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Prenatal Substance Exposure: Maternal Screening and Neonatal Identification and Management

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Objectives After completing this article, readers should be able to:

1. Describe physical and neurobehavioral problems of neonates who were exposed to maternal substances of abuse.
2. Delineate the purpose of universal screening.
3. Characterize the areas of inquiry represented by the 4P's Plus assessment.
4. Describe the significant features of neonatal abstinence syndrome.
5. Delineate supportive measures for management of infants exposed prenatally to substances of abuse.

Introduction

Over the past 2 decades, neonatologists have cared for growing numbers of infants who were exposed passively in utero to a variety of licit and illicit drugs consumed by their mothers (Table 1). These infants present a complex web of medical and social problems. Information from the recently published *National Household Survey on Drug Abuse: 1996 to 1998* indicated that 45% of women of childbearing age in the United States had used an illegal drug over their lifetime. Within a subsample of 1,249 pregnant women, 3% currently were using an illicit substance, and 54% currently were using alcohol, tobacco, or both.

Implications of Prenatal Substance Exposure

Substances that act on the central nervous system usually are highly lipophilic and of relatively low molecular weight (<1,000 g/mol). These characteristics facilitate crossing from maternal to fetal circulation, and there is rapid equilibration of free drug between mother and fetus. Once drugs cross the placenta, they tend to accumulate in the fetus. Most studied drugs have a longer half-life in the fetus than in the adult because the enzymes involved in the metabolic process of glucuronidation and oxidation are not fully developed in the fetus. In addition, the immature renal function of the fetus may delay the excretion of drugs that have been metabolized to an excretable form.

Neonates passively exposed to maternal substances of abuse demonstrate both physical and neurobehavioral difficulties. There is an increased rate of intrauterine growth retardation and microencephaly. Interacting with the direct effects of alcohol and illicit drugs is the greater likelihood of drug- or alcohol-using women to smoke cigarettes, have infections complicating their pregnancy, and have inadequate prenatal care. In addition, cocaine and amphetamines have a direct effect on the uterus, causing contractions. Thus, it is not surprising that there is a high rate of prematurity among prenatally exposed infants.

In addition, children who have been exposed prenatally to substances of abuse may suffer a range of physical problems, often based on the direct toxic effect of the substance (such as alcohol) or the interruption of adequate blood flow to developing organs caused by substances such as cocaine or amphetamines. Alcohol can produce structural changes in the face and head; cocaine or methamphetamine use during pregnancy can result in limb reduction deformities. Prenatal exposure to alcohol or other drugs also may interfere with neonatal neurobehavior, especially in the arenas of motor functioning, orientation (affecting the newborn's ability to respond to auditory and visual stimuli), and state regulation (state changes tend to be abrupt and inappropriate).

Over the long term, children who have fetal alcohol syndrome (FAS) have intelligence

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Table 1. Annual Estimates of United States Neonates Prenatally Exposed to Substances

Tobacco	1,203,000
Alcohol	823,000
Illicit drugs	202,000

quotients (IQs) that range from approximately 20 to 105, with a mean of 68, and many alcohol-exposed children who do not have the characteristic FAS features have consistently lower IQ scores than nonexposed children. Importantly, even alcohol-exposed children who have “normal” IQs demonstrate difficulty with behavioral regulation, impulsivity, social deficits, and poor judgment, causing difficulties in day-to-day management in the classroom and home. Although some deficits seen in alcohol-exposed children may stem from the family environment, human studies have demonstrated that prenatal alcohol exposure can produce a broad spectrum of significant abnormalities of various brain structures, including the frontal lobes, limbic system, hippocampus, amygdala, basal ganglia, and corpus callosum as well as ventricular and cerebellar anomalies. These abnormalities translate into significant neurocognitive deficits in the older child.

