-exposed child.¹⁸⁶ The available literature on the effect of prenatal cocaine exposure on growth throughout childhood is not conclusive. Although several studies document the negative effects of prenatal cocaine exposure on postnatal growth,^{187–189} others do not.^{126,190,191} No studies are available linking prenatal methamphetamine exposure to postnatal growth problems. However, 1 study of unspecified amphetamine use suggests that in utero exposure may be associated with poor growth throughout early childhood.¹⁹²

Behavior

After controlling for a variety of potentially confounding socioeconomic, psychosocial, family, and health variables, a number of studies have identified independent effects of prenatal tobacco exposure on long-term behavioral outcomes extending from early childhood into adulthood. For example, impulsivity and attention problems have been identified in children prenatally exposed to nicotine.^{193–195} In addition, prenatal tobacco exposure has been associated with hyperactivity¹⁹⁶ and negative¹⁹⁷ and externalizing behaviors in children,^{198–200} which appear to continue through adolescence and into adulthood in the form of higher rates of delinquency, criminal behavior, and substance abuse.^{201–206} Prenatal alcohol exposure is linked with significant attention problems in offspring^{207–210} as well as adaptive behavior problems spanning early childhood to adulthood.²¹¹ Problems identified included disrupted school experiences, delinquent

and criminal behavior, and substance abuse. Kelly et al²¹² published an in-depth review of the effects of prenatal alcohol exposure on social behavior. Inattention and impulsivity at 10 years of age have been associated with prenatal marijuana exposure.²¹³ Hyperactivity and short attention span have been noted in toddlers prenatally exposed to opiates,²¹⁴ and older exposed children have demonstrated memory and perceptual problems.²¹⁵ Caregiver reports of child behavior problems in preschool-aged²¹⁶ and elementary school-aged children^{217,218} have not been related to cocaine exposure, except in combination with other risk factors.^{219–221} However, in longitudinal modeling of caregiver reports at 3, 5, and 7 years of age, the multisite Maternal Lifestyles Study revealed that prenatal cocaine exposure had an independent negative effect on trajectories of behavior problems.²²² There have been teacher reports of behavior problems in prenatally exposed children,²²³ although again, findings have not been consistent across studies,¹⁹⁰ and some have been moderated by other risks.²²⁴ There also have been reports in this age group of deficits in attention processing¹⁹⁰ and an increase in symptoms of attention-deficit/hyperactivity disorder and oppositional defiant disorder self-reported by the exposed children.^{217,218} To date, no studies are available that link prenatal methamphetamine exposure with long-term behavioral problems. However, 1 study of unspecified amphetamine use during pregnancy suggests a possible association with externalizing behaviors and peer problems.^{225,226}

Cognition/Executive Functioning

The link between prenatal nicotine exposure and impaired cognition is not nearly as strong as the link with

behavioral problems. However, studies of both young and older children prenatally exposed to nicotine have revealed abnormalities in learning and memory^{227,228} and slightly lower IQ scores.^{201,229–231} Prenatal alcohol exposure frequently is cited as the most common, preventable cause of non-genetic intellectual disability. Although IQ scores are lower in alcohol-exposed offspring,^{207,232} they can be variable. Additionally, prenatal alcohol exposure has been associated with poorer memory and executive functioning skills.²³³ Marijuana has not been shown to affect general IQ, but it has been associated with deficits in problem-solving skills that require sustained attention and visual memory, analysis, and integration^{230,231,234–236} and with subtle deficits in learning and memory.²³⁷ Longitudinal studies of prenatal opiate exposure have not produced consistent findings with regard to developmental sequelae. Although developmental scores tend to be lower in exposed infants, these differences no longer exist when appropriate medical and environmental controls are included in the analyses.^{238–240} With little exception,²⁴¹ prenatal cocaine exposure has not predicted overall development, IQ, or school readiness among toddlers, elementary school-aged children, or middle school-aged children.^{190,242–250} However, several studies have revealed alterations in various aspects of executive functioning,^{221,241} including visual-motor ability,²⁴⁴ attention,^{251–253} and working memory.²⁵⁴ To date, limited data are available revealing an association between prenatal methamphetamine exposure and IQ.²⁵⁵

Language

Poor language development in early childhood after prenatal nicotine exposure has been reported,^{227,256,257} as have poor language and reading abilities in 9- to 12-year-olds.²⁵⁸ Prenatal

alcohol exposure has been shown to interfere with the development and use of language,²⁵⁹ possibly leading to long-term problems in social interaction.²⁶⁰ No effect of prenatal marijuana exposure on language development has been identified in children through 12 years of age.^{227,258} Subtle language delays have been associated with prenatal cocaine exposure.^{256,261,262} Currently, no data are available relating the prenatal use of opiates or methamphetamine to language development in exposed offspring.

Achievement

The literature available evaluating academic achievement is limited. In nicotine-exposed children, Batstra et al²⁰⁰ identified poorer performance on arithmetic and spelling tasks that were part of standardized Dutch achievement tests. Howell et al²³² reported poorer performance in mathematics on achievement tests in adolescents who had been exposed prenatally to alcohol. Streissguth et al²⁶³ describe a variety of significant academic and school problems related to prenatal alcohol exposure, primarily associated with deficits in reading and math skills throughout the school years.^{263–266} Prenatal marijuana exposure has been associated with academic underachievement, particularly in the areas of reading and spelling.²⁶⁷ School achievement is not an area that has been studied adequately with regard to prenatal opiate exposure. Reported effects of cocaine exposure on school achievement are variable. In the longitudinal Maternal Lifestyle Study, 7-year-old children with prenatal cocaine exposure had a 79% increased odds of having an individualized educational plan (adjusted for IQ),²⁶⁸ and Morrow et al²⁴⁹ found 2.8 times the risk of learning disabilities among children with prenatal cocaine exposure

compared with their peers who were not exposed to drugs prenatally. However, other studies do not support significant cocaine effects on school achievement.^{190,269} No data are available for the effects of methamphetamine on school achievement. Cernerud et al²⁷⁰ reported on 65 children prenatally exposed to amphetamines. At 14 to 15 years of age, the children in their cohort scored significantly lower on mathematics tests than did their classmates who were not exposed to amphetamines prenatally and had a higher rate of grade retention than the Swedish norm.

Predisposed to Own Drug Use

A limited number of studies are available that have investigated the association between prenatal substance exposure and subsequent drug abuse in exposed offspring. These studies did not document cause and effect, and it remains to be determined how much of the association can be linked to prenatal exposure versus socioeconomic, environmental, and genetic influences. Studies available for prenatal nicotine exposure suggest an increased risk of early experimentation²⁷¹ and abuse of nicotine in exposed offspring.^{272,273} Brennan et al²⁷⁴ reported an association of prenatal nicotine exposure with higher rates of hospitalization for substance abuse in adult offspring.

Mounting clinical data support an increased risk of ethanol abuse later in life after prenatal exposure.^{275,277} Prenatal marijuana exposure has been associated with an increased risk for marijuana and cigarette use in exposed offspring.²⁷⁵ Insufficient data are available to draw any conclusions relative to the affects of prenatal opiate, cocaine, or methamphetamine exposure on the risk for tobacco, problem alcohol, or illicit drug use later in life.

SUMMARY

Although methodologic differences between studies and limited data in the extant literature make generalization of the results for several of the drugs difficult, some summary statements can be made by using the current knowledge base (Table 2).

The negative effect of prenatal nicotine exposure on fetal growth has been known for decades; however, longitudinal studies do not reveal a consistent effect on long-term growth. Clinical studies have failed to reach a consensus regarding congenital anomalies, and there is no evidence of a withdrawal syndrome in the newborn infant. Recent studies document a negative effect of prenatal exposure on infant neurobehavior as well as on long-term behavior, cognition, language, and achievement.

Alcohol remains the most widely studied prenatal drug of abuse, and the evidence is strong for fetal growth problems, congenital anomalies, and abnormal infant neurobehavior. There has been no convincing evidence of a neonatal withdrawal syndrome. Ongoing longitudinal studies continue to document long-term effects on growth, behavior, cognition, language, and achievement, and alcohol is the most common identifiable teratogen associated with intellectual disability.

Although there have been studies revealing subtle abnormalities in infant neurobehavior related to prenatal marijuana exposure, there have been no significant effects documented for fetal growth, congenital anomalies, or withdrawal. Long-term studies reveal effects of prenatal exposure on behavior, cognition, and achievement but not on language or growth.

