Infants of Drug-dependent Mothers

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Objectives

After completing this article, readers should be able to:

1. Recognize the effects of maternal substance use on the developing fetus, neonate, and growing child.
2. Describe the effect of maternal substance use on the mother-infant dyad.
3. Discuss the factors that may serve as mediators and moderators of the effects of maternal substance use on the child.
4. Understand the complex context within which the substance-abusing mother and her infant must be considered.
5. Evaluate and manage the substance-exposed dyad.

Introduction

In utero substance exposure continues to pose a public health and societal dilemma. Prenatal exposure to legal and illegal substances is a substantial and preventable risk factor for developmental alterations in infants. Intrauterine substance exposure affects more newborns than many other common major medical conditions, making the problem of the substance-exposed infant an inevitable concern for all pediatricians. Of the 4.3 million infants born annually in the United States, between 800,000 and 1 million are born to women who used drugs during pregnancy; approximately 1 in 9 infants is exposed to alcohol, 1 in 5 is exposed to nicotine, and 1 in 20 is exposed to illegal drugs. Opioid use during pregnancy is a growing concern due to the rise in abuse of prescription opioids (eg, hydrocodone, oxycodone) in women of childbearing age.

Currently, 5.4 million children live with a parent who has a substance use disorder, and 3.4 million live with a mother who has a substance use disorder in the United States. (1) Resumption of drug use following childbirth is an additional concern; in a recent report, cigarette, alcohol, binge alcohol, and marijuana use rates were higher in women with a child younger than 3 months of age (20.4%, 31.9%, 10.0%, and 3.8%, respectively) compared with rates of use in the third trimester of pregnancy (13.9%, 6.2%, 1.0%, and 1.4%, respectively). (2) Pregnant adolescents represent a special population because young women ages 15 to 17 years report a higher rate of use of illicit drugs and misuse of prescription drugs than same-age nonpregnant peers. (3) Even a woman who has decided not to use substances during a pregnancy may do so inadvertently during the early stages before the pregnancy is recognized.

Initial studies examining specific effects of maternal drug use on the infant did not account for the wide spectrum of associated risk factors for birth outcomes, particularly psychosocial risk factors, or failed to estimate the proportion of risk attributable to a presumed biologic mechanism versus these other factors. For these reasons, the traditional teratology model has been replaced by a transactional or multiple-risk model in which the psychoactive substance exposure is considered a marker or risk indicator in a contextual framework to explain the outcome of the prenatally substance-exposed newborn.

Multiple risk and protective factors have been investigated for their roles as mediators or moderators of the effects of maternal drug use on the developing child. Factors such as amount of drug, timing of use during gestation, use of several (illicit and licit) substances, and issues related to the postnatal caregiving environment need to be considered. Medical complications in the neonatal period, such as prematurity and low birthweight (LBW), can affect the expression of the effects of the substances in the infant and child. Furthermore,

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substance abuse frequently is associated with multiple social, psychosocial, behavioral, and biomedical maternal and child risk factors, including poverty, stress, psychiatric comorbidity, violence exposure, lack of social support, physical abuse, sexually transmitted infections, poor nutrition, and poor medical care.

The prevalence of psychiatric disorders among the population of substance-dependent women is of particular importance because these disorders frequently warrant the need for prescribed medications that have psychoactive effects. It is estimated that nearly half of all substance-abusing pregnant women have a coexistent axis I disorder, as described in the *Diagnostic and Statistical Manual of Mental Disorders*. (4) Depression is especially prevalent in drug-dependent pregnant populations, and anxiety and personality disorders are frequent comorbid conditions. Psychotropic medications are prescribed for women nearly twice as often as they are for men, and these maternal medications can affect infant functioning, as can the disorder for which the medication is prescribed.

The purpose of this review is to examine the current and relevant scientific literature regarding the effects of maternal substance use on the developing child and the factors that may serve as mediators and moderators of the effects of maternal substance use on the child as well as provide some recommendations for clinicians evaluating and treating substance-abusing mothers and their substance-exposed infants. The goal is to make clinicians aware of the severity of the potential effects of maternal drug use on the developing child, the myriad and largely indefinable mechanisms by which maternal substance use may affect the infant, and the importance of early and adequate diagnosis and treatment of the substance-exposed mother-child dyad. Improving the clinical approach to these patients may allay the negative short- and long-term consequences of maternal drug use on the developing child.

