NeoReviews™
AN OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF THE PEDIATRICS

New Methods for Neonatal Drug Screening

Daphne Chan, Julia Klein and Gideon Koren

Neoreviews 2003;4;e236
DOI: 10.1542/neo.4-9-e236

New Methods for Neonatal Drug Screening

Daphne Chan, BSc,*
Julia Klein, MSc,*
Gideon Koren, MD*

Objectives

After completing this article, readers should be able to:

1. Describe perinatal and neonatal complications of maternal use of cocaine, alcohol, opiates, and barbiturates in pregnancy.
2. List established cutoffs of conventional immunoassays of urine for common substances of abuse.
3. List the advantages of using meconium testing for substances of abuse.
4. Describe the role of fatty acid ethyl esters in detecting prenatal alcohol exposure.

Introduction

Maternal substance use during pregnancy can have direct consequences on both the developing fetus and the mother and is a significant public health concern. The prevalence of gestational use of drugs of abuse varies, depending on the study population and method of detection, but it generally ranges from 1% to 15%. (1) One of the largest epidemiologic studies conducted in the United States documented that although most pregnant women decrease the use of substances as the pregnancy progresses, a significant proportion of them remain regular users, even in the third trimester (eg, ethanol [13%], cannabis [9.3%], cocaine [10%], and heroin [1%]). (2) Various perinatal and neonatal complications can result from prenatal exposure to common drugs of abuse. (3) The use of cocaine during pregnancy is associated with increased risks of preterm labor, intrauterine growth retardation, and neurobehavioral abnormalities. Heavy alcohol use during pregnancy leads to fetal alcohol spectrum disorder, which is characterized by an array of congenital malformations, central nervous system abnormalities, and neurodevelopmental deficits. Neonates exposed to opiates, alcohol, and barbiturates in utero are at risk of developing neonatal abstinence syndrome, which is characterized by irritability, gastrointestinal dysfunction, respiratory distress, and other nonspecific symptoms. (1) Data in the literature conflict regarding adverse events in the immediate postnatal period that can be attributed to prenatal exposure to other illicit drugs. Thus, early identification of neonates in whom substance exposure is suspected is important for appropriate treatment intervention and subsequent postnatal development.

Traditional methods of neonatal drug screening involve primarily a maternal interview, which usually underestimates the extent of exposure due to shame, embarrassment, and fear of litigation and other medical-legal concerns. Gupman and associates (4) found that rates of alcohol and illicit drug use varied with the use of different validated screening instruments, such as the Michigan Alcoholism Screening Test (MAST), CAGE, and T-ACE. Physicians' records yielded the lowest prevalence estimates compared with those derived from structured interviews with the administration of screening instruments, suggesting the lack of attention devoted to addiction disorders by many clinicians in primary care of pregnant women. In another study, the MAST and Drug Abuse Screening Test (DAST) failed to detect most mothers who experienced severe addiction to alcohol as well as current users of illicit drugs. (5)

Many women who have addiction disorders receive very little or no prenatal care. Therefore, structured interviews and ongoing monitoring of drug-seeking behaviors during pregnancy is impossible in most cases. On admission for delivery, there frequently is insufficient time to obtain a detailed prenatal history because of obvious immediate obstetric and perinatal concerns. Hence, the detection of prenatal substance exposure

*Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children, Toronto, Ontario, Canada.

must rely on clinical experience and observation for peripartum and neonatal complications. However, many pregnancies involving prenatal substance use are uneventful, which makes detection of intrauterine drug exposure more difficult. Throughout the years, various biochemical assays have been developed to determine objectively, qualitatively, or quantitatively the extent of prenatal substance exposure. The use of different matrices, including maternal and fetal urine or plasma, maternal and neonatal hair, and neonatal meconium, has been verified for most common drugs of abuse (eg, cocaine, cannabis, opiates). Recently, a novel screening method for prenatal alcohol exposure was developed for neonatal meconium. Immunoassays (eg, radioimmunoassay [RIA], enzyme multiplied immunoassay technique [EMIT], fluorescence polarization immunoassay [FPIA], enzyme-linked immunosorbent assay [ELISA]) have been used widely for mass screening, with positive samples confirmed by more specific techniques, such as high-performance liquid chromatography (HPLC) and gas chromatography-mass spectrometry (GC-MS). This article reviews some of these methods, focusing on the advantages and disadvantages of different detection methods in the clinical setting.

Drug Transfer to the Fetus

The placenta is an important organ within the maternal-fetal compartment. (6) Contrary to earlier beliefs, it is not an absolute barrier. In fact, most drugs can cross the placenta, depending on their molecular size, degree of ionization, extent of plasma protein or placental tissue binding, and lipid solubility. Substances can cross the placenta via simple passive diffusion, facilitated diffusion, or active transport. Most drugs of abuse are lipid-soluble and cross the placenta readily, limited primarily by the rate of placental blood flow. Ethanol is hydrophilic, but because of its small molecular size, it also is transferred readily across the placenta. The ultimate fetal exposure is a balance between the rate of maternal consumption, metabolism, and elimination; placental metabolism and transfer; and fetal metabolism and clearance.