The most significant effect of prenatal opiate exposure is neonatal abstinence syndrome. There have been documented effects on fetal growth (but not on long-term growth) and infant neurobehavior as well as long-term effects on behavior. There is not a consensus as to the effects of prenatal opiate exposure on cognition, and few data are available regarding language and achievement.

TABLE 2 Summary of Effects of Prenatal Drug Exposure

	Nicotine	Alcohol	Marijuana	Opiates	Cocaine	Methamphetamine
Short-term effects/birth outcome						
Fetal growth	Effect	Strong effect	No effect	Effect	Effect	Effect
Anomalies	No consensus on effect	Strong effect	No effect	No effect	No effect	No effect
Withdrawal	No effect	No effect	No effect	Strong effect	No effect	*
Neurobehavior	Effect	Effect	Effect	Effect	Effect	Effect
Long-term effects						
Growth	No consensus on effect	Strong effect	No effect	No effect	No consensus on effect	*
Behavior	Effect	Strong effect	Effect	Effect	Effect	*
Cognition	Effect	Strong effect	Effect	No consensus on effect	Effect	*
Language	Effect	Effect	No effect	*	Effect	*
Achievement	Effect	Strong effect	Effect	*	No consensus on effect	*

* Limited or no data available.

Prenatal cocaine exposure has a negative effect on fetal growth and subtle effects on infant neurobehavior. However, there is little evidence to support an association with congenital anomalies or withdrawal. There is not a consensus regarding the effects of prenatal cocaine exposure on either long-term growth or achievement; however, there are documented long-term effects on behavior and subtle effects on language. Although there is little evidence to support an effect on overall cognition, a number of studies have documented effects on specific areas of executive function.

Studies on prenatal methamphetamine exposure are still in their infancy. Early studies have documented an effect of prenatal exposure on fetal growth and infant neurobehavior but no association with congenital anomalies and no data regarding infant withdrawal or any long-term effects.

REFERENCES

1. Becker RF, Little CR, King JE. Experimental studies on nicotine absorption in rats during pregnancy. 3. Effect of subcutaneous injection of small chronic doses upon mother, fetus, and neonate. *Am J Obstet Gynecol.* 1968;100(7):957–968
2. Jones KL, Smith DW. Recognition of the fetal alcohol syndrome in early infancy. *Lancet.* 1973;302(7836):999–1001
3. Jones KL, Smith DW, Ulleland CN, Streissguth P. Pattern of malformation in offspring of chronic alcoholic mothers. *Lancet.* 1973;1(7815):1267–1271
4. Finnegan LP. Pathophysiological and behavioural effects of the transplacental transfer of narcotic drugs to the foetuses and neonates of narcotic-dependent mothers. *Bull Narc.* 1979;31(3-4):1–58
5. Chasnoff IJ, Burns WJ, Schnoll SH, Burns KA. Cocaine use in pregnancy. *N Engl J Med.* 1985;313(11):666–669
6. Oro AS, Dixon SD. Perinatal cocaine and methamphetamine exposure: maternal and neonatal correlates. *J Pediatr.* 1987; 111(4):571–578
7. Fried PA. Postnatal consequences of maternal marijuana use in humans. *Ann N Y Acad Sci.* 1989;562:123–132
8. Eyler FD, Behnke M, Wobie K, Garvan CW, Tebbett I. Relative ability of biologic specimens and interviews to detect prenatal cocaine use. *Neurotoxicol Teratol.* 2005;27(4):677–687
9. Harrell AV. Validation of self-report: the research record. *NIDA Res Monogr.* 1985; 57:12–21
10. Maisto SA, McKay JR, Connors GJ. Self-report issues in substance abuse: state of the art and future directions. *Behav Assess.* 1990;12(1):117–134
11. Day NL, Wagener DK, Taylor PM. Measurement of substance use during pregnancy: methodologic issues. *NIDA Res Monogr.* 1985;59:36–47
12. Magura S, Moses B. *Assessing Risk and Measuring Change in Families: The Family Risk Scales.* Washington, DC: Child Welfare League of America; 1987
13. Jacobson SW, Chiodo LM, Sokol RJ, Jacobson JL. Validity of maternal report of prenatal alcohol, cocaine, and smoking in relation to neurobehavioral outcome. *Pediatrics.* 2002;109(5):815–825
14. Kwong TC, Shearer D. Detection of drug use during pregnancy. *Obstet Gynecol Clin North Am.* 1998;25(1):43–64
15. Lee MJ. Marijuana and tobacco use in pregnancy. *Obstet Gynecol Clin North Am.* 1998;25(1):65–83
16. Lozano J, Garcia-Algar O, Vall O, de la Torre R, Scaravelli G, Pichini S. Biological matrices for the evaluation of in utero exposure to drugs of abuse. *Ther Drug Monit.* 2007;29(6):711–734
17. Chiu HT, Isaac Wu HD, Kuo HW. The relationship between self-reported tobacco exposure and cotinines in urine and blood for pregnant women. *Sci Total Environ.* 2008;406(1-2):331–336
18. Lester BM, ElSohly M, Wright LL, et al. The Maternal Lifestyle Study: drug use by meconium toxicology and maternal self-report. *Pediatrics.* 2001;107(2):309–317
19. Casanova OQ, Lombardero N, Behnke M, Eyler FD, Conlon M, Bertholf RL. Detection of cocaine exposure in the neonate. Analyses of urine, meconium, and

LEAD AUTHORS

Marylou Behnke, MD
Vincent C. Smith, MD

COMMITTEE ON SUBSTANCE ABUSE, 2012–2013

Sharon Levy, MD, Chairperson
Seth D. Ammerman, MD
Pamela Kathern Gonzalez, MD
Sheryl Ann Ryan, MD
Lorena M. Siqueira, MD, MSPH
Vincent C. Smith, MD

PAST COMMITTEE MEMBERS

Marylou Behnke, MD
Patricia K. Kokotailo, MD, MPH
Janet F. Williams, MD, Immediate Past Chairperson

LIAISON

Vivian B. Faden, PhD – *National Institute on Alcohol Abuse and Alcoholism*
Deborah Simkin, MD – *American Academy of Child and Adolescent Psychiatry*

STAFF

Renee Jarrett
James Baumberger

COMMITTEE ON FETUS AND NEWBORN, 2012–2013

Lu-Ann Papile, MD, Chairperson
Jill E. Baley, MD
William Benitz, MD
Waldemar A. Carlo, MD
James J. Cummings, MD
Eric Eichenwald, MD
Praveen Kumar, MD
Richard A. Polin, MD
Rosemarie C. Tan, MD, PhD
Kasper S. Wang, MD

FORMER COMMITTEE MEMBER

Kristi L. Watterberg, MD

LIAISONS

CAPT Wanda D. Barfield, MD, MPH – *Centers for Disease Control and Prevention*
Ann L. Jefferies, MD – *Canadian Pediatric Society*
George A. Macones, MD – *American College of Obstetricians and Gynecologists*
Erin L. Keels APRN, MS, NNP-BC – *National Association of Neonatal Nurses*
Tonse N. K. Raju, MD, DCH – *National Institutes of Health*