Effects of Maternal Drug Use on the Developing Fetus

Research on the pediatric effects of maternal drug use poses complex challenges because it often is difficult to make this correlation accurately, given the multiple biologic and psychosocial factors that may act as mediators or moderators of the effects of drugs on the infant. Animal models traditionally have been used to define effects of in utero substance exposure. However, generalizing results from animal studies to humans is hampered by differences in timing of brain maturation. Drugs of abuse cross the placenta and may influence early development through several pathophysiologic pathways. Their teratologic effects are dependent on the intersection of the exposure, the temporal and regional emergence of critical developmental processes, and the sensitivity of the developing specific brain structure or neural circuit to the drug. Exposure during the first half of gestation may affect processes related to cytogenesis and histogenesis, whereas effects during the second half of gestation may compromise progressive events (eg, brain growth and differentiation) and regressive events (eg, programmed cell death). Alterations of these events have the capacity to modify brain development as well as the ability of the developing brain to recover from injury. (5)

Drugs can affect fetal brain development through indirect and direct mechanisms. Indirect effects may be due to variations in maternal physiology and placental functioning. For example, potential indirect mechanisms of nicotine exposure include maternal and fetal undernutrition caused by smoking-induced anorexia, hypoxia due to increased carboxyhemoglobin and vasoconstriction, placental hypertrophy, and reduced transplacental transport of nutrients. Direct effects of the drugs include alterations in the development of neurotransmitter and neuromodulator systems, many of which are present during early embryogenesis and have pleiotropic effects on brain development.

Marijuana produces its psychoactive effects through specific brain cannabinoid receptors that regulate multiple developmental processes such as neuronal proliferation, migration, differentiation, survival, and synaptogenesis. Methamphetamines are potent sympathomimetic agents that exert their action by releasing dopamine and serotonin, blocking monoamine reuptake mechanisms, and inhibiting monoamine oxidase, resulting in increases in synaptic concentrations of the neurotransmitters dopamine and norepinephrine. Opioids are metabolized into morphine, and mechanisms of action are mediated by opioid, principally mu, receptors. Opioid receptors are present in several areas of the brain, and several mechanisms could be affected by opioid exposure. Morphine can affect migration and survival of neurons in rats (6) and increase apoptosis in human fetal microglia and neurons. (7)

Fetal programming is a mechanism that has been gaining consideration in linking adverse events occurring in utero and related outcomes (eg, enhanced risk for medical, behavioral, or psychiatric problems) in later life. Fetal programming, originally known as the "Barker" or "fetal origins hypothesis," (8) assumes that nongenetic factors such as unfavorable intrauterine conditions can permanently organize or imprint physiologic and behav-

ioral systems and disrupt normal fetal functioning, which may result in later disorders. This mechanism has been implicated in the causal pathway underlying long-term deficits observed in alcohol-exposed offspring. (9)(10) Research in animals and emerging studies in humans suggest that epigenetic changes in regulatory genes and growth-related genes play a significant role in fetal programming. These epigenetic changes are heritable but reversible alterations in gene expression caused by mechanisms other than changes in DNA sequence. It is believed that epigenetic changes can persist through multiple cell divisions and cell differentiation and even be passed on to progeny.

Based on this theory, maternal substance use could produce significant changes in the regulation of various offspring genes that may be involved in diverse functional systems through epigenetic mechanisms. For example, a study in mice indicated that maternal cocaine exposure during the second and third trimesters of gestation resulted in multiple alterations in the methylation states of offspring DNA with persistent effects, suggesting that maternal cocaine use could produce potentially profound structural and functional modifications in the epigenomic programs. (11)

How these potential mechanisms contribute individually and collectively to altered brain growth and maturation has not been well established, but it is known that most drugs act through different mechanisms with individual developmental consequences. In the case of cocaine, the drug crosses the placenta and acts at the presynaptic level, affecting the fetus by blocking the reuptake of the neurotransmitters dopamine, norepinephrine, and serotonin; elevating circulating catecholamine concentrations; and causing vasoconstriction in the fetoplacental unit. Cocaine affects neuronal formation and proliferation and disrupts neuronal migration, resulting in changes to cortical architecture. In addition, cocaine has been implicated as an intrauterine stressor that alters fetal programming, changing developmental trajectories. (12)

Finally, maternal and fetal genotypes and ecogenetic considerations (ie, the concept that the combination of a particular susceptible genome and drug/toxin exposure is necessary for adverse effects to become apparent) also may affect outcome.

