Identification and Management of the Drug-Exposed Newborn

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Over the past two decades, neonatologists have found themselves caring for growing numbers of infants passively exposed to a variety of licit and illicit drugs consumed by their mothers. These infants represent a frustrating challenge, for they present a complex web of medical and social problems. Information from the recently published *National Household Survey on Drug Abuse: 1996-1998* indicated that 45% of women of child-bearing 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 and/or tobacco.

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<th>Annual Estimates of U.S. Neonates Prenatally Exposed to Substances</th>
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<tbody>
<tr>
<td>Tobacco</td>
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<td>Alcohol</td>
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<td>Illicit drugs</td>
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Implications of Prenatal Substance Exposure

Substances that act on the central nervous system are usually highly lipophilic and of relatively low molecular weight (<1000 g/mol). These characteristics facilitate the substances' 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. The majority of drugs that have been studied have a longer half-life in the fetus than in the adult. This occurs 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 fact that drug or alcohol-using women are more likely 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 also is a high rate of prematurity among prenatally-exposed infants.

In addition, children who have been prenatally exposed 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, while 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 areas 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).

Long term, children with Fetal Alcohol Syndrome (FAS) have IQ's that range from the 20's to 105 with a mean of 68, and many alcohol-exposed children without the characteristic FAS features have consistently lower IQ scores than non-exposed children. Importantly, even alcohol-exposed children with a "normal IQ" demonstrate difficulty with behavioral regulation, impulsivity,
social deficits, and poor judgment causing difficulties in day to day management in the classroom and home. While 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, and 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, in this way increasing the availability of these transmitters at the receptor sites and producing the cocaine “high” by increasing neuronal excitability. Over a period of chronic exposure, a dampening effect may be produced by down-regulation 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 is key in 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 long term outcome for the child.
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, health care providers 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’ definition of “small amounts” covered a wide range, with 4% of obstetricians stating 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 providers 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 with 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 concentration of the substance in the urine. With the delayed ability of the neonatal renal system to concentrate urine, 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 will be reported as 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 last few years. The advantage of meconium testing lies in the fact that this approach can identify substances the

Common Indications for Toxicology Testing in the Neonate

- No prenatal care
- Abruptio placenta
- Premature delivery
- Intrauterine growth retardation
- Cardiovascular accident of mother or child
mother used throughout the third trimester of pregnancy. However, such testing is expensive, and it usually takes several days to obtain results, often after the child has been discharged from the hospital.

There are specific clinical conditions in which urine or meconium toxicology testing is indicated. Commonly accepted indications for toxicology analysis include no prenat al 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.

Clinical Presentation of the Neonate with Prenatal Substance Exposure

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, as noted in the accompanying table, are a high pitched cry, sweating, tremulousness, excoriation of the extremities, vomiting, and diarrhea.

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<th>Signs of Neonatal Abstinence Syndrome</th>
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<td>Signs of Neonatal Abstinence Syndrome</td>
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<td>-----------------------------------------------</td>
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<tr>
<td>Autonomic system dysfunction</td>
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<tr>
<td>Yawning</td>
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<td>Nasal stuffiness</td>
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<td>Sweating</td>
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<td>Low-grade fever</td>
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<td>Skin mottling</td>
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<td>Gastrointestinal abnormalities</td>
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<td>Diarrhea</td>
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<td>Vomiting</td>
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<td>Poor feeding</td>
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<td>Regurgitation</td>
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<td>Dysmature swallowing</td>
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<td>Tachypnea</td>
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<td>Skin excoriations</td>
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<td>Neurobehavioral anomalies</td>
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Symptoms of neonatal withdrawal from narcotics may be present at birth but may not reach a peak until three to four days of life. However, onset of withdrawal depends on many factors, and symptoms may not appear until ten to fourteen days. Withdrawal from opiates persists in a subacute form for four to six months after birth, with a peak in symptoms at around six weeks of age. Neurologic irritability due to intrauterine opiate exposure has been noted with abnormalities of the Moro reaction documented through as late as seven to eight months of age.