It has been more difficult to discern the exact impact of prenatal exposure to illicit drugs on long-term development of the child. However, biochemical research has begun to gather evidence of possible linkages between behavior regulation problems and prenatal exposure to cocaine, heroin, amphetamines, and other illicit drugs. For example, cocaine blocks the reuptake of the biogenic amines serotonin, dopamine, and norepinephrine, thereby increasing the availability of these transmitters at the receptor sites and producing the cocaine “high” by increasing neuronal excitability. With chronic exposure, a dampening effect may be produced by downregulation of the postsynaptic dopaminergic receptors in the brain. Many of the common illicit substances have an impact on the dopamine system. Thus, children exposed to marijuana, cocaine, heroin, or other illicit substances may suffer a wide range of mild-to-severe physical and neurobehavioral problems.

Most importantly, there is clear evidence that recognizing the substance-exposed infant and implementing early intervention services for the child and mother are

keys to minimizing the acute and long-term effects of prenatal substance exposure. Thus, even if the infant exhibits no clinically significant difficulties in the neonatal period, identification of the substance-exposed infant can improve his or her long-term outcome.

Maternal Screening

Barriers to Screening

Several studies have explored the barriers to screening for substance use in pregnant and parenting women. When screening for alcohol or drug use is implemented in clinical practice, it often focuses on targeted populations rather than the general population. Clinicians often state that they can “tell” who is an alcoholic or drug user by looking at the person. A 1990 study of substance use in pregnancy in Pinellas County, Florida, revealed that although the overall use of licit and illicit substances was approximately 15% in African-American and Caucasian women within the population, urine toxicology screening or intensive evaluation for substance use was ten times more likely ordered for African-American than Caucasian women. This study showed that physicians’ perception of women at high risk for substance use in pregnancy was based on two factors: race and social class. More recent similar studies have documented these same biased selection criteria driving screening and assessment for alcohol and illicit drug use in pregnancy in North Carolina, Illinois, and Iowa.

The Purpose of Universal Screening

Universal screening of the postpartum woman for substance use serves a first-level function within the clinical setting of the nursery or neonatal intensive care unit by identifying the presence or absence of risk for the neonate due to prenatal substance exposure. The purpose of screening a newborn’s mother is identification of risk, not diagnosis. Screening is initiated by the clinician rather than by the patient. A good screening strategy serves as an initial process that leads to fuller assessment and perhaps diagnosis of a new mother’s substance use problem.

Full clinical assessment of the mother’s substance use serves a second- or third-level function, with patient evaluation and diagnosis leading to treatment. In practical terms, most assessment for substance abuse is performed outside the pediatrician’s or neonatologist’s immediate direction by a team trained to provide an in-depth evaluation. Most clinical assessments use a multiproblem approach to substance use evaluation. An assessment not only evaluates the woman’s substance use, but it also examines the personal and psychosocial

issues affecting the woman and her ability to care for her new infant. For postpartum women, the clinical assessment should address comprehensive support services needed to intervene successfully on behalf of the woman, the family, and the child.

The role of the neonatologist or pediatrician, therefore, becomes one of screening postpartum women for substance use. Results of the subsequent assessment on a targeted population of at-risk women can be used to guide early intervention efforts for the child as well as referrals for treatment for the mother. Such a universal screening and assessment strategy focuses on a public health model and moves a community away from the punitive approach taken in some states.

Use of a Screening Instrument

Many of the commonly recognized screening instruments are not useful for pregnant or postpartum women. The CAGE, although easy to administer and having very good validity, sensitivity, and specificity, primarily targets heavy alcoholic use and does not provide a method for identifying newborns at lower exposure levels for early intervention. Nor does the CAGE address illicit drug use. The NET is similar to the CAGE in that it targets only heavy alcohol use. It may not identify early-stage at-risk drinkers or users of illicit substances. The T-ACE was designed specifically for office detection of risk drinking among obstetric patients. It has been validated as a reliable screening instrument for obstetric practice, and the tolerance question helps sidestep the denial often found in alcohol users. Again, however, heavy drinkers are the primary targets of the T-ACE, and it may not identify more moderate drinkers in a prenatal care setting.