Effects of prenatal exposures have been shown to be sex-specific. For example, prenatal morphine exposure induces physiologic and behavioral changes involving the stress response in the adult rat that differ between sexes. (13) Prenatal exposure to alcohol alters hypothalamic-pituitary axis responsivity differently in male and female offspring in both animals and in humans. (14) Prenatal exposure to cigarettes increases the risk for developmental psychopathology in human boys but not girls. (15) Male infants have been found to be more vulnerable to maternal methadone use. (16)

Clinically Observable Effects of In Utero Substance Exposure on the Newborn

Regardless of mechanisms of harm and confounding by other risk factors, it is accepted that neonates exposed to substances during pregnancy are at increased risk for a variety of conditions that portend future developmental and other difficulties. The following are the most widely recognized clinical conditions associated with in utero drug exposure.

Drug-related Adverse Birth Outcomes

Nearly all drugs of abuse have been associated with drug-related adverse outcomes such as preterm birth, LBW, and growth restriction. Many substances used by drug-dependent women can shorten gestation and impair fetal growth without resulting in preterm deliveries or LBW, as traditionally defined.

Neonatal Abstinence Syndrome (NAS)

NAS is a group of signs indicating dysfunction of respiratory, gastrointestinal, or nervous system regulation that develops after the cessation of the maternal drug supply at delivery. Neonatal withdrawal is associated primarily with opiates, sedative-hypnotics, and alcohol, but most psychoactive drugs used during pregnancy, including antidepressants, antipsychotics, and nicotine, can produce "withdrawal-like symptoms" in the newborn. Other than for opioids, there are difficulties in ascribing any signs of neonatal withdrawal to any particular substance because algorithms used to define NAS are specific to neonatal opioid withdrawal, and signs of withdrawal to other substances are likely to be qualitatively and quantitatively different. Nonopioid substances that have been described as having specific abstinence syndromes generally present with infants exhibiting signs that are described by the Finnegan Neonatal Abstinence Scoring System. (17) However, most newborns exposed to these substances do not reach cut-off values for pharmacologic treatment and may have symptoms not included in the Finnegan Scoring System. In addition, generally no specific treatments for nonopioid-exposed infants exist. The infant's display of NAS can affect maternal functioning and interaction with the newborn, further compounding the threat to progressive neurode-

velopment. Other factors, such as prematurity, can affect the course and presentation of NAS. (18)

Neurobehavioral and Regulatory Impairment

Signs displayed by drug-exposed infants that reflect difficulties in their ability to maintain organized behavioral and physiologic responses to external or internal stimulation indicate neurobehavioral and regulatory impairment, alternatively labeled homeostatic instability or dysregulation. Frequently observed neurobehavioral problems of substance-exposed infants include tremors; irritability; difficulty being consoled; hypertonicity; increased startle response or exaggerated Moro reflex; and respiratory, feeding, and sleeping problems. Behavioral assessment of signs of regulatory dysfunction displayed by the substance-exposed infant has been facilitated by using the Neonatal Intensive Care Unit (NICU) Network Neurobehavioral Scale. (19) This scale, developed as a neurobehavioral assessment tool for the at-risk infant, is used to evaluate how stressors, such as in utero substance exposure, affect infant self-organizing neurobehavioral capacities. A systematic assessment of the neurobehavioral functioning of the substance-exposed neonate in the domains of state control regulation, motor and tone functioning, reactivity to sensory stimulation, and autonomic signs of stress, can define areas of concern that can be used to design an individualized care plan. (20)

Structural Changes

Congenital anomalies have been variably reported for almost all drugs of abuse. Aside from alcohol, which has a clearly defined pattern of birth defects, large outcome studies evaluating the correlation between congenital anomalies and periconceptional drug use generally find no positive associations. (21) Advances in brain magnetic resonance imaging-based methods have identified some alterations of brain structures and patterns of functional activation in offspring of mothers who used licit (eg, alcohol and tobacco) and illicit (eg, cocaine, methamphetamine, marijuana) drugs during pregnancy. Although these findings are limited by the complexities of separating the specific effects of each drug from other confounding variables and the impracticality of using such methods in the clinical setting, particularly during the neonatal period, these methods may advance the understanding of the underlying structures affected by prenatal drug exposure to improve diagnosis and provision of therapeutic resources for affected infants, children, and young adults.

