

Prenatal Tobacco, Marijuana, Stimulant, and Opiate Exposure: Outcomes and Practice Implications

Abuse of drugs by pregnant women both in the United States and worldwide has raised many questions regarding the effects of prenatal drug exposure on the developing fetus and subsequent child outcomes. Studies using the neurobehavioral teratology model have been undertaken to determine specific prenatal drug effects on cognitive and behavioral development. Here we summarize the findings of studies that have investigated the developmental effects of prenatal exposure to tobacco, marijuana, stimulants, and opiates. These studies consider the timing and amount of prenatal exposure; other drug exposures; maternal characteristics; and other health, nutritional, and environmental factors. We review treatment options for pregnant, substance-dependent women and therapeutic interventions for exposed children.

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Several well-designed and methodologically sound studies have described long-term effects of specific prenatal drug exposures on children's health and development. Some longitudinal studies now extend into late adolescence and early adulthood and assess vulnerability to substance abuse and dependence.

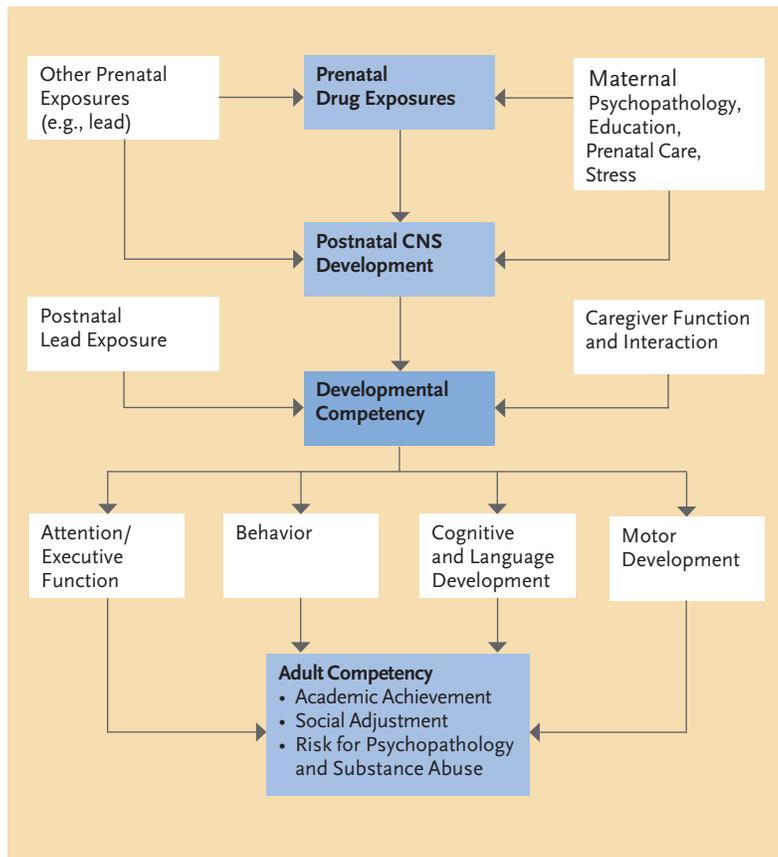
The psychoactive substances widely used by women of childbearing age include alcohol, tobacco, marijuana, stimulants, and opioids. Here we summarize current knowledge of the effects of prenatal exposure to each of these drugs, except alcohol. The extensive research on prenatal alcohol exposure has been reviewed elsewhere (Manji et al., 2009; O'Connor and Paley, 2009; Paley and O'Connor, 2009). We also discuss promising findings from trials of interventions to help pregnant and postpartum substance-abusing women and prenatally drug-exposed children.

A MODEL FOR INVESTIGATION: NEUROBEHAVIORAL TERATOLOGY

The conceptual framework used to study prenatal drug exposure is neurobehavioral teratology, which addresses the impact of prenatal exposure to a foreign agent on a child's central nervous system (CNS) and behavior. An important principle of teratology is that the harm caused by a toxic agent is a function of several factors, including the individual's genetic makeup, the fetal and postnatal environment, the dose of the agent, and the developmental stage of the fetus at the time of exposure. Vorhees (1989) has added two specific neurobehavioral tenets:

- Damage to the CNS during the prenatal period continues to have effects through fetal, neonatal, infant, and childhood development; and

FIGURE 1. Model to Study Effects of Prenatal Drug Exposure on Developmental Outcomes



Adapted from Mayes, 2002.

Drug metabolites interact with an individual's genetic makeup to influence cognitive development and behavior.

- CNS injury may result in behavioral impairments rather than physical birth defects.

Mayes (2002) developed a model for neurobehavioral teratology research that highlights the direct and indirect effects of prenatal drug exposure and the ongoing reciprocal influences of CNS disruption, maternal characteristics, and environmental factors (Figure 1).

Women often abuse more than one drug, so a child's problems frequently reflect the combined impact of multiple exposures. Substance-abusing women often also have other characteristics that can result in fetal harm, including high stress, lack of prenatal care, sexually transmitted infections, and high-risk behaviors such as drug-trade activities that expose them to violence. Once the child is born, influences that may come into play include low maternal IQ and verbal abilities, maternal psychopathology and chaotic lifestyle, exposure to lead or other toxins, and placement in institutional or foster care. The child's CNS disruption can hinder his or her odds of reaching full developmental and academic potential

directly and in combination with parental and environmental factors. For example, a parent's poor functioning in the caregiver role may compound the limiting impact that a child's drug-related irritability and reduced self-regulatory abilities have on opportunities for regular, language-rich dyadic exchange. A child's drug-related cognitive and learning disabilities may derail social and vocational adjustment, and both may increase the odds of substance abuse, psychopathology, and involvement with the criminal justice system.