STAFF

Jim Couto, MA

- amniotic fluid from mothers and infants exposed to cocaine. *Arch Pathol Lab Med*. 1994;118(10):988–993
20. Köhler E, Avenarius S, Rabsilber A, Gerloff C, Jorch G. Assessment of prenatal tobacco smoke exposure by determining nicotine and its metabolites in meconium. *Hum Exp Toxicol*. 2007;26(6):535–544
 21. Bailey DN. Drug screening in an unconventional matrix: hair analysis. [editorial; comment] *JAMA*. 1989;262(23):3331
 22. Joseph RE, Jr, Su TP, Cone EJ. In vitro binding studies of drugs to hair: influence of melanin and lipids on cocaine binding to Caucasoid and Africoid hair. *J Anal Toxicol*. 1996;20(6):338–344
 23. Jurado C, Kintz P, Menéndez M, Repetto M. Influence of the cosmetic treatment of hair on drug testing. *Int J Legal Med*. 1997;110(3):159–163
 24. Henderson GL, Harkey MR, Zhou C, Jones RT, Jacob P III. Incorporation of isotopically labeled cocaine into human hair: race as a factor. *J Anal Toxicol*. 1998;22(2):156–165
 25. Jacqz-Aigrain E, Zhang D, Maillard G, Luton D, André J, Oury JF. Maternal smoking during pregnancy and nicotine and cotinine concentrations in maternal and neonatal hair. *BJOG*. 2002;109(8):909–911
 26. Winecker RE, Goldberger BA, Tebbett IR, et al. Detection of cocaine and its metabolites in breast milk. *J Forensic Sci*. 2001;46(5):1221–1223
 27. Montgomery D, Plate C, Alder SC, Jones M, Jones J, Christensen RD. Testing for fetal exposure to illicit drugs using umbilical cord tissue vs meconium. *J Perinatol*. 2006;26(1):11–14
 28. Hansen RL, Evans AT, Gillogley KM, Hughes CS, Krener PG. Perinatal toxicology screening. *J Perinatol*. 1992;12(3):220–224
 29. Behnke M, Eyler FD, Conlon M, Woods NS, Casanova OQ. Multiple risk factors do not identify cocaine use in rural obstetrical patients. *Neurotoxicol Teratol*. 1994;16(5):479–484
 30. Ellsworth MA, Stevens TP, D'Angio CT. Infant race affects application of clinical guidelines when screening for drugs of abuse in newborns. *Pediatrics*. 2010;125(6). Available at: www.pediatrics.org/cgi/content/full/125/6/e1379
 31. Behnke M, Eyler FD, Conlon M, Casanova OQ, Woods NS. How fetal cocaine exposure increases neonatal hospital costs. *Pediatrics*. 1997;99(2):204–208
 32. Stahl SM. *Essential Psychopharmacology: Neuroscience Basis and Practical Application*, 2nd ed. New York, NY: Cambridge Press; 2000
 33. Bauer CR, Shankaran S, Bada HS, et al. The Maternal Lifestyle Study: drug exposure during pregnancy and short-term maternal outcomes. *Am J Obstet Gynecol*. 2002;186(3):487–495
 34. Mosier HD, Jr, Jansons RA. Distribution and fate of nicotine in the rat fetus. *Teratology*. 1972;6(3):303–311
 35. Luck W, Nau H, Hansen R, Steldinger R. Extent of nicotine and cotinine transfer to the human fetus, placenta and amniotic fluid of smoking mothers. *Dev Pharmacol Ther*. 1985;8(6):384–395
 36. Koren G. Fetal toxicology of environmental tobacco smoke. *Curr Opin Pediatr*. 1995;7(2):128–131
 37. Lehtovirta P, Forss M. The acute effect of smoking on intervillous blood flow of the placenta. *Br J Obstet Gynaecol*. 1978;85(10):729–731
 38. Ahlsten G, Ewald U, Tuvemo T. Maternal smoking reduces prostacyclin formation in human umbilical arteries. A study on strictly selected pregnancies. *Acta Obstet Gynecol Scand*. 1986;65(6):645–649
 39. Joschko MA, Dreosti IE, Tulsi RS. The teratogenic effects of nicotine in vitro in rats: a light and electron microscope study. *Neurotoxicol Teratol*. 1991;13(3):307–316
 40. Lichtensteiger W, Schlumpf M. Prenatal nicotine exposure: biochemical and neuroendocrine bases of behavioral dysfunction. *Dev Brain Dysfunc*. 1993;6(4–5):279–304
 41. Seidler FJ, Albright ES, Lappi SE, Slotkin TA. In search of a mechanism for receptor-mediated neurobehavioral teratogenesis by nicotine: catecholamine release by nicotine in immature rat brain regions. *Brain Res Dev Brain Res*. 1994;82(1–2):1–8
 42. Slotkin TA. Fetal nicotine or cocaine exposure: which one is worse? *J Pharmacol Exp Ther*. 1998;285(3):931–945
 43. Hellström-Lindahl E, Seiger A, Kjaeldgaard A, Nordberg A. Nicotine-induced alterations in the expression of nicotinic receptors in primary cultures from human prenatal brain. *Neuroscience*. 2001;105(3):527–534
 44. Holsclaw DS, Jr, Topham AL. The effects of smoking on fetal, neonatal, and childhood development. *Pediatr Ann*. 1978;7(3):201–222
 45. Abel EL. Smoking and pregnancy. *J Psychoactive Drugs*. 1984;16(4):327–338
 46. Hazelhoff Roelfzema W, Roelofsen AM, Copius Peereboom-Stegeman JH. Light microscopic aspects of the rat placenta after chronic cadmium administration. *Sci Total Environ*. 1985;42(1–2):181–184
 47. Aaronson LS, Macnee CL. Tobacco, alcohol, and caffeine use during pregnancy. *J Obstet Gynecol Neonatal Nurs*. 1989;18(4):279–287
 48. Floyd RL, Zahniser SC, Gunter EP, Kendrick JS. Smoking during pregnancy: prevalence, effects, and intervention strategies. *Birth*. 1991;18(1):48–53
 49. Brien JF, Clarke DW, Smith GN, Richardson B, Patrick J. Disposition of acute, multiple-dose ethanol in the near-term pregnant ewe. *Am J Obstet Gynecol*. 1987;157(1):204–211
 50. Szeto HH. Kinetics of drug transfer to the fetus. *Clin Obstet Gynecol*. 1993;36(2):246–254
 51. Sulik KK, Johnston MC, Webb MA. Fetal alcohol syndrome: embryogenesis in a mouse model. *Science*. 1981;214(4523):936–938
 52. West JR, Hodges CA, Black AC Jr. Prenatal exposure to ethanol alters the organization of hippocampal mossy fibers in rats. *Science*. 1981;211(4485):957–959
 53. Kennedy LA. The pathogenesis of brain abnormalities in the fetal alcohol syndrome: an integrating hypothesis. *Teratology*. 1984;29(3):363–368
 54. Fisher SE. Selective fetal malnutrition: the fetal alcohol syndrome. *J Am Coll Nutr*. 1988;7(2):101–106
 55. Hoff SF. Synaptogenesis in the hippocampal dentate gyrus: effects of in utero ethanol exposure. *Brain Res Bull*. 1988;21(1):47–54
 56. Clarren SK, Astley SJ, Bowden DM, et al. Neuroanatomic and neurochemical abnormalities in nonhuman primate infants exposed to weekly doses of ethanol during gestation. *Alcohol Clin Exp Res*. 1990;14(5):674–683
 57. Druse MJ, Tajuddin N, Kuo A, Connerty M. Effects of in utero ethanol exposure on the developing dopaminergic system in rats. *J Neurosci Res*. 1990;27(2):233–240
 58. Jollie WP. Effects of sustained dietary ethanol on the ultrastructure of the visceral yolk-sac placenta of the rat. *Teratology*. 1990;42(5):541–552
 59. Michaelis EK. Fetal alcohol exposure: cellular toxicity and molecular events involved in toxicity. *Alcohol Clin Exp Res*. 1990;14(6):819–826
 60. Schenker S, Becker HC, Randall CL, Phillips DK, Baskin GS, Henderson GI. Fetal alcohol syndrome: current status of pathogenesis. *Alcohol Clin Exp Res*. 1990;14(5):635–647
 61. West JR, Goodlett CR, Bonthuis DJ, Hamre KM, Marcussen BL. Cell population depletion associated with fetal alcohol brain