Infants exposed to non-opiate drugs, such as cocaine and methamphetamines, exhibit a high rate of prematurity, intrauterine growth retardation, and asphyxia related to abruptio placenta at the time of delivery. However, these infants must be understood within the context of polydrug abuse, for 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 quite subtle to marked irritability, hypertonicity, and seizures. In addition, these infants can exhibit congenital anomalies, significant feeding and sleeping problems, and hypersensitivity to touch, movement and eye contact.
Management of the Infant with Prenatal Substance Exposure

The differential diagnosis for infants with signs of neonatal abstinence or neurobehavioral difficulties associated with exposure to non-opiates includes hyperthyroidism, intracranial hemorrhage, perinatal anoxia, hypoglycemia, hypocalcemia, sepsis, and hyperviscosity. This differential subsequently guides the child’s evaluation. Toxicologic studies should be utilized as described above.

In addition, based on clinical presentation, a cerebral CAT scan can identify intracranial bleeds or infarcts, and a renal ultrasound will 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, since pharmacologic therapy can prolong hospitalization and exposes the infant to additional agents which often are not necessary. Swaddling, pacifiers, low lighting, oscillating cribs, and avoidance of abrupt changes in the infant’s environment will all be helpful. Frequent small feedings are preferable and should provide 150 to 250 calories per 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 should especially 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 here that the scoring systems developed for evaluating the degree of neonatal abstinence are specific to narcotic withdrawal and are not applicable to those infants exposed to nonopiates such as cocaine or methamphetamine.

Most information regarding the pharmacologic treatment of neonates affected by prenatal exposure is based on experience derived from the therapy regarding narcotic withdrawal. There rarely is a need to provide such pharmacologic treatment to the infant who has been prenatally exposed to nonopiate drugs.

Several agents have served as 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 major 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 per dose every three to four
hours until the symptoms of withdrawal are controlled. Alternatively,
methadone at an initial dose of 1 to 2 mg b.i.d., is an excellent agent for treating
neonatal narcotic withdrawal. A neonatal abstinence score is helpful in titrating
the dose of paregoric or methadone, and the medication should be tapered off
after symptoms have been stabilized for four to five days. It should be noted that
a major concern regarding the use of opiate preparations in neonates is the
marked respiratory depressant effect.

Diazepam also has been used by some clinicians in a dosage of 1 to 2 mg every
eight to twelve hours. Diazepam rapidly suppresses narcotic withdrawal
symptoms in the neonate; however, the newborn infant has a limited capacity to
metabolize diazepam, and total elimination may take up to one month.
Parenteral diazepam contains benzyl alcohol and sodium benzoate, which may
displace bilirubin for conjugation and excretion; therefore, diazepam should not
be used in an icteric or premature 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 with diazepam.

Phenobarbital will quiet the infant with 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 of phenobarbital with
maintenance doses of 2 to 8 mg/kg per 24 hours to keep the medication at a
therapeutic blood level has been reported to control withdrawal symptoms.
Blood 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 of phenobarbital should be decreased
to allow the drug level to decrease by 10 to 20% per day.

It again should be emphasized that infants with neurobehavioral difficulties
related to prenatal exposure to nonopiates rarely if ever require pharmacologic
treatment. However, if an infant in this situation should require medication,
phenobarbital, given in the same manner as for opiate withdrawal described above, would be the medication of choice.

It appears that the frequency and severity of the problem of drug abuse in pregnancy has not changed over the last thirty years. Although the specific drugs change with shifts in popularity and availability, the fact remains that there still are numerous infants being prematurely exposed 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 which combine with maternal characteristics to affect such complex processes as mother-infant interaction? Protecting an infant from the effects of illicit substance use by its mother protects it from being affected by only one aspect of a multidimensional pathological system. It is the pathological system, not the drug use alone, which must be addressed in any therapeutic endeavor.

Suggested Reading