The TWEAK was developed to screen for risky drinking during pregnancy and has demonstrated moderately high sensitivity (79%) and specificity (83%) in a sample of pregnant women when detecting consumption of at least 1 oz/d of absolute alcohol and had high sensitivity and relatively high specificity when used to identify DSM-III Alcohol Use Disorder among a population of pregnant women. However, the TWEAK does not identify risk for the use of illicit drugs.

The 4P's, as cited by Morse and associates, is a four-question screen specifically designed to identify quickly obstetric patients in need of in-depth assessment or follow-up monitoring for alcohol or illicit drug use. It can be integrated easily into the initial prenatal visit and used for follow-up screening through the pregnancy. The four questions are broad-based and highly sensitive, requiring only yes or no answers from the patient regard-

Table 2. The 4P's Plus

• <i>Parents</i>	Did either of your parents ever have a problem with alcohol or drugs?
• <i>Partner</i>	Does your partner have a problem with alcohol or drugs?
• <i>Past</i>	Have you ever drunk alcohol?
• <i>Pregnancy</i>	<ul style="list-style-type: none"> —In the month before you knew you were pregnant, how many cigarettes did you smoke? —In the month before you knew you were pregnant, how many beers/glasses of wine or liquor did you drink?

ing her alcohol or drug use problems during the current pregnancy, in the past, in her partner, and in her parents. One positive answer to any question is considered a positive screening result and indicates that the patient requires more in-depth evaluation. The questions can be reworded to address specifically alcohol or any illicit drugs. The high sensitivity of this instrument makes it likely that false-positive screening results will occur. The 4P's never has been evaluated for validity, sensitivity, or specificity, but clinical use of the instrument in a general obstetric clinic did not appear to screen successfully for substance use.

The 4P's Plus

Over the past 10 years, studies have been conducted to develop the 4P's Plus, a five-question screen specifically designed to identify quickly obstetric patients in need of in-depth assessment or follow-up monitoring (Table 2). Taking less than 1 minute to perform, it also has been found to be successful in the immediate postpartum period. The five questions are broad-based and highly sensitive. The predictive validity of the 4P's Plus was evaluated on a sample of 2,000 Medicaid-eligible women. If a woman has used any alcohol or any tobacco in the month before she knew she was pregnant, she had a 34% risk of having used alcohol or illicit drugs during the pregnancy.

Based on this research, a positive response to the first P, for Parents, does not predict substance use by the woman during the pregnancy. However, most clinicians are comfortable initiating the 4P's Plus as an extension of the family history. The second P, for Partner, is similar to the first P, in that a positive response does not predict the woman's use of alcohol or other drugs in pregnancy. However, this is a good screening question for domestic violence, given the close link between substance abuse

and violence in the home. A positive response to the third P, for Past, places the woman at 10% (low) risk for alcohol use during pregnancy, an indication for the institution of prevention services for the mother as part of the child's intervention plan, especially if the mother plans on breastfeeding. The two questions related to the fourth P, for Present Pregnancy, are open-ended. Any use of tobacco or alcohol in the month before the woman knew she was pregnant places the woman at 34% risk for using or having used alcohol and illicit drugs during pregnancy. This is considered high risk and an indication for referral of the new mother to a social worker or substance abuse specialist for further assessment of maternal substance use.

The 4P's Plus has been field tested in a variety of settings and communities involving more than 10,000 pregnant and postpartum women. For example, in 2002, 5,082 women were screened in Fresno, California, by their primary care physicians with the 4P's Plus through a universal screening program. Among these women, 18% had a positive screening result for risk of alcohol or illicit drug use, and 10% were found to need substance abuse treatment. Further, among women who had positive responses to the second P regarding the Partner having a problem with alcohol or drugs, 65% were found to need drug treatment.