Because of this merging of effects, research to evaluate the specific effects of prenatal exposure to a particular drug must include assessment of key covariates known to affect the developmental and behavioral outcomes under study (Table 1). Studies must generally include an adequate number of subjects to achieve statistical power, and longitudinal studies must retain most subjects over many years. A sufficiently large control group of similar sex, race, and socioeconomic status (SES) is essential. Recently, investigators have begun to apply new technologies to relate behavioral findings of prenatally drug-exposed children to brain structure and function and genetics.

DRUG ACTION IN THE DEVELOPING FETUS

Although the placenta was once thought to protect the fetus against exposure to toxins, it is now known that metabolites of drugs, including cocaine, opiates, amphetamines, marijuana, and tobacco, enter the fetal bloodstream. Active metabolites can penetrate the fetal blood-brain barrier and interfere with early neuronal cell development or cause neuronal death (Lee et al., 2008). Researchers hypothesize that drug metabolites interact with an individual's genetic makeup to influence cognitive development and behavior. Thus, for example, some individuals may be genetically more susceptible than others to cocaine's deleterious effects on development.

Maternal drug abuse also affects the fetus indirectly. For example, crack cocaine, heroin, tobacco, and marijuana cause vasoconstriction that restricts the fetal oxygen supply. As well, substance abuse often conflicts with healthy maternal practices—such as eating a nutrient-rich diet and accessing prenatal care—that reduce pregnancy complications such as diabetes, preeclampsia, and preterm labor. Conditions that commonly co-occur with drug abuse, including sexually transmitted infections, depression, post-traumatic stress disorder, and exposure to chronic stress and violence, also may lead to fetal injury. Neonatal abstinence syndrome (NAS), which

occurs after opiate use during pregnancy, puts the infant under physiological stress that increases the risk of health and possibly developmental problems.

Neuroimaging studies have revealed evidence of physiological brain changes in prenatally drug-exposed children, some of which correlated with the results of behavioral assessments. However, the studies need to be replicated, because they had small sample sizes and some lacked controls for possible confounding factors.

TOBACCO

Despite wide awareness that smoking is bad for both mother and developing fetus, in 2007, an estimated 16.4 percent of pregnant American women were current tobacco smokers (SAMHSA, 2008). Although pregnant women overall had lower smoking rates than nonpregnant women, pregnant 15- to 17-year-olds had higher smoking rates than their nonpregnant age mates.

Smoking increases a woman's risk of ectopic pregnancy and placenta previa, both of which increase the odds of maternal mortality. Women who smoke during pregnancy are somewhat less likely to develop preeclampsia than those who do not smoke; however, among pregnant women who develop preeclampsia, smoking seems to increase mortality (Cnattingius, 2004).

Tobacco use has also been linked to low birth weight and pregnancy complications, including prematurity, placental abruption, and intrauterine death. Low birth

weight suggests that the fetus has not obtained important nutrients and oxygen, which are important for optimal brain growth and neuronal development. Some evidence indicates that maternal tobacco use during pregnancy doubles the likelihood of sudden infant death syndrome (Salihu and Wilson, 2007; Table 2).

Neonates who were exposed to tobacco prenatally are more excitable, have greater muscle tension, require more handling to be calmed, and show more signs of CNS stress (e.g., abnormal sucking, excessive gas, gaze aversion) than unexposed infants (Law et al., 2003). Dose-response relationships have been established between maternal tobacco use, as measured by levels of salivary cotinine (the active metabolite of nicotine) or self-report, and signs of physiological stress.

Infant CNS functional abnormalities related to prenatal tobacco exposure include deficits in self-regulation (the infant's ability to soothe or quiet itself) (Table 3). At 2 to 4 weeks and at 7 months of age, prenatally tobacco-exposed infants exhibited, compared with unexposed infants, more negative affect and manifestations of sadness, distress in response to limitations, decreased soothability, and fear during a test used to assess emotional self-regulation (Schuetze and Eiden, 2007; Schuetze, Eiden, and Coles, 2007). Low birth weight and reduced head growth may underlie these disturbances.

Prenatal tobacco exposure has been consistently associated with lower IQ throughout childhood (Fried, 2002; Herrmann, King, and Weitzman, 2008). In one study, children of women who smoked more than 16 cigarettes a day while pregnant had a mean IQ in the average range, but 8 points lower than those of unexposed children (Fried, Watkinson, and Gray, 2003). Children prenatally exposed to tobacco are also at increased risk for attention problems during the early elementary school years (Cornelius et al., 2007; Langley et al., 2005; Linnet et al., 2003).