- damage: mechanisms of BAC-dependent cell loss. *Alcohol Clin Exp Res*. 1990;14(6):813–818
62. Wigal SB, Amsel A, Wilcox RE. Fetal ethanol exposure diminishes hippocampal beta-adrenergic receptor density while sparing muscarinic receptors during development. *Brain Res Dev Brain Res*. 1990;55(2):161–169
 63. Brien JF, Smith GN. Effects of alcohol (ethanol) on the fetus. *J Dev Physiol*. 1991;15(1):21–32
 64. Ledig M, Megias-Megias L, Tholey G. Maternal alcohol exposure before and during pregnancy: effect on development of neurons and glial cells in culture. *Alcohol Alcohol*. 1991;26(2):169–176
 65. Miller MW, Nowakowski RS. Effect of prenatal exposure to ethanol on the cell cycle kinetics and growth fraction in the proliferative zones of fetal rat cerebral cortex. *Alcohol Clin Exp Res*. 1991;15(2):229–232
 66. Smith GN, Patrick J, Sinervo KR, Brien JF. Effects of ethanol exposure on the embryo-fetus: experimental considerations, mechanisms, and the role of prostaglandins. *Can J Physiol Pharmacol*. 1991;69(5):550–569
 67. Gressens P, Lammens M, Picard JJ, Evrard P. Ethanol-induced disturbances of gliogenesis and neurogenesis in the developing murine brain: an in vitro and in vivo immunohistochemical and ultrastructural study. *Alcohol Alcohol*. 1992;27(3):219–226
 68. Kotch LE, Sulik KK. Experimental fetal alcohol syndrome: proposed pathogenic basis for a variety of associated facial and brain anomalies. *Am J Med Genet*. 1992;44(2):168–176
 69. Miller MW, Robertson S. Prenatal exposure to ethanol alters the postnatal development and transformation of radial glia to astrocytes in the cortex. *J Comp Neurol*. 1993;337(2):253–266
 70. Bailey JR, Cunny HC, Paule MG, Slikker W Jr. Fetal disposition of delta 9-tetrahydrocannabinol (THC) during late pregnancy in the rhesus monkey. *Toxicol Appl Pharmacol*. 1987;90(2):315–321
 71. Abrams RM, Cook CE, Davis KH, Niederreither K, Jaeger MJ, Szeto HH. Plasma delta-9-tetrahydrocannabinol in pregnant sheep and fetus after inhalation of smoke from a marijuana cigarette. *Alcohol Drug Res*. 1985–1986;6(5):361–369
 72. Hutchings DE, Martin BR, Gamagaris Z, Miller N, Fico T. Plasma concentrations of delta-9-tetrahydrocannabinol in dams and fetuses following acute or multiple prenatal dosing in rats. *Life Sci*. 1989;44(11):697–701
 73. Murthy NV, Melville GN, Wynter HH. Contractile responses of uterine smooth muscle to acetylcholine and marijuana extract. *Int J Gynaecol Obstet*. 1983;21(3):223–226
 74. Dalterio SL. Cannabinoid exposure: effects on development. *Neurobehav Toxicol Teratol*. 1986;8(4):345–352
 75. Fisher SE, Atkinson M, Chang B. Effect of delta-9-tetrahydrocannabinol on the in vitro uptake of alpha-amino isobutyric acid by term human placental slices. *Pediatr Res*. 1987;21(1):104–107
 76. Walters DE, Carr LA. Changes in brain catecholamine mechanisms following perinatal exposure to marijuana. *Pharmacol Biochem Behav*. 1986;25(4):763–768
 77. Morgan B, Brake SC, Hutchings DE, Miller N, Gamagaris Z. Delta-9-tetrahydrocannabinol during pregnancy in the rat: effects on development of RNA, DNA, and protein in offspring brain. *Pharmacol Biochem Behav*. 1988;31(2):365–369
 78. Walters DE, Carr LA. Perinatal exposure to cannabinoids alters neurochemical development in rat brain. *Pharmacol Biochem Behav*. 1988;29(1):213–216
 79. Rodríguez de Fonseca F, Cebeira M, Fernández-Ruiz JJ, Navarro M, Ramos JA. Effects of pre- and perinatal exposure to hashish extracts on the ontogeny of brain dopaminergic neurons. *Neuroscience*. 1991;43(2-3):713–723
 80. Chiriboga CA. Fetal alcohol and drug effects. *Neurologist*. 2003;9(6):267–279
 81. Gerdin E, Rane A, Lindberg B. Transplacental transfer of morphine in man. *J Perinat Med*. 1990;18(4):305–312
 82. Zagon IS, McLaughlin PJ, Weaver DJ, Zagon E. Opiates, endorphins and the developing organism: a comprehensive bibliography. *Neurosci Biobehav Rev*. 1982;6(4):439–479
 83. Lee CC, Chiang CN. Maternal-fetal transfer of abused substances: pharmacokinetic and pharmacodynamic data. *NIDA Res Monogr*. 1985;60:110–147
 84. Wang C, Pasulka P, Perry B, Pizzi WJ, Schnoll SH. Effect of perinatal exposure to methadone on brain opioid and alpha 2-adrenergic receptors. *Neurobehav Toxicol Teratol*. 1986;8(4):399–402
 85. Hammer RP, Jr, Ricalde AA, Seatriz JV. Effects of opiates on brain development. *Neurotoxicology*. 1989;10(3):475–483
 86. Ricalde AA, Hammer RP Jr. Perinatal opiate treatment delays growth of cortical dendrites. *Neurosci Lett*. 1990;115(2-3):137–143
 87. Hauser KF, Stiene-Martin A. Characterization of opioid-dependent glial development in dissociated and organotypic cultures of mouse central nervous system: critical periods and target specificity. *Brain Res Dev Brain Res*. 1991;62(2):245–255
 88. Zagon IS, McLaughlin PJ. The perinatal opioid syndrome: laboratory findings and clinical implications. In: Sonderegger TB, ed. *Perinatal Substance Abuse: Research Findings and Clinical Implications*. Baltimore, MD: Johns Hopkins University Press; 1992:207–223
 89. Malanga CJ, III, Kosofsky BE. Mechanisms of action of drugs of abuse on the developing fetal brain. *Clin Perinatol*. 1999;26(1):17–37, v–vi
 90. Mayes LC. Neurobiology of prenatal cocaine exposure effect on developing monoamine systems. *Infant Ment Health J*. 1994;15(2):121–133
 91. Dow-Edwards DL. Developmental toxicity of cocaine: mechanisms of action. In: Lewis M, Bendersky M, eds. *Mothers, Babies, and Cocaine: The Role of Toxins in Development*. Hillsdale, NJ: Lawrence Erlbaum Associates Inc; 1995:5–17
 92. Levitt P, Harvey JA, Friedman E, Simansky K, Murphy EH. New evidence for neurotransmitter influences on brain development. *Trends Neurosci*. 1997;20(6):269–274
 93. Whitaker-Azmitia PM. Role of the neurotrophic properties of serotonin in the delay of brain maturation induced by cocaine. *Ann N Y Acad Sci*. 1998;846:158–164
 94. Harvey JA. Cocaine effects on the developing brain: current status. *Neurosci Biobehav Rev*. 2004;27(8):751–764
 95. Lauder JM. Discussion: neuroteratology of cocaine relationship to developing monoamine systems. *NIDA Res Monogr*. 1991;114:233–247
 96. Woods JR Jr. Adverse consequences of prenatal illicit drug exposure. *Curr Opin Obstet Gynecol*. 1996;8(6):403–411
 97. Mayes LC. Developing brain and in utero cocaine exposure: effects on neural ontogeny. *Dev Psychopathol*. 1999;11(4):685–714
 98. Stanwood GD, Levitt P. Drug exposure early in life: functional repercussions of changing neuropharmacology during sensitive periods of brain development. *Curr Opin Pharmacol*. 2004;4(1):65–71
 99. Burchfield DJ, Lucas VW, Abrams RM, Miller RL, DeVane CL. Disposition and pharmacodynamics of methamphetamine in pregnant sheep. *JAMA*. 1991;265(15):1968–1973
 100. Won L, Bubula N, McCoy H, Heller A. Methamphetamine concentrations in fetal and maternal brain following prenatal