Matrices of Interest

Urine

Maternal and fetal urine are the matrices tested most frequently for practical reasons. Urine is a preferred sample because of the kidney's ability to concentrate drugs and their metabolites to levels higher than those detected in plasma. Urine also usually is free of proteins and cellular debris. However, the time of detection for each substance varies, depending on the time of the last intake, dose and mode of administration, metabolism, and type of detection method employed. A recent review by Vandevenne and associates (7) suggested the following detection times for various drugs using established cutoffs of conventional immunoassays: up to 5 days for amphetamines, between 2 and 4 days for infrequent cannabis users and up to 1 month for heavy chronic users, between 24 and 36 hours for a single intravenous dose of cocaine, and up to 1 to 3 weeks for higher cocaine doses using various methods of administration. Another review by Reinarz and Ecord (3) reported similar values and additional information about the detection time of other drugs of abuse in maternal urine: 24 hours for short-acting barbiturates and up to 3 weeks for long-acting barbiturates, 3 days for benzodiazepines, 3 days for methadone, 48 hours for opiates, and 8 days for phencyclidine (PCP). Ethanol, because of its rapid elimination, is detectable only within 6 to 8 hours of last consumption.

Although urine is the most common matrix tested, it has certain disadvantages. Most drugs are detected in urine only within hours to several days after consumption. It is not uncommon for expecting mothers to stop taking substances a few days prior to delivery. Accordingly, these mothers likely will test negative (ie, false-negative) at the time of delivery, and their newborns also may have negative urine toxicologic screen results. Although collection of urine samples from mothers is easy and noninvasive, it is much more difficult in the neonate. Only small volumes of urine are voided in the immediate postnatal period when the drugs still can be detected. The urine collection apparatus adapted for newborns is not efficient in collecting neonatal urine and may create discomfort and cause skin rashes.

A large number of prevalence studies have been conducted in the past decade using maternal or neonatal urine screening as a detection method for prenatal substance exposure. A review of 16 studies (Table 1) suggests that 3% to 27% of neonates in different geographic locations were exposed to drugs of abuse in utero. Seven of the studies compared the rates detected by urine testing and maternal interview and found conflicting results. Martinez Crespo and associates (17) found that 50% to 60% of mothers who tested positive for different substances denied their use. Two studies found a two- to fivefold increased rate of detection when urine toxicology was used. (13)(22) Of particular interest is that the reverse was true for the detection of gestational alcohol exposure, with three studies finding that maternal interview revealed far more cases of alcohol users than urine screening. (13)(17)(22) This may be due to the rapid

Table 1. The Use of Urine Screening in Prevalence Studies of Gestational Drug Use Over the Past Decade

Study	Sample Size	Duration	Matrix Screened	Drugs (% of All Positive Screens)	Comment (% Positive in Entire Study Population)
Agarwal et al (8)	N = 14,690 (N = 38 tested)	2 y	Neonatal urine	Not specified	Overall 0.25% positive in population; 26% of tested cohort positive
Berenson et al (9)	N = 336	8 mo	Maternal urine	Marijuana, cocaine, or multiple drugs	Overall 27.1% positive
Bosio et al (10)	N = 504	6 wk	Maternal urine	Ethanol (1.4%), cannabis (1%), benzodiazepines (0.8%), opiates (0.4%), cocaine (0.2%), amphetamines (0.2%), methadone (0.2%)	Overall 3.6% positive
Buchi et al (11)	N = 792	19 d	Maternal urine	Ethanol (4%), cannabis (2.9%), cocaine (1.1%), amphetamines (0.6%)	Overall 7.8% positive
Chasnoff et al (12)	N = 715	6 mo	Maternal urine	Cannabis (11.9%), cocaine (3.4%), alcohol (1%), opiates (0.3%)	Overall 14.8% positive
Christmas et al (13)	N = 302	5 mo	Maternal urine	Cannabis (9.6%), cocaine (5.3%), sedative/hypnotic (1.7%), narcotics (1%)	Overall 13.6% positive; 26.8% of positive cases involved polydrug use
Horrigan et al (14)	N = 560	Not specified	Maternal urine	Not specified	Overall 14.8% positive
Jacob et al (15)	N = 351	6 mo	Maternal urine	Cannabis (5.4%), barbiturates (4.8%), alcohol (4.6%), opiates (2.6%), amphetamines (1.7%), benzodiazepines (0.85%), phencyclidine (0.28%)	Overall 16.2% positive; 22.8% of positive cases involved polydrug use
Land and Kushner (16)	N = 290	4 mo	Maternal urine	Cannabis (44.9%), cocaine (42.3%), opiates (25.6%), barbiturates (9%), benzodiazepines (9%), amphetamines (7%)	Overall 27% positive; 25% of positive cases involved polydrug use
Martinez Crespo et al (17)	N = 1,773	15 mo	Maternal urine	Ethanol (5.2%), heroin (1.7%), cocaine (0.8%)	Overall 7.7% positive
Ney et al (18)	N = 141	6 mo	Maternal urine	Cocaine (9.9%), cannabis (6.4%), opiates (1.4%), other (4.2%)	Overall 17% positive (suspected preterm labor cohort)
Noble et al (19)	N = 29,494	2 y	Maternal urine	Ethanol (6.7%), marijuana (1.9%), opiates (1.5%), cocaine (1.1%)	Overall 11.4% positive
Pegues et al (20)	N = 3,554	2 mo	Maternal urine	Marijuana (6.2%), cocaine (1.3%), opiates (0.6%), barbiturates (0.6%), amphetamines (0.1%)	Overall 8.4% positive; prevalence did not change between three trimesters
Schulman et al (21)	N = 204 (mothers); N = 1,196 (infants, N = 304 tested)	1 mo (5 mo for neonates)	Maternal and neonatal urine	**Mothers:** cocaine (6.9%), opiates (1.5%), methadone (1.5%), amphetamines/barbiturates (1.5%) **Neonates:** cocaine (15.1%), methadone (2.96%), barbiturates (2.3%), opiates (0.66%), other (0.66%)	**Mothers:** overall 9.3% positive; 2% of positive cases involved polydrug use **Neonates:** Overall 6.9% positive in population; 27% of tested cohort positive and 5.6% polydrug use
Sloan et al (22)	N = 181	10 mo	Maternal urine	Marijuana (9.4%), cocaine, barbiturates, ethanol, benzodiazepines (0.6% each)	Overall 11.6% positive
Ware et al (23)	N = 105	1 mo	Neonatal urine	Not specified	Overall 9.5% positive