Conduct disorder can be an adverse outcome of prenatal tobacco exposure. In one study, adolescent children of mothers whose blood cotinine levels during pregnancy had been in the top 20 percent of those tested were twice as likely as the 20 percent of children with the least exposure to develop a conduct disorder (Braun et al., 2008). Postnatal exposure to secondhand smoke may also contribute substantially to diagnoses of conduct disorder in U.S. children (Braun et al., 2008). Recent data suggest that prenatal tobacco exposure may promote later conduct disorders by inhibiting the brain enzyme monoamine oxidase (MAO) during fetal development

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TABLE 1. Maternal and Caregiver Covariates to Be Considered in Prenatal Substance Exposure Research

Prenatal drug use
Socioeconomic status
Marital status
Parity
Prenatal care
Psychological distress
Quality of home environment
Race
Cognitive ability
Years of education

TABLE 2. Prenatal Drug Exposure: Potential Effects on Birth and Pregnancy Outcomes

TOBACCO	MARIJUANA	STIMULANTS	HEROIN/OPIOIDS
Pregnancy complications	No fetal growth effects	Cocaine	Stillbirth
Prematurity	No physical abnormalities	Prematurity	Prematurity
Decreased birth weight		Decreased birth weight	Decreased birth weight
Decreased birth length		Decreased birth length	Decreased birth length
Decreased birth head circumference		Decreased birth head circumference	Decreased birth head circumference
Sudden infant death syndrome (SIDS)		Intraventricular hemorrhage	Fetal and neonatal abstinence syndrome
Increased infant mortality rate		Methamphetamine	Sudden infant death syndrome (SIDS)
		Small for gestational age	
		Decreased birth weight	

Behavioral interventions are recommended as the first treatment options to help pregnant women stop smoking.

(Baler et al., 2008). MAO participates in the regulation of the levels of monoaminergic neurotransmitters that are critical for fetal forebrain development.

Prenatal tobacco exposure has also been implicated in depression and anxiety in early childhood through late adolescence (Robinson et al., 2008). However, these internalizing symptoms have not received as much attention as conduct disorder, perhaps because they are less disruptive to families and classrooms.

Prenatal tobacco exposure appears to increase the likelihood of tobacco use in childhood and early adolescence. In one study, the risk differential of exposed and unexposed children at age 10 was more than five-fold after controlling for environmental factors, other prenatal exposures, current maternal smoking, and child and maternal psychological covariates (Cornelius et al., 2005). However, when the children in this study were 14, prenatal tobacco exposure was no longer a significant predictor of their tobacco use when factors such as peer smoking were taken into account.

A magnetic resonance imaging (MRI) study of children aged 10 to 14 found reductions in cortical gray matter and parenchyma volumes, as well as head circumference, in those whose mothers had smoked while pregnant (Rivkin et al., 2008). Some researchers have suggested that prenatal tobacco exposure accelerates puberty among males (Fried, James, and Watkinson, 2001).

Treatment Recommendations

Behavioral interventions are recommended as the first treatment options to help pregnant women stop smoking (Oncken and Kranzler, 2009; Slotkin, 1998). Several studies have demonstrated that contingency management (CM), a strategy that dispenses cash or other tangible prizes as incentives for achieving treatment goals, helps pregnant smokers maintain abstinence (Donatelle et al., 2000; Heil, Scott, and Higgins, 2009; Higgins et al., 2004). CM may be more effective with low-income pregnant smokers (Donatelle et al., 2004), whose quit rates with CM have ranged from 19 to 40 percent, compared with 6.6 to 20.5 percent with other behavioral interventions. On its own, cognitive-behavioral therapy (CBT) yields only modest reductions in smoking-cessation rates among pregnant women. Combined treatment with CBT and nicotine replacement therapy (NRT) is more effective than CBT alone for pregnant moderate to heavy smokers (Osadchy, Kazmin, and Koren, 2009).

Although NRT is widely used and effective in the general population, there are concerns regarding its effectiveness for pregnant smokers and safety for the fetus. At issue is whether the risks for both mother and child outweigh the harmful effects of cigarette smoking on the fetus. Some researchers endorse the use of NRT under a physician's close supervision in combination with behavioral interventions for moderate to heavy

smokers (Osadchy, Kazmin, and Koren, 2009). For heavy smokers, the benefits of NRT likely outweigh the risks of smoking during pregnancy because NRT (1) usually delivers a dose of nicotine less than or the same as what the person gets from smoking, (2) may eliminate fetal exposure to other toxins in cigarette smoke, and (3) may reduce the overall dose and duration of nicotine exposure (Oncken and Kranzler, 2003). When used, NRT therapy should begin as early in the pregnancy as possible, because a fetus may be especially sensitive to the adverse effects of nicotine exposure after the first trimester (Slotkin, 1998). The safety and efficacy of bupropion, another medication that is effective for smokers in the general population, has not been established for pregnant smokers (Oncken and Kranzler, 2003).

Abstinence from smoking during the first 2 weeks of a quit attempt is critical to long-term success (Higgins et al., 2006). It is therefore important to closely monitor early abstinence and adjust treatment as needed. Clinicians should continue to encourage women to quit even if they initially fail, because quitting at any time before childbirth reduces the risk of complications for both the mother and child.

MARIJUANA

The Ottawa Prenatal Prospective Study (OPPS), the Maternal Health Practices and Child Development (MHPCD) study, and other well-controlled studies have not implicated *in utero* marijuana exposure in any major fetal growth or physical abnormalities (Day et al., 1992; Fried and Smith, 2001; Table 2). The OPPS study did find a 1-week-shorter gestation period and two abnormalities associated with the visual system: true ocular hypertelorism (widely spaced eyes) and severe epicanthus (skin folds at the corners of the upper eyelids) among infants whose mothers smoked more than five joints per week while pregnant (Fried and Smith, 2001). However, the study authors concluded that the visual abnormalities were likely related to prenatal alcohol exposure rather than directly to marijuana exposure.