- exposure. *Neurotoxicol Teratol.* 2001;23(4):349–354
101. Golub M, Costa L, Crofton K, et al. NTP-CERHR Expert Panel Report on the reproductive and developmental toxicity of amphetamine and methamphetamine. *Birth Defects Res B Dev Reprod Toxicol.* 2005;74(6):471–584
 102. Cui C, Sakata-Haga H, Ohta K, et al. Histological brain alterations following prenatal methamphetamine exposure in rats. *Congenit Anom (Kyoto).* 2006;46(4):180–187
 103. Simpson WJ. A preliminary report on cigarette smoking and the incidence of prematurity. *Am J Obstet Gynecol.* 1957;73(4):807–815
 104. Yerushalmy J. The relationship of parents' cigarette smoking to outcome of pregnancy—implications as to the problem of inferring causation from observed associations. *Am J Epidemiol.* 1971;93(6):443–456
 105. Persson PH, Grennert L, Gennser G, Kullander S. A study of smoking and pregnancy with special references to fetal growth. *Acta Obstet Gynecol Scand Suppl.* 1978;78(S78):33–39
 106. Olsen J. Cigarette smoking in pregnancy and fetal growth. Does the type of tobacco play a role? *Int J Epidemiol.* 1992;21(2):279–284
 107. Zarén B, Lindmark G, Gebre-Medhin M. Maternal smoking and body composition of the newborn. *Acta Paediatr.* 1996;85(2):213–219
 108. Hoff C, Wertelecki W, Blackburn WR, Mendenhall H, Wiseman H, Stumpe A. Trend associations of smoking with maternal, fetal, and neonatal morbidity. *Obstet Gynecol.* 1986;68(3):317–321
 109. Day N, Cornelius M, Goldschmidt L, Richardson G, Robles N, Taylor P. The effects of prenatal tobacco and marijuana use on offspring growth from birth through 3 years of age. *Neurotoxicol Teratol.* 1992;14(6):407–414
 110. Barnett E. Race differences in the proportion of low birth weight attributable to maternal cigarette smoking in a low-income population. *Am J Health Promot.* 1995;10(2):105–110
 111. Lightwood JM, Phibbs CS, Glantz SA. Short-term health and economic benefits of smoking cessation: low birth weight. *Pediatrics.* 1999;104(6):1312–1320
 112. DiFranza JR, Aligne CA, Weitzman M. Prenatal and postnatal environmental tobacco smoke exposure and children's health. *Pediatrics.* 2004;113(suppl 4):1007–1015
 113. Fried PA, Watkinson B, Gray R. Growth from birth to early adolescence in offspring prenatally exposed to cigarettes and marijuana. *Neurotoxicol Teratol.* 1999;21(5):513–525
 114. Fenercioglu AK, Tamer I, Karatekin G, Nuhoglu A. Impaired postnatal growth of infants prenatally exposed to cigarette smoking. *Tohoku J Exp Med.* 2009;218(3):221–228
 115. Mills JL, Graubard BI, Harley EE, Rhoads GG, Berendes HW. Maternal alcohol consumption and birth weight. How much drinking during pregnancy is safe? *JAMA.* 1984;252(14):1875–1879
 116. Streissguth AP, Martin DC, Martin JC, Barr HM. The Seattle longitudinal prospective study on alcohol and pregnancy. *Neurobehav Toxicol Teratol.* 1981;3(2):223–233
 117. Fried PA, O'Connell CM. A comparison of the effects of prenatal exposure to tobacco, alcohol, cannabis and caffeine on birth size and subsequent growth. *Neurotoxicol Teratol.* 1987;9(2):79–85
 118. Greene T, Ernhart CB, Sokol RJ, et al. Prenatal alcohol exposure and preschool physical growth: a longitudinal analysis. *Alcohol Clin Exp Res.* 1991;15(6):905–913
 119. Jacobson JL, Jacobson SW, Sokol RJ. Effects of prenatal exposure to alcohol, smoking, and illicit drugs on postpartum somatic growth. *Alcohol Clin Exp Res.* 1994;18(2):317–323
 120. Fried PA. Marijuana use during pregnancy: consequences for the offspring. *Semin Perinatol.* 1991;15(4):280–287
 121. English DR, Hulse GK, Milne E, Holman CD, Bower CI. Maternal cannabis use and birth weight: a meta-analysis. *Addiction.* 1997;92(11):1553–1560
 122. 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(2):229–237
 123. Hulse GK, Milne E, English DR, Holman CD. The relationship between maternal use of heroin and methadone and infant birth weight. *Addiction.* 1997;92(11):1571–1579
 124. Bada HS, Das A, Bauer CR, et al. Gestational cocaine exposure and intrauterine growth: maternal lifestyle study. *Obstet Gynecol.* 2002;100(5 pt 1):916–924
 125. Chouteau M, Namerow PB, Leppert P. The effect of cocaine abuse on birth weight and gestational age. *Obstet Gynecol.* 1988;72(3 pt 1):351–354
 126. Amaro H, Zuckerman B, Cabral H. Drug use among adolescent mothers: profile of risk. *Pediatrics.* 1989;84(1):144–151
 127. Zuckerman B, Frank DA, Hingson R, et al. Effects of maternal marijuana and cocaine use on fetal growth. *N Engl J Med.* 1989;320(12):762–768
 128. Zuckerman B, Frank DA. Prenatal cocaine exposure: nine years later. [editorial; comment] *J Pediatr.* 1994;124(5 pt 1):731–733
 129. Richardson GA. Prenatal cocaine exposure. A longitudinal study of development. *Ann N Y Acad Sci.* 1998;846:144–152
 130. Bauer CR, Langer JC, Shankaran S, et al. Acute neonatal effects of cocaine exposure during pregnancy. *Arch Pediatr Adolesc Med.* 2005;159(9):824–834
 131. Little BB, Snell LM, Gilstrap LC III. Methamphetamine abuse during pregnancy: outcome and fetal effects. *Obstet Gynecol.* 1988;72(4):541–544
 132. Nguyen D, Smith LM, Lagasse LL, et al. Intrauterine growth of infants exposed to prenatal methamphetamine: results from the infant development, environment, and lifestyle study. *J Pediatr.* 2010;157(2):337–339
 133. Bauer CR. Perinatal effects of prenatal drug exposure. Neonatal aspects. *Clin Perinatol.* 1999;26(1):87–106
 134. Cornelius MD, Day NL. The effects of tobacco use during and after pregnancy on exposed children. *Alcohol Res Health.* 2000;24(4):242–249
 135. 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(4):481–488
 136. Wyszynski DF, Duffy DL, Beaty TH. Maternal cigarette smoking and oral clefts: a meta-analysis. *Cleft Palate Craniofac J.* 1997;34(3):206–210
 137. Wyszynski DF, Wu T. Use of US birth certificate data to estimate the risk of maternal cigarette smoking for oral clefting. *Cleft Palate Craniofac J.* 2002;39(2):188–192
 138. Lammer EJ, Shaw GM, Iovannisci DM, Van Waes J, Finnell RH. Maternal smoking and the risk of orofacial clefts: Susceptibility with NAT1 and NAT2 polymorphisms. *Epidemiology.* 2004;15(2):150–156
 139. Little J, Cardy A, Arslan MT, Gilmour M, Mossey PA; United Kingdom-based case-control study. Smoking and orofacial clefts: a United Kingdom-based case-control study. *Cleft Palate Craniofac J.* 2004;41(4):381–386
 140. Little J, Cardy A, Munger RG. Tobacco smoking and oral clefts: a meta-analysis. *Bull World Health Organ.* 2004;82(3):213–218