The research, development, and clinical experience with the 4P's Plus has shown it to be a viable procedure for instituting universal substance use screening in pregnant women. Although experience with the postpartum woman in the month following delivery is more limited, the instrument appears to be a viable methodology for identifying neonates at high risk for prenatal substance exposure. Such early identification is necessary to enhance the institution of the early intervention services that have been shown to improve significantly the long-term outcome of alcohol- and drug-exposed children.

Neonatal Screening

Despite the fact that maternal use of alcohol, tobacco, and other drugs during pregnancy has been shown to cross all social, economic, and racial barriers, clinicians often are reluctant to address this issue within the context of primary care. A 2000 survey of 600 obstetricians conducted by the American College of Obstetrics and Gynecology documented that few obstetricians formally screen pregnant women for substance use. In fact, the survey found that 80% of obstetricians tell their patients that "small amounts" of alcohol are safe to drink during pregnancy. Unfortunately, the obstetricians' definitions of "small amounts" covered a wide range, with 4% stating

Table 3. Common Indications for Toxicology Testing in the Neonate

- No prenatal care
- Abruptio placentae
- Preterm delivery
- Intrauterine growth retardation
- Cardiovascular accident of mother or child

that eight drinks or more per week are safe for the fetus. In contrast, a recent study documented that more than one drink per week places the child at increased risk for delinquent behavior and overall problem behavior, one drink per week places the child at increased risk for hyperactive and aggressive behaviors, and *any* alcohol use in pregnancy places the child at more than three times increased risk for delinquent behavior.

Many prenatal and neonatal care clinicians hesitate to implement formal interview procedures because they assume urine toxicologies to be the most appropriate methodology for screening. However, the use of urine toxicologies at one point in time to identify women or infants who have had prenatal exposure limits identification to those infants whose mothers used substances in only the approximately 48 hours prior to delivery. In addition, urine toxicologies measure the concentration of the substance in the urine. With the delayed ability of the neonatal renal system to concentrate urine, the concentration of the substance in the urine of the newborn often falls below federally established thresholds for detection. Thus, more often than not, the urine toxicology report is negative, even though the infant was exposed to significant amounts of a drug.

Testing the neonate's meconium for alcohol or illicit drug exposure during gestation has become more popular over the past few years. The advantage of meconium testing is that this approach can identify substances the mother used throughout the third trimester of pregnancy. However, such testing is expensive, and it usually requires several days to obtain results, often after the child has been discharged from the hospital.

There are specific clinical conditions for which urine or meconium toxicology testing is indicated (Table 3). Commonly accepted indications for toxicology analysis include no prenatal care or intrauterine growth retardation, preterm delivery, abruptio placentae, or cardiovascular accidents in mother or child, especially in those

cases in which there are no other reasons for the poor outcome.

The Neonate Exposed to Substances Prenatally

Clinical Presentation

The earliest studies of infants affected by prenatal exposure focused on those neonates whose mothers used narcotics, usually either heroin or methadone, during pregnancy. Narcotic-exposed infants demonstrate a high rate of perinatal morbidity and mortality, with increased rates of prematurity, intrauterine growth retardation, and microcephaly. Neurologically, the infants exhibit signs and symptoms similar to adults going through heroin withdrawal. The most significant features of the neonatal abstinence syndrome are a high-pitched cry, sweating, tremulousness, excoriation of the extremities, vomiting, and diarrhea (Table 4).

Symptoms of neonatal withdrawal from narcotics may be present at birth but may not reach a peak until 3 to 4 days after delivery. However, onset of withdrawal depends on many factors, and symptoms may not appear until 10 to 14 days. Withdrawal from opiates persists in a subacute form for 4 to 6 months after birth, with a peak in symptoms at about 6 weeks of age. Neurologic irritability due to intrauterine opiate exposure has been noted, with abnormalities of the Moro reaction documented through as late as 7 to 8 months of age.