Studies of neonatal neurobehavioral outcomes of prenatal marijuana exposure have observed mild withdrawal symptoms and poor autonomic control, particularly of state regulation (the ability to adjust one's level of alertness as required for a task). Autonomic control was normal, however, when assessed at 6 months or 1 year of age (Fried, 1995; Table 3).

The OPPS and MHPCD study examined the relationship between marijuana exposure and developmental

problems throughout childhood. Children of women who smoked one or more marijuana joints a day during the first trimesters were more likely than controls to exhibit deficits in school achievement, particularly in reading and spelling (Goldschmidt et al., 2004). Prenatal marijuana exposure had persistent negative effects through age 16 on higher-order thinking, including problem solving, memory, planning, impulsivity, and attention (Fried, 2002; Fried, Watkinson, and Gray, 2003; Goldschmidt et al., 2008; Richardson, Goldschmidt, and Larkby, 2007). Researchers did not find overall suppression of IQ.

Prenatal marijuana exposure may have long-term emotional and behavioral consequences. At age 10, children who had been exposed to the drug during their first and third trimester of gestation reported more depressive symptoms than did unexposed controls (Gray, 2005). Among 16- to 21-year-olds, prenatal exposure to marijuana at least doubled the risk of both tobacco and marijuana use (Day, Goldschmidt, and Thomas, 2006; Porath and Fried, 2005). Adolescents with histories of daily prenatal marijuana exposure were 1.3 times as likely as those with less or no exposure to be high-frequency users of the drug, even after extensive control for other factors known to increase the risk of adolescent substance abuse (Day, Goldschmidt, and Thomas, 2006).

A recent functional MRI study of 18- to 22-year-olds linked prenatal marijuana exposure to altered neural functioning during a psychological test that involves remembering the placement of images that flash on a screen. Compared with a control group, the exposed group showed greater activation of neurons in the inferior and middle frontal gyri and superior temporal gyri (Smith et al., 2006).

Treatment Recommendations

Although they have not been studied specifically with pregnant users, CBT, motivational enhancement, and CM therapies have been demonstrated to be effective for reducing marijuana use (McRae, Budney, and Brady, 2003). Controlled studies of pharmacotherapies for marijuana dependence are still needed, as is intervention research specifically targeting pregnant marijuana users.

COCAINE AND OTHER STIMULANTS

Several recent prospective studies have examined the consequences of prenatal cocaine exposure. Relatively few, in contrast, have addressed prenatal exposure to methamphetamine, ecstasy, or methylphenidate (Ritalin

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TABLE 3. Prenatal Drug Exposure: Potential Effects on Central Nervous System Development, Cognitive Function, and Behavior*

TOBACCO	MARIJUANA	STIMULANTS	OPIATES
Disturbed maternal-infant interaction Excitability Hypertonia Stress abstinence signs Conduct disorder Reduced IQ Aggression Antisocial behavior Impulsivity ADHD Tobacco use and dependence	Mild withdrawal symptoms Delayed state regulation Reading, spelling difficulty Executive function impairment Early tobacco and marijuana use	Cocaine <i>Neonatal/Infancy</i> Early neurobehavioral deficits: Orientation, state regulation, autonomic stability, attention, sensory and motor asymmetry, jitteriness Poor clarity of infant cues during feeding interaction Delayed information processing General cognitive delay <i>Childhood</i> Lower nonverbal perceptual reasoning Lower weight for height Lower weight curve trajectories Attention problems Disruptive behaviors by self-report and caregiver report	Neonatal abstinence syndrome Less rhythmic swallowing Strabismus Possible delay in general cognitive function Anxiety Aggression Feelings of rejection Disruptive/inattentive behavior
		Methamphetamine Poor movement quality (3rd trimester exposure) Lower arousal Increased lethargy Increased physiological stress No mental or motor delay (infant/toddler)	

*Effects may be subtle and transient.

or Concerta) or other stimulant medications used to treat attention-deficit/hyperactivity disorder (ADHD).

Cocaine

At the height of the most recent crack-cocaine epidemic, in the late 1980s and the first half of the 1990s, an estimated 100,000 prenatally exposed children were born yearly in the United States. As many as 18 percent of live births were affected in some urban, primarily low-SES areas (Kandel, Warner, and Kessler, 1998; Ostrea et al., 1992; SAMHSA, 2000). Nearly 2 million Americans living today were prenatally exposed to cocaine, many of whom are now adolescents or young adults. Currently, an estimated 50,000 infants are

born in the Nation each year having been prenatally exposed to cocaine.

Impact on neonatal and infant development

A majority of studies have reported that infants with histories of prenatal cocaine exposure have reduced weight, head circumference, and/or length at birth (Bada et al., 2005; Eyler et al., 1998; Singer et al., 2002b; Zuckerman et al., 1989). A meta-analysis of 33 studies conducted between 1989 and 1997 attempted to distinguish the direct effects of cocaine, as opposed to other risks commonly associated with cocaine abuse (e.g., abuse of other drugs, poor prenatal care) on these and other neonatal features and on pregnancy complications. The

results confirmed two problems as directly attributable to cocaine-related physiological stress in the prenatal environment: amniotic sac rupture more than 1 hour before labor begins and separation of the placenta from the uterus prior to delivery (Addis et al., 2001).