141. American Academy of Pediatrics, Committee on Substance Abuse and Committee on Children With Disabilities. Fetal alcohol syndrome and alcohol-related neurodevelopmental disorders. *Pediatrics*. 2000;106(2 pt 1):358–361
142. Astley SJ, Clarren SK, Little RE, Sampson PD, Daling JR. Analysis of facial shape in children gestationally exposed to marijuana, alcohol, and/or cocaine. *Pediatrics*. 1992;89(1):67–77
143. Behnke M, Eyler FD, Garvan CW, Wobie K. The search for congenital malformations in newborns with fetal cocaine exposure. *Pediatrics*. 2001;107(5). Available at: www.pediatrics.org/cgi/content/full/107/5/e74
144. Law KL, Stroud LR, LaGasse LL, Niaura R, Liu J, Lester BM. Smoking during pregnancy and newborn neurobehavior. *Pediatrics*. 2003;111(6 pt 1):1318–1323
145. Godding V, Bonnier C, Fiasse L, et al. Does in utero exposure to heavy maternal smoking induce nicotine withdrawal symptoms in neonates? *Pediatr Res*. 2004;55(4):645–651
146. Pierog S, Chandavasu O, Wexler I. Withdrawal symptoms in infants with the fetal alcohol syndrome. *J Pediatr*. 1977;90(4):630–633
147. Fried PA, Makin JE. Neonatal behavioural correlates of prenatal exposure to marijuana, cigarettes and alcohol in a low risk population. *Neurotoxicol Teratol*. 1987;9(1):1–7
148. Finnegan LP, Connaughton JF, Jr, Kron RE, Emich JP. Neonatal abstinence syndrome: assessment and management. *Addict Dis*. 1975;2(1-2):141–158
149. Chasnoff IJ, Hatcher R, Burns WJ. Polydrug- and methadone-addicted newborns: a continuum of impairment? *Pediatrics*. 1982;70(2):210–213
150. Fischer G, Johnson RE, Eder H, et al. Treatment of opioid-dependent pregnant women with buprenorphine. *Addiction*. 2000;95(2):239–244
151. Johnson RE, Jones HE, Fischer G. Use of buprenorphine in pregnancy: patient management and effects on the neonate. *Drug Alcohol Depend*. 2003;70(suppl 2):S87–S101
152. Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med*. 2010;363(24):2320–2331
153. Eyler FD, Behnke M, Garvan CW, Woods NS, Wobie K, Conlon M. Newborn evaluations of toxicity and withdrawal related to prenatal cocaine exposure. *Neurotoxicol Teratol*. 2001;23(5):399–411
154. Smith L, Yonekura ML, Wallace T, Berman N, Kuo J, Berkowitz C. Effects of prenatal methamphetamine exposure on fetal growth and drug withdrawal symptoms in infants born at term. *J Dev Behav Pediatr*. 2003;24(1):17–23
155. Hudak ML, Tan RC; American Academy of Pediatrics, Committee on Drugs, Committee on Fetus and Newborn. Clinical report: neonatal drug withdrawal. *Pediatrics*. 1998;101(6):1079–1088
156. Picone TA, Allen LH, Olsen PN, Ferris ME. Pregnancy outcome in North American women. II. Effects of diet, cigarette smoking, stress, and weight gain on placentas, and on neonatal physical and behavioral characteristics. *Am J Clin Nutr*. 1982;36(6):1214–1224
157. Dempsey DA, Hajnal BL, Partridge JC, et al. Tone abnormalities are associated with maternal cigarette smoking during pregnancy in in utero cocaine-exposed infants. *Pediatrics*. 2000;106(1 pt 1):79–85
158. Streissguth AP, Barr HM, Martin DC. Maternal alcohol use and neonatal habituation assessed with the Brazelton scale. *Child Dev*. 1983;54(5):1109–1118
159. Brazelton TB. *Neonatal Behavioral Assessment Scale*, 2nd ed. Philadelphia, PA: JB Lippincott Co; 1984
160. Eyler FD, Behnke M. Early development of infants exposed to drugs prenatally. *Clin Perinatol*. 1999;26(1):107–150, vii
161. Smith LM, LaGasse LL, Derauf C, et al. Prenatal methamphetamine use and neonatal neurobehavioral outcome. *Neurotoxicol Teratol*. 2008;30(1):20–28
162. Howard CR, Lawrence RA. Breast-feeding and drug exposure. *Obstet Gynecol Clin North Am*. 1998;25(1):195–217
163. Cobrinik RW, Hood RT, Jr, Chusid E. The effect of maternal narcotic addiction on the newborn infant; review of literature and report of 22 cases. *Pediatrics*. 1959;24(2):288–304
164. Perez-Reyes M, Wall ME. Presence of delta9-tetrahydrocannabinol in human milk. *N Engl J Med*. 1982;307(13):819–820
165. Steiner E, Villén T, Hallberg M, Rane A. Amphetamine secretion in breast milk. *Eur J Clin Pharmacol*. 1984;27(1):123–124
166. Chasnoff IJ, Lewis DE, Squires L. Cocaine intoxication in a breast-fed infant. *Pediatrics*. 1987;80(6):836–838
167. Ferguson BB, Wilson DJ, Schaffner W. Determination of nicotine concentrations in human milk. *Am J Dis Child*. 1976;130(8):837–839
168. Steldinger R, Luck W, Nau H. Half lives of nicotine in milk of smoking mothers: implications for nursing. *J Perinat Med*. 1988;16(3):261–262
169. Luck W, Nau H. Nicotine and cotinine concentrations in serum and urine of infants exposed via passive smoking or milk from smoking mothers. *J Pediatr*. 1985;107(5):816–820
170. Schwartz-Bickenbach D, Schulte-Hobein B, Abt S, Plum C, Nau H. Smoking and passive smoking during pregnancy and early infancy: effects on birth weight, lactation period, and cotinine concentrations in mother's milk and infant's urine. *Toxicol Lett*. 1987;35(1):73–81
171. Hopkinson JM, Schanler RJ, Fraley JK, Garza C. Milk production by mothers of premature infants: influence of cigarette smoking. *Pediatrics*. 1992;90(6):934–938
172. Cobo E. Effect of different doses of ethanol on the milk-ejecting reflex in lactating women. *Am J Obstet Gynecol*. 1973;115(6):817–821
173. Little RE, Anderson KW, Ervin CH, Worthington-Roberts B, Clarren SK. Maternal alcohol use during breast-feeding and infant mental and motor development at one year. *N Engl J Med*. 1989;321(7):425–430
174. Anderson PO. Alcohol and breastfeeding. *J Hum Lact*. 1995;11(4):321–323
175. Jakubovic A, Tait RM, McGeer PL. Excretion of THC and its metabolites in ewes' milk. *Toxicol Appl Pharmacol*. 1974;28(1):38–43
176. American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. *Pediatrics*. 2001;108(3):776–789
177. Gartner LM, Morton J, Lawrence RA, et al; American Academy of Pediatrics Section on Breastfeeding. Breastfeeding and the use of human milk. *Pediatrics*. 2005;115(2):496–506
178. Dunn HG, McBurney AK, Ingram S, Hunter CM. Maternal cigarette smoking during pregnancy and the child's subsequent development: I. Physical growth to the age of 6 1/2 years. *Can J Public Health*. 1976;67(6):499–505
179. Naeye RL. Influence of maternal cigarette smoking during pregnancy on fetal and childhood growth. *Obstet Gynecol*. 1981;57(1):18–21
180. Rantakallio P. A follow-up study up to the age of 14 of children whose mothers smoked during pregnancy. *Acta Paediatr Scand*. 1983;72(5):747–753
181. Fogelman KR, Manor O. Smoking in pregnancy and development into early adulthood. *BMJ*. 1988;297(6658):1233–1236
182. Day NL, Richardson GA, Geva D, Robles N. Alcohol, marijuana, and tobacco: effects of prenatal exposure on offspring growth and morphology at age six. *Alcohol Clin Exp Res*. 1994;18(4):786–794
183. Vik T, Jacobsen G, Vatten L, Bakketeig LS. Pre- and post-natal growth in children of