Postnatal Problems due to Environmental or Caregiving Deficiencies

Infant neurodevelopmental or behavioral problems can be created by an overstimulating or insensitive environment or a caregiver's style of interaction. When caregivers are not trained or able to interpret and respond to physiologic or behavioral signs of dysregulation created by external or internal stimuli, the caregiver's actions or interactive style can impair the recovery of the infant and perpetuate dysregulated responses. This impairment, in turn, can affect basic functions such as feeding, sleeping, and interactive patterns that may contribute to altered developmental trajectories. Neurodevelopmental difficulties also can be caused or exacerbated by maternal psychopathology or postnatal drug use, which may provide the infant with further postnatal passive or active exposure to substances (eg, secondhand smoke or substances via human milk).

The Effects of Individual Substances on the Neonate

Although it is difficult to ascribe any particular symptom to any particular substance, because most overlap (Table) and are nonspecific, full appreciation of the complexities and clinical status of the exposed neonate requires consideration of the effects of individual substances.

Table. Observed Effects of Substance Abuse in the Newborn

	Nicotine	Alcohol	Marijuana	Cocaine	Opioids	PCP	Methamphetamine	Benzodiazepines
Prematurity	Yes	Yes	No	Yes	Yes/No	No	Yes/No	Yes
Low birthweight	Yes	Yes	No	Yes	Yes/No	No	Yes	Yes
Neurobehavioral symptoms	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
NAS	Yes	Yes	No	No?	Yes	Yes/No	Yes?	Yes
Congenital malformations	Yes/No	Yes	No?	Yes/No	No	Yes	Yes?	Yes/No

Yes/No=both have been reported, ?=controversial or unclear findings, NAS=neonatal abstinence syndrome, PCP=phencyclidine

Nicotine

Nicotine has been described as a neuroteratogen that compromises critical neural pathways in the developing brain. (22) Nicotine crosses the placenta, and the fetus is exposed to concentrations that are 15% higher than in the maternal bloodstream. Cigarette use also involves exposure to substances that interfere with oxygen delivery and use, such as carbon monoxide and hydrogen cyanide; these additional factors may participate in the overall effects of smoking. Nicotine exposure during gestation includes effects that have been found to be related to secondhand smoke as well as nicotine replacement therapies. (23) Neurobehavioral symptoms described in exposed neonates include impairment of arousal, irritability and hyperexcitability, hypertonicity, and tremors. (24)(25)

Reports of sporadic congenital anomalies associated with nicotine consist principally of higher incidences of orofacial clefts, neural tube defects, and cryptorchidism, although large-scale studies have found no significant increase in gross malformations. (26) Prenatally nicotine-exposed infants are at increased risk for preterm birth and sudden infant death syndrome (27) as well as fetal growth restriction, which has been linked to subsequent development of both neonatal and adult disease. (28) Dose-dependent LBW has been associated with maternal smoking. (29) Heavily nicotine-exposed infants have been described as having withdrawal syndromes. (30)(31)

Alcohol

Alcohol exposure during gestation is a significant risk factor for poor infant outcomes. Alcohol passes through the placenta, and the amniotic fluid is a reservoir for ethanol, which increases availability of the drug to the fetus. Maternal alcohol use can produce preterm birth, LBW, and fetal alcohol spectrum disorder. Fetal alcohol syndrome is characterized by specific facial features, growth deficiency, central nervous system abnormalities, behavioral abnormalities, and intellectual disability. (32) A neonatal alcohol withdrawal phenomenon has been described in children born to alcoholic mothers and includes jitteriness, irritability, seizures, opisthotonus, abdominal distention, (33)(34) excessive mouthing movements, and reflex abnormalities. (35)

Marijuana

Delta^9-tetrahydrocannabinol is the major psychoactive ingredient in cannabis. Cannabis constituents cross the placenta and are stored in amniotic fluid. Prolonged fetal exposure can result from regular marijuana use. Minor physical anomalies (ocular hypertelorism and epicanthus) have been reported in heavy users of cannabis, but there is a lack of a definitive relationship between physical anomalies and prenatal cannabis exposure in general. Neurobehavioral effects of in utero cannabis exposure range from mild deficits in visual functioning, heightened tremors, startling, jitteriness, hypotonia, and lethargy (36) to difficulties with arousal, regulation, and excitability. (37) Although shorter gestational periods have been reported among heavy marijuana users, (38) neither LBW nor preterm birth have generally been reported.