Considerable evidence implicates prenatal cocaine exposure in subtle CNS abnormalities. When assessed with the Brazelton Neonatal Behavioral Assessment Scale, exposed infants showed deficits—albeit with much variability—in orientation, habituation, state regulation, autonomic stability, reflexes, tone, motor performance, irritability, alertness, and excitability (Singer et al., 2000). Compared with infants of mothers with similarly low SES who used other drugs during pregnancy, cocaine-exposed infants showed higher rates of sensory and motor asymmetry, poor muscle tone, jitteriness (Singer et al., 2000), and reduced novelty preference (Singer et al., 1999). Both of these studies correlated greater prenatal cocaine exposure with poorer assessment scores in non-verbal reasoning (Table 3).

Studies of the impact of prenatal cocaine exposure on development during the first 3 years of life have produced inconsistent results. For example, among low-SES children who may also have been prenatally exposed to alcohol, tobacco, and marijuana, Richardson and colleagues reported an association between cocaine exposure during the second and third trimester of gestation and decrements in motor but not in mental abilities, as measured by the Bayley Scales of Infant Development (BSID) (Richardson, Goldschmidt, and Willford, 2008). In contrast, Frank and colleagues (2002) reported no correlation between cocaine exposure and either mental or motor scores on the same instrument. Singer and colleagues (2002a) used the BSID mental development index to compare prenatally cocaine-exposed and non-cocaine-exposed 2-year-olds; the cocaine-exposed group scored 6 points lower and were twice as likely to have significant mental delay. Other research suggests that cocaine has an indirect effect on mental development through reduced head size (Behnke et al., 2006a).

Because cocaine targets the monoaminergic (dopamine, norepinephrine, epinephrine, and serotonin) neurotransmitter systems, which are known to regulate attention, researchers have been interested in the drug's impact on children's capacity for attention. Studies indicate that prenatal cocaine exposure can impair visual attention, visual processing speed, and visual memory in infancy and throughout the first year of life (Jacobson et al., 1996; Singer et al., 1999; 2005).

How cocaine effects measured in infancy will play out in later childhood, adolescence, and adulthood is unclear. Early CNS abnormalities are considered potential early warning signs of underlying damage that may manifest later as self-regulatory problems. However, psychological assessments made before age 4 are generally weak predictors of how a child will perform later, although reduced novelty preference has been correlated with subsequent low IQ.

Impact on children 4 years and up

No childhood physical abnormalities have been definitively attributed to prenatal cocaine exposure (Minnes et al., 2006). However, some evidence points to enduring growth consequences with lower weight-to-height ratios at 6 years of age (Minnes et al., 2006) and slower head circumference and weight trajectories from 1 to 10 years (Richardson, Goldschmidt, and Larkby, 2007).

As children grow older, psychological assessments become more stable. Subtle negative effects involving perceptual reasoning have been associated with prenatal cocaine exposure in children 4 to 9 years of age (Singer et al., 2004; 2008). Perceptual reasoning refers to one's ability to envision solutions to nonverbal problems, such as recreating a spatial design with 3D colored blocks.

Problems of attention are particularly worrisome because they relate to poor school achievement and behavior problems. Prenatally cocaine-exposed 4- to 7-year-olds performed below standard norms on tests that measure sustained attention (Bandstra et al., 2001) and selective attention (Noland et al., 2005). On the tests, which require subjects to watch a computer screen and respond appropriately each time a particular image or stimulus appears, they made more than the average number of incorrect responses, indicating impulsivity, and omitted more correct responses (Accornero et al., 2007), indicating general inattention.

Rule breaking, aggression, and other externalizing behaviors are associated with prenatal cocaine exposure and are attributed to a lack of self-regulation. Ratings completed by teachers, experimenters, and caregivers indicate that being prenatally cocaine-exposed, being male, and living in a high-risk environment are each independently predictive of aggressive behavior (Bendersky, Bennett, and Lewis, 2006). Linares and colleagues (2006) reported that among prenatally cocaine-exposed 6-year-olds:

- 17 percent reported symptoms of oppositional defiant disorder, compared with 9 percent of unexposed age mates; and

Considerable evidence implicates prenatal cocaine exposure in subtle CNS abnormalities.

- 12 percent reported clinically elevated levels of ADHD symptoms, compared with 7 percent of unexposed peers.

At 10 years, boys with histories of prenatal cocaine exposure were more likely than unexposed boys to report high-risk traits, including aggression, substance use, and disregard for safety, on the Youth Risk Behavior Survey (Bennett, Bendersky, and Lewis, 2007). Teachers attribute high rates of behavioral problems, particularly hyperactivity, to prenatally cocaine-exposed boys (Delaney-Black et al., 2004). One longitudinal study associated clinically elevated delinquent behavior with prenatal cocaine exposure in girls (Minnes et al., 2010). Some studies have found that recent caregiver drug use and psychological symptoms, but not prenatal cocaine exposure, predicted behavioral problems (Accornero et al., 2002; 2006; Sheinkopf et al., 2006; Warner et al., 2006b). Overall, however, the evidence suggests that children with prenatal cocaine exposure should be routinely screened for behavioral problems.

There are growing concerns regarding the widespread use of stimulant medications for ADHD by women of childbearing age.