- women who smoked in pregnancy. *Early Hum Dev*. 1996;45(3):245–255
184. Fried PA, James DS, Watkinson B. Growth and pubertal milestones during adolescence in offspring prenatally exposed to cigarettes and marijuana. *Neurotoxicol Teratol*. 2001;23(5):431–436
 185. Davies JK, Bledsoe JM. Prenatal alcohol and drug exposures in adoption. *Pediatr Clin North Am*. 2005;52(5):1369–1393, vii
 186. Shankaran S, Lester BM, Das A, et al. Impact of maternal substance use during pregnancy on childhood outcome. *Semin Fetal Neonatal Med*. 2007;12(2):143–150
 187. Hurt H, Brodsky NL, Betancourt L, Braitman LE, Malmud E, Giannetta J. Cocaine-exposed children: follow-up through 30 months. *J Dev Behav Pediatr*. 1995;16(1):29–35
 188. 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(4):489–496
 189. Minnes S, Robin NH, Alt AA, et al. Dysmorphic and anthropometric outcomes in 6-year-old prenatally cocaine-exposed children. *Neurotoxicol Teratol*. 2006;28(1):28–38
 190. Richardson GA, Conroy ML, Day NL. Prenatal cocaine exposure: effects on the development of school-age children. *Neurotoxicol Teratol*. 1996;18(6):627–634
 191. Kilbride H, Castor C, Hoffman E, Fuger KL. Thirty-six-month outcome of prenatal cocaine exposure for term or near-term infants: impact of early case management. *J Dev Behav Pediatr*. 2000;21(1):19–26
 192. Eriksson M, Jonsson B, Steneroth G, Zetterström R. Cross-sectional growth of children whose mothers abused amphetamines during pregnancy. *Acta Paediatr*. 1994;83(6):612–617
 193. Kristjansson EA, Fried PA, Watkinson B. Maternal smoking during pregnancy affects children's vigilance performance. *Drug Alcohol Depend*. 1989;24(1):11–19
 194. Fried PA, Watkinson B, Gray R. A follow-up study of attentional behavior in 6-year-old children exposed prenatally to marijuana, cigarettes, and alcohol. *Neurotoxicol Teratol*. 1992;14(5):299–311
 195. Thapar A, Fowler T, Rice F, et al. Maternal smoking during pregnancy and attention deficit hyperactivity disorder symptoms in offspring. *Am J Psychiatry*. 2003;160(11):1985–1989
 196. Kotimaa AJ, Moilanen I, Taanila A, et al. Maternal smoking and hyperactivity in 8-year-old children. *J Am Acad Child Adolesc Psychiatry*. 2003;42(7):826–833
 197. Brook JS, Brook DW, Whiteman M. The influence of maternal smoking during pregnancy on the toddler's negativity. *Arch Pediatr Adolesc Med*. 2000;154(4):381–385
 198. Day NL, Richardson GA, Goldschmidt L, Cornelius MD. Effects of prenatal tobacco exposure on preschoolers' behavior. *J Dev Behav Pediatr*. 2000;21(3):180–188
 199. Wakschlag LS, Hans SL. Maternal smoking during pregnancy and conduct problems in high-risk youth: a developmental framework. *Dev Psychopathol*. 2002;14(2):351–369
 200. Batstra L, Hadders-Algra M, Neeleman J. Effect of antenatal exposure to maternal smoking on behavioural problems and academic achievement in childhood: prospective evidence from a Dutch birth cohort. *Early Hum Dev*. 2003;75(1-2):21–33
 201. Naeye RL. Cognitive and behavioral abnormalities in children whose mothers smoked cigarettes during pregnancy. *J Dev Behav Pediatr*. 1992;13(6):425–428
 202. Fergusson DM, Horwood LJ, Lynskey MT. Maternal smoking before and after pregnancy: effects on behavioral outcomes in middle childhood. *Pediatrics*. 1993;92(6):815–822
 203. Fergusson DM, Woodward LJ, Horwood LJ. Maternal smoking during pregnancy and psychiatric adjustment in late adolescence. *Arch Gen Psychiatry*. 1998;55(8):721–727
 204. Williams GM, O'Callaghan M, Najman JM, et al. Maternal cigarette smoking and child psychiatric morbidity: a longitudinal study. *Pediatrics*. 1998;102(1). Available at: www.pediatrics.org/cgi/content/full/102/1/e11
 205. Räsänen P, Hakko H, Isohanni M, Hodgins S, Järvelin MR, Tiihonen J. Maternal smoking during pregnancy and risk of criminal behavior among adult male offspring in the Northern Finland 1966 Birth Cohort. *Am J Psychiatry*. 1999;156(6):857–862
 206. Weissman MM, Warner V, Wickramaratne PJ, Kandel DB. Maternal smoking during pregnancy and psychopathology in offspring followed to adulthood. *J Am Acad Child Adolesc Psychiatry*. 1999;38(7):892–899
 207. Nanson JL, Hiscock M. Attention deficits in children exposed to alcohol prenatally. *Alcohol Clin Exp Res*. 1990;14(5):656–661
 208. Streissguth AP, Sampson PD, Olson HC, et al. Maternal drinking during pregnancy: attention and short-term memory in 14-year-old offspring—a longitudinal prospective study. *Alcohol Clin Exp Res*. 1994;18(1):202–218
 209. Streissguth AP, Bookstein FL, Sampson PD, Barr HM. Attention: prenatal alcohol and continuities of vigilance and attentional problems from 4 through 14 years. *Dev Psychopathol*. 1995;7(3):419–446
 210. Coles CD, Platzman KA, Raskind-Hood CL, Brown RT, Falek A, Smith IE. A comparison of children affected by prenatal alcohol exposure and attention deficit, hyperactivity disorder. *Alcohol Clin Exp Res*. 1997;21(1):150–161
 211. Streissguth AP, Bookstein FL, Barr HM, Sampson PD, O'Malley K, Young JK. Risk factors for adverse life outcomes in fetal alcohol syndrome and fetal alcohol effects. *J Dev Behav Pediatr*. 2004;25(4):228–238
 212. Kelly SJ, Day N, Streissguth AP. Effects of prenatal alcohol exposure on social behavior in humans and other species. *Neurotoxicol Teratol*. 2000;22(2):143–149
 213. Goldschmidt L, Day NL, Richardson GA. Effects of prenatal marijuana exposure on child behavior problems at age 10. *Neurotoxicol Teratol*. 2000;22(3):325–336
 214. Rosen TS, Johnson HL. Long-term effects of prenatal methadone maintenance. *NIDA Res Monogr*. 1985;59:73–83
 215. Lifschitz MH, Wilson GS. Patterns of growth and development in narcotic-exposed children. *NIDA Res Monogr*. 1991;114:323–339
 216. Warner TD, Behnke M, Hou W, Garvan CW, Wobie K, Eyer FD. Predicting caregiver-reported behavior problems in cocaine-exposed children at 3 years. *J Dev Behav Pediatr*. 2006;27(2):83–92
 217. Accornero VH, Anthony JC, Morrow CE, Xue L, Bandstra ES. Prenatal cocaine exposure: an examination of childhood externalizing and internalizing behavior problems at age 7 years. *Epidemiol Psychiatr Soc*. 2006;15(1):20–29
 218. Linares TJ, Singer LT, Kirchner HL, et al. Mental health outcomes of cocaine-exposed children at 6 years of age. *J Pediatr Psychol*. 2006;31(1):85–97
 219. Sood BG, Nordstrom Bailey B, Covington C, et al. Gender and alcohol moderate caregiver reported child behavior after prenatal cocaine. *Neurotoxicol Teratol*. 2005;27(2):191–201
 220. Bendersky M, Bennett D, Lewis M. Aggression at age 5 as a function of prenatal exposure to cocaine, gender, and environmental risk. *J Pediatr Psychol*. 2006;31(1):71–84
 221. Dennis T, Bendersky M, Ramsay D, Lewis M. Reactivity and regulation in children prenatally exposed to cocaine. *Dev Psychol*. 2006;42(4):688–697

222. Bada HS, Das A, Bauer CR, et al. Impact of prenatal cocaine exposure on child behavior problems through school age. *Pediatrics*. 2007;119(2). Available at: www.pediatrics.org/cgi/content/full/119/2/e348
223. Delaney-Black V, Covington C, Templin T, et al. Teacher-assessed behavior of children prenatally exposed to cocaine. *Pediatrics*. 2000;106(4):782–791
224. Nordstrom Bailey B, Sood BG, Sokol RJ, et al. Gender and alcohol moderate prenatal cocaine effects on teacher-report of child behavior. *Neurotoxicol Teratol*. 2005;27(2):181–189
225. Eriksson M, Billing L, Steneroth G, Zetterström R. Health and development of 8-year-old children whose mothers abused amphetamine during pregnancy. *Acta Paediatr Scand*. 1989;78(6):944–949
226. Billing L, Eriksson M, Jonsson B, Steneroth G, Zetterström R. The influence of environmental factors on behavioural problems in 8-year-old children exposed to amphetamine during fetal life. *Child Abuse Negl*. 1994;18(1):3–9
227. Fried PA, O'Connell CM, Watkinson B. 60- and 72-month follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol: cognitive and language assessment. *J Dev Behav Pediatr*. 1992;13(6):383–391
228. Cornelius MD, Ryan CM, Day NL, Goldschmidt L, Willford JA. Prenatal tobacco effects on neuropsychological outcomes among preadolescents. *J Dev Behav Pediatr*. 2001;22(4):217–225
229. Olds DL, Henderson CR, Jr, Tatelbaum R. Intellectual impairment in children of women who smoke cigarettes during pregnancy. *Pediatrics*. 1994;93(2):221–227
230. Fried PA. Adolescents prenatally exposed to marijuana: examination of facets of complex behaviors and comparisons with the influence of in utero cigarettes. *J Clin Pharmacol*. 2002;42(suppl 11):97S–102S
231. Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 13- to 16-year-olds prenatally exposed to cigarettes and marijuana. *Neurotoxicol Teratol*. 2003;25(4):427–436
232. Howell KK, Lynch ME, Platzman KA, Smith GH, Coles CD. Prenatal alcohol exposure and ability, academic achievement, and school functioning in adolescence: a longitudinal follow-up. *J Pediatr Psychol*. 2006;31(1):116–126
233. Koditwakku PW, Kalberg W, May PA. The effects of prenatal alcohol exposure on executive functioning. *Alcohol Res Health*. 2001;25(3):192–198
234. Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marijuana. *Neurotoxicol Teratol*. 1998;20(3):293–306
235. Fried PA, Smith AM. A literature review of the consequences of prenatal marijuana exposure. An emerging theme of a deficiency in aspects of executive function. *Neurotoxicol Teratol*. 2001;23(1):1–11
236. Fried PA, Watkinson B. Differential effects on facets of attention in adolescents prenatally exposed to cigarettes and marijuana. *Neurotoxicol Teratol*. 2001;23(5):421–430
237. Richardson GA, Ryan C, Willford J, Day NL, Goldschmidt L. Prenatal alcohol and marijuana exposure: effects on neuropsychological outcomes at 10 years. *Neurotoxicol Teratol*. 2002;24(3):309–320
238. Lifschitz MH, Wilson GS, Smith EO, Desmond MM. Factors affecting head growth and intellectual function in children of drug addicts. *Pediatrics*. 1985;75(2):269–274
239. Kaltenbach K, Finnegan LP. Children exposed to methadone in utero: assessment of developmental and cognitive ability. *Ann N Y Acad Sci*. 1989;562:360–362
240. Kaltenbach KA, Finnegan LP. Prenatal narcotic exposure: perinatal and developmental effects. *Neurotoxicology*. 1989;10(3):597–604
241. Bennett DS, Bendersky M, Lewis M. Children's intellectual and emotional-behavioral adjustment at 4 years as a function of cocaine exposure, maternal characteristics, and environmental risk. *Dev Psychol*. 2002;38(5):648–658
242. Wasserman GA, Kline JK, Bateman DA, et al. Prenatal cocaine exposure and school-age intelligence. *Drug Alcohol Depend*. 1998;50(3):203–210
243. Hurt H, Malmud E, Betancourt LM, Brodsky NL, Giannetta JM. A prospective comparison of developmental outcome of children with in utero cocaine exposure and controls using the Battelle Developmental Inventory. *J Dev Behav Pediatr*. 2001;22(1):27–34
244. Arendt RE, Short EJ, Singer LT, et al. Children prenatally exposed to cocaine: developmental outcomes and environmental risks at seven years of age. *J Dev Behav Pediatr*. 2004;25(2):83–90
245. Messinger DS, Bauer CR, Das A, et al. The maternal lifestyle study: cognitive, motor, and behavioral outcomes of cocaine-exposed and opiate-exposed infants through three years of age. *Pediatrics*. 2004;113(6):1677–1685
246. Pulsifer MB, Radonovich K, Belcher HM, Butz AM. Intelligence and school readiness in preschool children with prenatal drug exposure. *Child Neuropsychol*. 2004;10(2):89–101
247. Singer LT, Minnes S, Short E, et al. Cognitive outcomes of preschool children with prenatal cocaine exposure. *JAMA*. 2004;291(20):2448–2456
248. Frank DA, Rose-Jacobs R, Beeghly M, Wilbur M, Bellinger D, Cabral H. Level of prenatal cocaine exposure and 48-month IQ: importance of preschool enrichment. *Neurotoxicol Teratol*. 2005;27(1):15–28
249. Morrow CE, Culbertson JL, Accornero VH, Xue L, Anthony JC, Bandstra ES. Learning disabilities and intellectual functioning in school-aged children with prenatal cocaine exposure. *Dev Neuropsychol*. 2006;30(3):905–931
250. Hurt H, Betancourt LM, Malmud EK, et al. Children with and without gestational cocaine exposure: a neurocognitive systems analysis. *Neurotoxicol Teratol*. 2009;31(6):334–341
251. Leech SL, Richardson GA, Goldschmidt L, Day NL. Prenatal substance exposure: effects on attention and impulsivity of 6-year-olds. *Neurotoxicol Teratol*. 1999;21(2):109–118
252. 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(6):545–559
253. Savage J, Brodsky NL, Malmud E, Giannetta JM, Hurt H. Attentional functioning and impulse control in cocaine-exposed and control children at age ten years. *J Dev Behav Pediatr*. 2005;26(1):42–47
254. Mayes L, Snyder PJ, Langlois E, Hunter N. Visuospatial working memory in school-aged children exposed in utero to cocaine. *Child Neuropsychol*. 2007;13(3):205–218
255. Chang L, Smith LM, LoPresti C, et al. Smaller subcortical volumes and cognitive deficits in children with prenatal methamphetamine exposure. *Psychiatry Res*. 2004;132(2):95–106
256. Delaney-Black V, Covington C, Templin T, et al. Expressive language development of children exposed to cocaine prenatally: literature review and report of a prospective cohort study. *J Commun Disord*. 2000;33(6):463–480, quiz 480–481
257. Fried PA, Watkinson B. 36- and 48-month neurobehavioral follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol. *J Dev Behav Pediatr*. 1990;11(2):49–58
258. Fried PA, Watkinson B, Siegel LS. Reading and language in 9- to 12-year olds prenatally