Cocaine

Cocaine-exposed infants are at risk for preterm birth and LBW. Neurobehavioral signs at birth include jitteriness and tremors, high-pitched cry, irritability, excessive suck, hyperalertness, autonomic instability, (39) hypertonicity, and excitability. (40) Congenital anomalies have been reported previously in cocaine-exposed infants, but larger and more recent studies have disputed those findings. (39) A dose-response relationship for a negative association with motor and state regulation capabilities has been reported. (41)

Opioids

Opioids are narcotic, analgesic substances that have morphine-like effects and include narcotic pain killers, heroin, and methadone, a synthetic opiate with similar pharmacologic properties to morphine that is used to treat individuals who have opiate addictions. Most studies report increased preterm birth and LBW related to opioid use, although few have controlled for associated risk factors. Those that have done so generally report no independent relationships between opiate use and growth parameters. The most notable opioid effect on the neonate is NAS, which may include tonal problems, tachypnea, feeding and sleeping problems, fever, and seizures among its signs. The tool used most commonly to evaluate opioid-related NAS is the Finnegan scale. (42) Evaluation of the opioid-exposed newborn using this scale is recommended every 3 to 4 hours during hospitalization, and surveillance should last for several days after birth. The scale contains 31 weighted (depending on symptom and severity) items. Opioid agonist pharmacotherapy is recommended for infants who have Finnegan scores above a threshold level.

Phencyclidine

Infants exposed in utero to phencyclidine (PCP) have been reported to display dysmorphologic features that

consist of microcephaly (43) and alterations in facial features. (44) Described neurobehavioral symptoms after delivery consist of decreased attention, high-pitched cry, poor visual tracking, coarse flapping tremors, lethargy, nystagmus/roving eye movements, poor feeding, and altered newborn reflexes. (43)(45) Although infants exposed to PCP generally are smaller and have lower gestational ages than nonexposed infants, PCP exposure is not associated with LBW or preterm birth. (46) An NAS has been described (47) and disputed (48) for PCP-exposed infants.

Methamphetamines

Despite concerns about infants exposed to this drug as rates of usage in the United States increase, there is a general dearth of reports involving in utero exposure. Isolated cases of cardiac defects, cleft lip, and biliary atresia have been reported. (49) Use during pregnancy also has been associated with increased rates of fetal distress and growth restriction, (50) resulting in small-for-gestational age size at birth. (50)(51)(52) Methamphetamine exposure has been associated with preterm birth, (50) but this linkage has been disputed more recently. (52) Neurobehavioral patterns of decreased arousal, increased stress, and poor quality of movement (53) have been described, as has a withdrawal syndrome in a few infants (4%). (54)

Benzodiazepines

One of the most commonly prescribed class of drugs during pregnancy, despite the absence of complete knowledge of their potential adverse effects, benzodiazepines also are commonly abused licit drugs, and exposure often is unrecognized due to inconsistent screening policies. Benzodiazepines cross the placenta and accumulate in the fetus to varying degrees, depending on the specific drug and its properties. Withdrawal phenomena have been reported in exposed infants. Signs include hypoventilation, irritability, hypertonicity, and "floppy infant syndrome," particularly after use in late gestation. (55)(56) These symptoms can appear within a few days to 3 weeks after birth and can last for several months. (57) There has been variable reporting on the relative risk of congenital anomalies in this group of infants. An increased risk of orofacial clefts was described in early case-control studies and refuted in later cohort studies. (58) Benzodiazepines appear to increase the risk of preterm birth and LBW. (59)

Management

The drug-dependent mother and her infant are a complex and highly vulnerable dyad that present a challenge to any clinician. Due to the often multiple negative experiences and maladaptive behaviors of the mother and the frequently confusing constellation of signs and symptoms of abstinence and neurobehavioral dysregulation of the infant, the dyad commonly is "out of sync" or "not bonding." Thus, they require a caring and well-trained clinician to ensure a successful neonatal adaptation and prevent the initiation of altered developmental and interactional trajectories. Provision of optimal care for the pair involves appropriate identification of the maternal substance abuse and other difficulties, careful and frequent observation of the infant, and delineation of individualized care plans for the dyad. Lack of acknowledgment of the maternal addiction and its implications for the newborn, usually stemming from lack of knowledge of addictions in general or lack of available resources postdischarge, can affect the prognosis for the dyad negatively.