Imaging studies

Several researchers have deployed brain imaging to study the effects of prenatal cocaine exposure. These studies documented:

- reduced gray matter in the right parietal and left occipital lobes and corpus callosum of 7- to 8-year-olds (Dow-Edwards et al., 2006; Singer et al., 2006) and the caudate in a group averaging 14 years of age (Avants et al., 2007);
- higher diffusion in white matter frontal projections at ages 10 to 11 (Warner et al., 2006a);
- decreased volume of the right anterior cerebellum at 11 years of age (Dow-Edwards et al., 2006; Behnke et al., 2006b);
- significantly smaller caudate in adolescents (Avants et al., 2007); and
- also in adolescents, more functional connectivity in the default mode network (related to arousal regulation) and a greater signal increase when shown emotionally arousing stimuli (Li et al., 2011).

Methamphetamine

In the only large-scale, well-controlled study of the effects of prenatal methamphetamine exposure—the Infant Development, Environment, and Lifestyle Study—exposed infants were 3.5 times as likely as controls to be small for gestational age and had a lower average birth weight (Smith et al., 2006). By using the Neonatal Intensive Care Unit Network Neurobehavioral Scale,

prenatal methamphetamine exposure has been associated with lower arousal from sleep, lack of energy, and physiological symptoms indicating withdrawal. Preliminary findings indicate no impact on scores on the BSID at age 1, 2, or 3 (Lester and Lagasse, 2010). Additional followup of this cohort at later ages is needed to evaluate more subtle learning and behavioral problems.

Stimulant Medications for ADHD

There are growing concerns regarding the widespread use of stimulant medications for ADHD by women of childbearing age. To date, research has uncovered no clear pattern of negative effects on pregnancy or offspring when the medications are taken at therapeutic doses (Humphreys et al., 2007). However, no well-controlled prospective studies have been completed.

Treatment Recommendations

All stimulant drugs, including prescribed medications, should be avoided during pregnancy. Women who wish to use prescribed stimulants during pregnancy should be assessed to determine whether the potential benefits to the mother outweigh any risk to the fetus (Goodman and Quinn, 2002).

CM is a reliably effective treatment for cocaine dependence in the general population, and the use of voucher-based incentives has demonstrated promising results with pregnant women (Higgins, Alessi, and Dantona, 2002). CM used in conjunction with behaviorally based substance abuse treatment can reinforce both cocaine abstinence and compliance with prenatal care in terms of weekly attendance at prenatal clinic visits (Elk et al., 1995; 1998). In one study, CM did not greatly reduce dropout from residential treatment participation, but improved outpatient treatment retention during the transition from residential care (Svikis et al., 2007).

Methamphetamine and cocaine abusers often respond similarly to treatment (Cretzmeyer et al., 2003). Although they have not been investigated with pregnant women, CBT, CM, and the Matrix Model may be the most effective treatment approaches for stimulant abuse and dependence (Winslow, Voorhees, and Pehl, 2007).

OPIATES

Rates of prenatal opiate exposure are difficult to obtain and vary widely from less than 1 percent to 21 percent, depending on the risk status of those screened and the time period (Ostrea, 1992; Yonkers et al., 2010). A U.S. multicenter study investigating the rates of prenatal

drug use by meconium analyses and maternal self-report indicated that 10.7 percent of 8,527 infants screened were exposed to cocaine or opiates (Lester et al., 2001). Although today more people abuse prescription pain relievers than illegal opiates, most research on opiates has involved subjects who are addicted to heroin or receiving opioid agonist therapy.

Fluctuations in an expectant mother's daily heroin use due to voluntary abstinence or lack of access to the drug affect the fetus as well. If abrupt, these changes can precipitate fetal abstinence syndrome, which increases the risk of premature delivery, low birth weight, stillbirth, and sudden infant death syndrome (Joseph, Stancliff, and Langrod, 2000; Table 2). NAS occurs when birth abruptly deprives an infant of opiates it received via the placenta during gestation. NAS can manifest with serious but usually not persistent CNS symptoms, such as seizures, in 2 to 11 percent of neonates (Bandstra et al., 2010).

Heroin exposure decreases birth weight, birth length, and head circumference, but has not been associated with congenital malformations. Prenatal opiate exposure has greater adverse impact than prenatal cocaine exposure on the infant CNS and autonomic nervous system (Das, Poole, and Bada, 2004), with effects that include abnormally high muscle tone, inconsolability, irritability, sneezing, stuffiness, excessive sucking, poor sucking ability, and high-pitched cry (Table 3). The high-pitched cry signifies a CNS abnormality that can result from increased cranial pressure or a congenital malformation. Infants who were exposed to both opiates and cocaine had louder and higher-pitched cries than infants exposed to either drug alone (Lester et al., 2002).

Followup studies of children prenatally exposed to opiates have had sample sizes too small to control for important covariates. Some have found evidence of delayed general cognitive function at 3 years (Wilson et al., 1979), lower verbal ability, and impaired reading and arithmetic skills (Ornoy et al., 2001); others found no cognitive delay at 6 to 13 years of age (deCubas and Field, 1993). Prenatal opiate exposure has frequently been associated with behavioral problems in childhood. One small study indicated that opiate-exposed children were more likely to have ADHD or other disruptive behavior diagnoses at 10 years of age (Hans, 1989).

In summary, studies of prenatal opiate exposure and infants' early cognitive development have yielded mixed results, but there seems to be a pattern linking the exposure to behavioral problems, including increases in ADHD and other disruptive behaviors.