- exposed to cigarettes and marijuana. *Neurotoxicol Teratol.* 1997;19(3):171–183
259. Mattson SN, Riley EP. A review of the neurobehavioral deficits in children with fetal alcohol syndrome or prenatal exposure to alcohol. *Alcohol Clin Exp Res.* 1998; 22(2):279–294
260. Coggins TE, Timler GR, Olswang LB. A state of double jeopardy: impact of prenatal alcohol exposure and adverse environments on the social communicative abilities of school-age children with fetal alcohol spectrum disorder. *Lang Speech Hear Serv Sch.* 2007;38(2):117–127
261. Bandstra ES, Morrow CE, Vogel AL, et al. Longitudinal influence of prenatal cocaine exposure on child language functioning. *Neurotoxicol Teratol.* 2002;24(3):297–308
262. Lewis BA, Singer LT, Short EJ, et al. Four-year language outcomes of children exposed to cocaine in utero. *Neurotoxicol Teratol.* 2004;26(5):617–627
263. Streissguth AP, Barr HM, Sampson PD. Moderate prenatal alcohol exposure: effects on child IQ and learning problems at age 7 1/2 years. *Alcohol Clin Exp Res.* 1990;14(5):662–669
264. Coles CD, Brown RT, Smith IE, Platzman KA, Erickson S, Falek A. Effects of prenatal alcohol exposure at school age. I. Physical and cognitive development. *Neurotoxicol Teratol.* 1991;13(4):357–367
265. Goldschmidt L, Richardson GA, Stoffer DS, Geva D, Day NL. Prenatal alcohol exposure and academic achievement at age six: a nonlinear fit. *Alcohol Clin Exp Res.* 1996; 20(4):763–770
266. Olson HC, Streissguth AP, Sampson PD, Barr HM, Bookstein FL, Thiede K. Association of prenatal alcohol exposure with behavioral and learning problems in early adolescence. *J Am Acad Child Adolesc Psychiatry.* 1997;36(9):1187–1194
267. Goldschmidt L, Richardson GA, Cornelius MD, Day NL. Prenatal marijuana and alcohol exposure and academic achievement at age 10. *Neurotoxicol Teratol.* 2004; 26(4):521–532
268. Levine TP, Liu J, Das A, et al. Effects of prenatal cocaine exposure on special education in school-aged children. *Pediatrics.* 2008;122(1). Available at: www.pediatrics.org/cgi/content/full/122/1/e83
269. Hurt H, Brodsky NL, Roth H, Malmud E, Giannetta JM. School performance of children with gestational cocaine exposure. *Neurotoxicol Teratol.* 2005;27(2):203–211
270. Cernerud L, Eriksson M, Jonsson B, Steneroth G, Zetterström R. Amphetamine addiction during pregnancy: 14-year follow-up of growth and school performance. *Acta Paediatr.* 1996;85(2):204–208
271. Cornelius MD, Leech SL, Goldschmidt L, Day NL. Prenatal tobacco exposure: is it a risk factor for early tobacco experimentation? *Nicotine Tob Res.* 2000;2(1):45–52
272. Buka SL, Shenassa ED, Niaura R. Elevated risk of tobacco dependence among offspring of mothers who smoked during pregnancy: a 30-year prospective study. *Am J Psychiatry.* 2003;160(11):1978–1984
273. Porath AJ, Fried PA. Effects of prenatal cigarette and marijuana exposure on drug use among offspring. *Neurotoxicol Teratol.* 2005;27(2):267–277
274. Brennan PA, Grekin ER, Mortensen EL, Mednick SA. Relationship of maternal smoking during pregnancy with criminal arrest and hospitalization for substance abuse in male and female adult offspring. *Am J Psychiatry.* 2002;159(1):48–54
275. Baer JS, Barr HM, Bookstein FL, Sampson PD, Streissguth AP. Prenatal alcohol exposure and family history of alcoholism in the etiology of adolescent alcohol problems. *J Stud Alcohol.* 1998;59(5):533–543
276. Yates WR, Cadoret RJ, Troughton EP, Stewart M, Giunta TS. Effect of fetal alcohol exposure on adult symptoms of nicotine, alcohol, and drug dependence. *Alcohol Clin Exp Res.* 1998;22(4):914–920
277. Alati R, Al Mamun A, Williams GM, O'Callaghan M, Najman JM, Bor W. In utero alcohol exposure and prediction of alcohol disorders in early adulthood: a birth cohort study. *Arch Gen Psychiatry.* 2006;63(9):1009–1016

Prenatal Substance Abuse: Short- and Long-term Effects on the Exposed Fetus
Marylou Behnke, Vincent C. Smith, COMMITTEE ON SUBSTANCE ABUSE and
COMMITTEE ON FETUS AND NEWBORN

Pediatrics 2013;131;e1009; originally published online February 25, 2013;

DOI: 10.1542/peds.2012-3931

Updated Information & Services	including high resolution figures, can be found at: http://pediatrics.aappublications.org/content/131/3/e1009.full.html
References	This article cites 272 articles, 45 of which can be accessed free at: http://pediatrics.aappublications.org/content/131/3/e1009.full.html#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Committee on Substance Abuse http://pediatrics.aappublications.org/cgi/collection/committee_on_substance_abuse
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://pediatrics.aappublications.org/site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: http://pediatrics.aappublications.org/site/misc/reprints.xhtml

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2013 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