All substance-exposed infants should receive supportive care and evaluation for signs and symptoms of evolving NAS and other regulatory problems. Standard supportive care for the exposed infant should include a quiet environment and gentle handling, swaddling, small and frequent feedings, and pacifier use. The individual functioning of each infant should be assessed thoroughly, evaluating the ability to regulate sleep/awake states; autonomic, sensory, motor, and interactive capacities; and displayed behaviors. Important behaviors include responses and sensitivities to auditory, tactile, and visual stimuli; motor capabilities; tremors and jitteriness; and style of communication, including eye contact, ability to calm with intervention, ability to signal needs, and signs of stress or abstinence. The infant's capacities and difficulties in each area should be addressed in individual care plans as well as in maternal-infant care.

For infants experiencing significant NAS symptomatology, pharmacotherapy is warranted. Medications used to treat the neurobehavioral symptoms related to prenatal exposure to psychoactive drugs vary widely among institutions. The most commonly used first-line medications for opioid withdrawal are opioids (oral morphine solution, tincture of opium) and methadone. (60) A major review advocates opioids as the drug of choice for neonatal opioid withdrawal. (61) For polydrug-exposed infants, commonly employed medications are opioids, phenobarbital, and methadone. (60) Weight-based versus symptom-based treatment strategies can be employed, and examples of both have been described. (62)(63) Little empirically based evidence supports the

use of one medication or one treatment strategy over the other, reflecting a paucity of randomized studies in this area. At the time of this writing, newer agents for the treatment of NAS, such as clonidine (64)(65) and buprenorphine, (66) are being explored and may have a role in the management of NAS.

By examining the newborn in the presence of the mother and evaluating her perceptions and responses to newborn signaling, the clinician can assess and demonstrate the infant's physiologic competencies and weaknesses while simultaneously evaluating maternal responsiveness and comprehension. Mothers and other caregivers can be taught to provide appropriate environments (eg, not over- or understimulating) for the infant. Infants who have significant NAS require medication and prolonged hospitalization. In situations where mothers are able to stay with their infants or visit regularly, this period can be used as a time of prolonged evaluation of the dyad and an opportunity to provide ongoing parenting support and instruction. Teaching of simple concepts, such as the importance of infant sleep, cueing, and schedules, can provide a basis for improved parenting skills in the mother as the child grows. Maternal satisfaction with the diminution of NAS symptoms associated with her handling can allay some guilt and depression. Interventions for the drug-dependent mother and exposed infant have been described (67) and are useful in the care of the dyad for providing a basis for improved parenting and infant/child development.

Drug-dependent women also require thoughtful and careful evaluation because their needs can be as complex as their difficulties. Evaluation for mood or other psychiatric disorders, emotional availability to the newborn, violence exposure, community support systems, and history of previous pregnancy outcomes is necessary. Addiction is a chronic disorder and must be addressed as such; all drug-using women should be referred to appropriate substance abuse treatment that will accept the infant. For women in treatment, conference (after consent) with treatment counselors to determine ongoing care plans is important. Mood disorders or other psychiatric comorbidity should be evaluated and addressed in ongoing postpartum care, particularly because women who have depression are at increased risk for postpartum depression. Postpartum guilt and anxiety, particularly for women who have infants experiencing NAS, is common, can interfere with dyadic communication, and must be gently addressed and monitored. Prejudicial or punitive attitudes, negative stereotyping, and conflicting advice have no place in the care of postpartum drug-dependent women because such attitudes only drive them away from treatment and other beneficial encounters at a time when treatment is most needed from those professionals most poised to help. Similarly, caregivers of the infant must refrain from stereotypical or prejudicial attitudes toward the mother. Referral to child protective or other