Treatment Recommendations

Since the late 1970s, it has been widely recognized that pregnant women addicted to heroin benefit from opioid agonist therapy with methadone. By stabilizing opiate withdrawal symptoms, such treatment reduces the use of illegal heroin and increases attendance in prenatal care, healthy diet, and other positive maternal health behaviors (SAMHSA, 2005; 2006). Methadone maintenance therapy stabilizes a mother's opiate dose at a low level and reduces physiological withdrawal effects for the fetus. Heroin-addicted women who receive such therapy have infants with higher birth weights and lower rates of intrauterine growth retardation than those who are untreated. However, newborns whose mothers are maintained on methadone have a high incidence of NAS (SAMHSA, 2005; 2006). It is recommended that NAS be treated by giving a very low dose of opiate to the infant and then slowly tapering the dose (O'Grady, Hopewell, and White, 2009).

Studies that have evaluated whether treating expectant mothers with methadone maintenance affects child development are difficult to compare because they have used different methodologies and measurements (Jones et al., 2008). A current NIDA-funded study called MOTHER is designed to address questions left open because of these methodological concerns. MOTHER will also seek to clarify whether methadone or buprenorphine is the superior pharmacotherapy for opioid-dependent pregnant women and their children (Jones et al., 2008). Buprenorphine, an alternative to methadone in opioid agonist therapy, is currently not FDA-approved for use during pregnancy because of a lack of adequate well-controlled studies with pregnant women.

Critical to the success of opioid agonist therapy is the use of supportive services, including behavioral therapy and assistance with domestic violence issues, employment, housing, food, and educational needs. Psychological interventions are indicated to address disruptions in the mother-child relationship, guilt, depression, low self-esteem and victimization, and past trauma.

INTERVENTIONS FOR DRUG-EXPOSED CHILDREN

Most research on intervention services for drug-exposed infants has evaluated intensive home-based services provided to substance-abusing mothers by community nurses. These services are designed to educate and support mothers to improve the home environment, parenting skills, and child development. Strengthen-

A prenatally drug-exposed infant's high-pitched cry may be due to a CNS abnormality that results from increased cranial pressure.

Studies demonstrate that early intervention services improve the home environment and mothers' parenting behavior.

ing maternal functioning has been the goal, because most studies of prenatal drug exposure have found that mothers' level of psychological distress consistently predicts prenatally exposed children's cognitive and behavioral outcomes (Minnes et al., 2010). Few studies have examined interventions that are drug-specific or directed to the infants themselves (Barnard and McKeganey, 2004).

Several studies demonstrate that early intervention services improve the home environment and mothers' parenting behavior. In one, nurses visited substance-abusing mothers and their infants every other week during the first 18 months of the child's life (Black et al., 1994). The nurses guided the women through a curriculum about normal child development, child care, and safety; modeled parent-child activities that promote child development; addressed mothers' concerns, such as relationship problems, affordable housing, and financial issues; and provided information about community resources and advocacy. The mothers who received the intervention were marginally more likely than a control group to be drug-free, keep primary health care appointments, be more emotionally responsive, provide a stimulating home environment, and score lower on a measure of child-abuse potential at the end of the 18-month study period.

As part of the Seattle Birth to 3 Program, paraprofessional advocates visited substance-abusing women and their children weekly for the first 6 weeks after birth, then at least biweekly, depending on need, for 3 years. The advocates worked to establish trusting relationships with the mothers and motivate them to identify and work toward personal goals. They made and monitored followup on community referrals for drug treatment and other services for mother and child, and offered guidance and supervision to ensure that the child was in a safe environment and received appropriate care. At 36 months postpartum, 69 percent of the children receiving the intervention service were in what the research team considered to be an appropriate custody situation relative to their mother's current use of alcohol/drugs (i.e., with mother in recovery for at least 6 months or not with mother unable to maintain abstinence), compared with 29 percent of children in a control group (Ernst et al., 1999).

Butz and colleagues (2001) found that mothers participating in another intensive home nurse intervention program reported a trend toward less parenting stress.

Child Development

Findings regarding the impact of intervention services on child development have been mixed, perhaps because the services usually consist of family case management rather than interventions directed specifically toward the children. Of note, even when children appeared to benefit from an intervention, exposed children in the comparison group who did not receive it usually performed within normal limits on developmental assessments.

Kilbride and colleagues (2000) followed a group of cocaine-exposed infants and their mothers for 3 years, providing intensive family case management, enriched nursery care, and regular evaluations, and found no differences in mean cognitive, psychomotor, or language quotients compared with a group of exposed infants who received only routine followup and a group of unexposed infants. However, at 36 months, verbal scores of the cocaine-exposed infants who received case management were significantly higher than those of the routinely managed children, suggesting that "early intervention may have offset detrimental effects of the crack cocaine environment on verbal development."

In another study, infants who participated in an intensive home intervention program had significantly higher mental and psychomotor development scores compared with control infants (Schuler, Nair, and Kettinger, 2003).

In contrast, Black and colleagues (1994) reported that children receiving home-based intervention services had somewhat higher cognitive scores relative to controls at 6 months of age, but not at 12 and 18 months. Ernst and colleagues (1999) found that the cognitive development of children of substance-abusing mothers who received in-home advocacy services was equivalent at 36 months to that of children whose mothers did not receive the services.

Impact of Child Placement

Drug-exposed infants are often placed outside of the mother's home in kinship, foster, or adoptive care to prevent child abuse or neglect. Researchers have investigated the possibility that such placement might avoid the ill effects of an unstable environment on children's development, but studies show inconsistent results. For example:

- Tyler and colleagues (1997) found that drug-exposed infants who remained with their biological mothers demonstrated better cognitive development at 6 months of age compared with infants placed in the

care of other relatives. In another study by Frank and colleagues (2002), infants in kinship care scored lower on mental development than infants in the care of their biological mothers or in foster care at 6 and 24 months of age (Frank et al., 2002). In the latter study, children in foster care lagged behind children in their biological mothers' care at 6 months, but surpassed them at 24 months.