Infants exposed to nonopiate drugs, such as cocaine and methamphetamines, exhibit a high rate of prematurity, intrauterine growth retardation, and asphyxia related to abruptio placentae at the time of delivery. However, these infants must be evaluated within the context of polydrug abuse because almost all women who are using drugs are using multiple substances, including tobacco and alcohol. Thus, the child's presentation in the neonatal nursery can vary across a wide spectrum from subtle to marked irritability, hypertonicity, and seizures. In addition, affected infants can exhibit congenital anomalies; significant feeding and sleeping problems; and hypersensitivity to touch, movement, and eye contact.

Management

The differential diagnosis for infants who have signs of neonatal abstinence or neurobehavioral difficulties associated with exposure to nonopiates includes hyperthyroidism, intracranial hemorrhage, perinatal anoxia, hypoglycemia, hypocalcemia, sepsis, and hyperviscosity. The differential diagnosis subsequently guides the child's evaluation. Toxicologic studies should be used as

Table 4. Signs of Neonatal Abstinence Syndrome

Neurologic signs

- Hypertonia
- Tremors
- Hyperreflexia
- Irritability and restlessness
- High-pitched cry
- Sleep disturbances
- Seizures

Autonomic system dysfunction

- Yawning
- Nasal stuffiness
- Sweating
- Sneezing
- Low-grade fever
- Skin mottling

Gastrointestinal abnormalities

- Diarrhea
- Vomiting
- Poor feeding
- Regurgitation
- Dysmature swallowing
- Failure to thrive

Respiratory signs

- Tachypnea
- Increased apnea

Miscellaneous

- Skin excoriation
- Neurobehavioral anomalies

described previously. In addition, based on clinical presentation, cerebral computed tomography can identify intracranial hemorrhages or infarcts, and renal ultrasonography can evaluate possible renal anomalies, which appear to occur at an increased rate in exposed neonates. However, the decision to perform these procedures should be based on clinical presentation rather than an automatic response to the exposure.

Primary treatment of neonatal symptoms related to prenatal substance exposure should be supportive because pharmacologic therapy can prolong hospitalization and exposes the infant to additional agents that often are not necessary. Swaddling, pacifiers, low lighting, oscillating cribs, and avoidance of abrupt changes in the infant's environment can be helpful. Frequent small feedings are preferable and should provide 150 to 250 kcal/kg per 24 hours for proper growth of the infant undergoing

abstinence. Specific attention to the child's neurobehavioral difficulties, especially hypersensitivity to auditory, tactile, and visual stimuli, should be noted and addressed accordingly.

Pharmacologic treatment of neonatal abstinence syndrome should be based on conclusions developed through the use of one of the various abstinence scoring methods. Excessive weight loss or dehydration due to vomiting and diarrhea, inability of the infant to feed or sleep, fever unrelated to infection, or seizures are the most common clinical indications for pharmacologic treatment. It should be noted that the scoring systems developed for evaluating the degree of neonatal abstinence are specific to narcotic withdrawal and are not applicable to infants exposed to nonopioids such as cocaine or methamphetamines.

Most information regarding the pharmacologic treatment of neonates affected by prenatal exposure is based on experience derived from the therapy of narcotic withdrawal. Rarely is there a need to provide such pharmacologic treatment to the infant who has been prenatally exposed to nonopioid drugs. Several agents form the basis for pharmacologic therapy of neonatal withdrawal from narcotics: opiate preparations such as paregoric (anhydrous morphine, 0.4 mg/mL), methadone, diazepam, and phenobarbital.

The primary advantage of paregoric is its ease of administration. In addition, infants treated with paregoric have improved and more efficient sucking behavior and exhibit better weight gain than infants treated with diazepam or phenobarbital. The dose of paregoric administered to an infant for treatment of abstinence symptoms ranges from 0.1 to 0.5 mL/dose every 3 to 4 hours until the symptoms of withdrawal are controlled. Alternatively, methadone at an initial dose of 1 to 2 mg BID is an excellent agent for treating neonatal narcotic withdrawal. A neonatal abstinence score is helpful for titrating the dose of paregoric or methadone, and the medication should be tapered after symptoms have been stabilized for 4 to 5 days. A major concern about the use of opiate preparations in neonates is the marked respiratory depressant effect.