Summary

- Nearly any psychoactive licit or illicit substance consumed by the pregnant woman is likely to result in enhanced risk of medical, developmental, and emotional/behavioral disability in the developing infant/child. These risks can be compounded by biologic and psychosocial factors associated with maternal addiction.
- Drug-dependent women do not use substances in isolation and they cannot escape the myriad complications of their internal and external environments and the attendant risks to the developing fetus and infant.
- The developmental trajectories of fetuses exposed to psychoactive substances may be altered by many factors, including disruption to neuroendocrine and neurotransmitter system development and fetal programming via stress hormone changes, resulting in altered set points for physiologic, metabolic, and behavioral outcomes. (69)
- Epigenetic models of developmental theory examining the intersecting influences of genes, physiology, and behavior with the physical, cultural, and social environment as well as other mechanisms have been implicated in the alteration of developmental trajectories. (5)
- These effects occur through the programming of cell fate and differentiation, in defining ultimate activity levels of specific functional systems, and in mediating environmental modulation of genetically based developmental programs. In this context, maternal substance use during gestation may directly or indirectly derail normal development by adversely modifying fetal/neonatal gene expression, resulting in disruption in brain development.
- The consequences of drug exposure can be seen at birth but sometimes do not emerge until later in life and may be produced at doses that are relatively harmless for adults.
- The role for all clinicians in the comprehensive care of the substance-exposed neonate should include thorough, comprehensive, and individual evaluation of the infant, the mother, and their interaction. Only through a willingness to understand and treat the mother who has drug addiction and the exposed infant as a pair, which may involve the extension of the boundaries of pediatric care, can we provide optimal care for substance-exposed infants, perhaps the most poorly understood, marginalized, and vulnerable segment of the pediatric population.

monitoring services, when appropriate, may be necessary, particularly for women who have positive urine toxicology screening results that indicate recent drug use at delivery or substance-abusing women not in drug treatment. However, these services are not warranted for most abstinent and stable methadone-maintained women enrolled in comprehensive substance abuse treatment.

Women receiving methadone maintenance may have difficulties with oversedation in the postpartum period due to changing medication needs and pain control and should be assessed for such reactions by pediatric clinicians who are likely to observe them. Communication with obstetric and mental health professionals is important in these cases. Breastfeeding is not contraindicated for women receiving methadone maintenance therapy but may not be advised for women relapsing to drug use close to term, women not in substance abuse treatment, or women experiencing difficulties in maintaining sobriety in an outpatient setting. Each woman desiring lactation must be evaluated individually. (68)

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PIR Quiz

Quiz also available online at http://pedsinreview.aappublications.org.

1. You are seeing a family who is considering adopting a newborn boy who has been exposed to drugs in utero. They ask for information about how drug exposure affects medical and behavioral issues as children mature. Your *best* response is that:

   A. Drug exposure effects manifest through physiologic rather than genetic mechanisms.
   B. Drug exposure in the third trimester is the most detrimental to long-term outcome.
   C. Effects of drug exposure in utero generally are the product of polydrug exposures and factors related to substance use.
   D. There is a common mechanism by which drugs exert their intrauterine effects.
   E. There is no difference in effects of drug exposure based on the sex of the fetus.

2. You are seeing a newborn in the nursery whose mother took prescribed benzodiazepines during pregnancy. One likely manifestation of benzodiazepine exposure in this baby is:

   A. Cardiac defects.
   B. Elevated bilirubin concentrations.
   C. Hyperventilation.
   D. Large-for-gestational age birthweight.
   E. Withdrawal symptoms lasting for several months.

3. An infant was born at term with birthweight 2.1 kg. The *most* likely intrauterine drug exposure associated with this infant's birthweight is:

   A. Diazepam.
   B. Fentanyl.
   C. Marijuana.
   D. Oxycodone.
   E. Phencyclidine.

4. An infant in the newborn nursery has tremors, poor feeding, and increased tone and is not easily consoled. An associated symptom of neonatal abstinence syndrome that might manifest in this infant is:

   A. Cardiac arrest.
   B. Hyperbilirubinemia.
   C. Hypothermia.
   D. Hypotonia.
   E. Seizure.

5. A 3-year-old boy has been asked to leave several child care settings because of his extreme hyperactivity and inattention. His birth weight was 2.3 kg. His growth parameters show height at the 20th percentile, weight at the 10th percentile, and head circumference less than the 3rd percentile. He is just beginning to speak a few words, and his mother relates that his developmental skills are similar to the skills of his 18-month-old brother. Magnetic resonance imaging of his brain shows absent corpus callosum. The intrauterine drug exposure *most* likely associated with these findings is:

   A. Alcohol.
   B. Benzodiazepines.
   C. Cocaine.
   D. Marijuana.
   E. Methamphetamines.

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