- Brown and colleagues (2004) observed more positive social-emotional development in 24-month-old cocaine-exposed children placed in nonparental care compared with those in parental care. Within the nonparental care group, those with nonkin caregivers scored higher in mental development, communicative gestures, and positive interactions during feeding than those in the care of relatives.
- Singer and colleagues (2004; 2008) consistently found that over time, cocaine-exposed children fared better in cognitive and language development when placed in non-kin foster care or adoptive homes than when raised in a relative's care or their birth mother's custody. These children experienced better home environments and had more educated, less depressed caregivers than children who remained with their mothers or with relatives (Lewis et al., 2004; Singer et al., 2004; 2008).
- Bada and colleagues (2008) found that instability in living arrangements, such as multiple moves, changes in caregivers, and prolonged involvement with child protection services, predicted negative behavioral outcomes during the first 3 years of life in a cohort of prenatally drug-exposed children. Total behavior problem scores on the Child Behavior Checklist increased 2.3 and 1.3 points, respectively, with each move per year and each year of child protective services involvement.

A Comprehensive Approach

Bandstra and colleagues (2010) have proposed a prevention and intervention model for substance-abusing mothers and their infants that addresses the complex, multiple risk factors associated with maternal drug use. The model proposes the delivery of medical and behavioral health and parenting services to the mother, health and development services to the child, and care coordination and family support to reduce the barriers to accessing services.

Intervention services for this population need to extend beyond infancy and the toddler years, since problems in cognitive, language, and behavioral functioning may persist throughout childhood. Developmental

TABLE 4. Suggested Interventions Following Prenatal Drug Exposure

MATERNAL/CAREGIVER	CHILD
Intensive home-based services <ul style="list-style-type: none"> • Mental health screening • Parenting skills training • Support for substance abstinence 	Specific individual therapy <ul style="list-style-type: none"> • Speech and language • Occupational • Behavioral
Mental health treatment	Early intervention/enrichment
Substance use treatment	Ongoing cognitive and behavioral assessment

assessment and intervention should continue during the preschool and school years, when children may benefit from enriched educational programs and screening for special education services. Problems can compound when cognitive demands increase during the early school years. Other critical transitional periods occur in the first, fourth, and sixth or seventh grades, when subtle learning or behavior problems may become more evident and lead to functional impairments (Weitzman et al., 2002). Externalizing behavior problems and inattention in particular should not be ignored, as they are known to interfere with school achievement, school completion, and the development of healthy relationships.

Parents should be trained in the skills necessary to address behavior problems throughout childhood to prevent more serious disruptive and risky behaviors in adolescence and young adulthood. Moreover, birth mothers are likely to need ongoing intervention to maintain sobriety and to address mental health symptoms and parenting. As the effects of prenatal drug exposure and their relationships with environmental factors become more clearly understood, more specific early intervention programs for drug-exposed children targeting areas of development that are known to be at risk should be developed and rigorously evaluated (Table 4).

CONCLUSION

Substance use during pregnancy can affect the developing fetus both directly, through passage of the drug through the placenta, and indirectly, through poor maternal health habits and environmental conditions. Numerous well-designed studies indicate that specific learning and behavior problems may result from prenatal exposure to tobacco and illicit drugs in combination with negative environmental conditions postpartum. Longitudinal studies indicate that some of the negative effects of

Intervention services for substance-abusing mothers and their children need to extend beyond infancy and the toddler years.

Pregnancy is a unique time when a woman may seek treatment out of concern for the health and well-being of her child.

cocaine, tobacco, and marijuana exposure persist into later childhood and adolescence. Although some early CNS symptoms remit over the first year of life, they may be precursors to later developmental outcomes.

Developmental outcomes of prenatally drug-exposed children are determined by factors including the specific drug or drugs, dosage, and timing of prenatal exposure as well as pre- and postnatal environmental conditions, including continued caregiver drug use, psychological symptoms, quality of the home environment, postnatal exposures to lead and other toxins, caregiver stability, and type of caregiver. The effects of negative environmental conditions associated with low SES may sometimes overshadow the effects of prenatal drug exposure.

Pregnancy is a unique time when a woman may seek treatment out of concern for the health and well-being of her child. To prevent postpartum substance abuse relapse, interventions should focus on cessation rather than temporary abstinence. The ongoing consequences of parental substance abuse on child growth and development should be emphasized, and followup should continue into the postpartum period (Muhuri and Gfroerer, 2009). Interventions that reduce substance abuse in the general population are now being investigated in pregnant substance abusers with promising results. The use of CM appears to increase treatment retention and

prolong abstinence in pregnant women with cocaine, opiate, and nicotine dependence. Some medications used to treat addiction, such as methadone, can be relatively safe for pregnant women and their babies. However, the safety and effectiveness of NRT for pregnant smokers requires further investigation.

Additional research is needed on the development of specific interventions for drug-exposed infants and children. Each child must be individually assessed for his or her cumulative risk factors, domain of developmental difficulty, and the quality of the caregiving environment. Developmental outcomes may be optimized by interventions that occur early in life, are tailored for specific problem areas, and target caregivers' level of stress, mental health functioning, continued substance abuse, and parenting interactions.

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