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TECHNICAL REPORT

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

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KEY WORDS

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

ABBREVIATIONS

AAP—American Academy of Pediatrics
THC—tetrahydrocannabinol

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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).

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

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 users[15] 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

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 controversial[18] 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 brain[100] 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 al[124] 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 exposure[131] as well as recent studies[132] 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.[133,143] Studies of fetal methamphetamine exposure in humans are limited. However, Little et al[131] reported no increase in the frequency of major anomalies in a small sample of exposed infants when compared with nonexposed 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 al[148] 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 al[154] 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 regulation[156] 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 cocaine[26] 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 hyperactivity[196] and negative[197] 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 al[212] 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-aged[216] 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 processing[190] 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 nongenetic 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 al[200] identified poorer performance on arithmetic and spelling tasks that were part of standardized Dutch achievement tests. Howell et al[232] reported poorer performance in mathematics on achievement tests in adolescents who had been exposed prenatally to alcohol. Streissguth et al[263] 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 al[249] 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 al[270] 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 experimentation[271] and abuse of nicotine in exposed offspring.[272,273] Brennan et al[274] 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.[273] 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.

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

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