Diazepam has been used by some clinicians in a dosage of 1 to 2 mg every 8 to 12 hours. Diazepam rapidly suppresses narcotic withdrawal symptoms in the neonate, but the newborn has a limited capacity to metabolize the drug, and total elimination may require up to 1 month. Because parenteral diazepam contains benzyl alcohol and sodium benzoate, which may displace bilirubin for conjugation and excretion, diazepam should not be used in an icteric or preterm infant. Use of diazepam can be

associated with depression of the neonatal sucking reflex, and late-onset seizures have occurred in neonates after cessation of treatment.

Phenobarbital quiets the infant who is experiencing neonatal withdrawal, but it does little for the gastrointestinal symptoms. Large doses of phenobarbital exert a marked sedative effect on the central nervous system of the infant and impair sucking. A neonatal loading dose of 16 mg/kg per 24 hours, with maintenance doses of 2 to 8 mg/kg per 24 hours to maintain therapeutic serum levels, has been reported to control withdrawal symptoms. Serum levels of phenobarbital should be followed closely and adjusted according to the infant's symptoms and the abstinence score results. After the infant's symptoms have stabilized, the daily dose should be decreased to allow the drug level to decrease by 10% to 20% per day.

Although infants who have neurobehavioral difficulties related to prenatal exposure to nonopioids rarely require pharmacologic treatment, if an affected infant does require medication, phenobarbital, administered as for opiate withdrawal, is the medication of choice.

Conclusion

It appears that the frequency and severity of the problem of drug abuse in pregnancy has not changed over the past 30 years. Although the specific drugs change with shifts in popularity and availability, numerous infants continue to be exposed prenatally to harmful substances. Neonatologists are faced with a number of critical issues. Which infants should be screened for substance exposure? Which developmental processes in the exposed infant are affected most? Are there critical periods for the fetus or the embryo? What are the subtle effects that combine with maternal characteristics to affect such complex processes as mother-infant interaction? Protecting an infant from the effects of illicit substance use by his or her mother protects against the effects of only one aspect of a multidimensional pathologic system. It is the pathologic system, not the drug use alone, that must be addressed in any therapeutic endeavor.

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NeoReviews Quiz

1. The *National Household Survey on Drug Abuse: 1996 to 1998* indicated that 45% of women of childbearing age in the United States have used an illicit drug over their lifetime. Of the following, the annual estimate of prenatal exposure to a substance of abuse is *highest* for:
 - A. Alcohol.
 - B. Cocaine.
 - C. Marijuana.
 - D. Methamphetamine.
 - E. Nicotine.
2. Children who have been exposed prenatally to substances of abuse may have physical deformities as well as neurodevelopmental deficits. Of the following, the substance of abuse *most* associated with limb reduction deformities is:
 - A. Alcohol.
 - B. Heroin.
 - C. Marijuana.
 - D. Methamphetamine.
 - E. Nicotine.
3. Various screening instruments have been developed to identify women at risk for substance abuse during pregnancy. Of the following, the screening instrument *most* useful for detection of the use of illicit drugs during pregnancy is the:
 - A. CAGE.
 - B. NET.
 - C. 4 P's.
 - D. T-ACE.
 - E. TWEAK.
4. A 3-day-old newborn exhibits irritability, restlessness, high-pitched cry, nasal stuffiness, poor feeding, and skin excoriation. The infant is also markedly jaundiced. Of the following, the drug that should be avoided in the pharmacologic treatment of this infant is:
 - A. Diazepam.
 - B. Methadone.
 - C. Paregoric.
 - D. Phenobarbital.
 - E. Phenytoin.

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