elimination of alcohol and the low sensitivity of immunoassays for alcohol. Four studies reported that 4% to 42% of cases were not identified by urine screening, possibly due to the reasons noted previously. (9)(14)(21)(23) Hattab and colleagues (24) attempted to modify existing screening immunoassays to detect subthreshold concentrations of illicit drugs in urine, but they achieved only minimal success (4.5% increased positive rate).

Meconium

In light of the variable sensitivity and technical issues surrounding urine testing, researchers have turned to meconium, a matrix unique to the newborn. Much of the early work in animal models and the development of meconium screening assays was conducted by Ostrea and colleagues in Detroit. (25)(26) Other groups also have engaged in the development of various meconium screening assays. (27)(28)(29)

Meconium is a complex matrix composed of water, sugar, lipids, trace materials, and other cellular debris. All substances that reach the fetal circulation theoretically appear in the meconial matrix. Drugs that are excreted into bile are deposited directly into meconium. Drugs that are excreted into fetal urine and amniotic fluid are swallowed by the fetus and eventually are found in meconium. Repeated cycles of fetal elimination and swallowing potentially increase the chance of detecting drugs in this matrix. Deposition of drugs into meconium theoretically begins around 12 to 13 weeks' gestation, when fetal swallowing begins, and continues until after delivery, when the neonate releases it. Fetal exposure to cocaine detected by meconium testing was documented in a fetus as young as 16 weeks' gestation. (25)

There are many advantages to meconium testing. Sample collection is easy, rapid, and noninvasive because it can be taken directly from the diaper into a sterile container without any contact with the neonate. Although some fetuses discharge meconium in utero, most release meconium within the first 3 days of postnatal life, when neonatal urine or blood often are negative for the drug in question. Because drugs accumulate in meconium from the beginning of the second trimester until birth, it provides a wide window of detection for all substances consumed by the mother during the second half of pregnancy.

Meconium testing has been employed in many studies in the past decade. The nine reviewed here found rates of prenatal exposure ranging from 3% to 61%, depending on the type of population investigated (eg, high-risk versus low-risk) (Table 2). The strength of meconium analysis over other matrices has been documented in five of the studies. Meconium testing increased the detection of fetal exposure by 28% compared with maternal report (10% versus 7.8%). (30) O'Connor and associates (33) analyzed neonatal urine in parallel to meconium and found three cases in which urine was negative and meconium was positive. They noted that there were no cases of positive urine with negative meconium, suggesting that meconium testing is more sensitive. Similarly, Maynard and coworkers (31) concluded that meconium testing was 93% sensitive (82% positive predictive value) compared with combined maternal and neonatal urine testing. Although the use of universal meconium screening remains controversial, the detection rate of prenatal drug exposure has been shown to increase significantly (0.2% to 4.5%) in a low-risk setting when comparing screening per physicians' orders with routine screening. (38)

Hair

The use of hair as a toxicologic screening matrix has been explored for almost 20 years. Its application has been particularly popular in forensics, sports medicine, and monitoring of adults who have addiction disorders. (39) Due to the specific technical expertise required for hair testing, this matrix is used only in the identification of prenatal drug exposure in a few skillful laboratories. Both maternal and neonatal hair can provide a detailed record of gestational drug exposure. (40) Although the mechanisms leading to incorporation of drugs and their metabolites into the growing hair shaft remain to be determined, many xenobiotics (chemicals foreign to the biologic system) and drugs of abuse have been documented in hair. Because adult hair grows at an average rate of 1 cm/mo, it is possible to test a mother's hair in three 3-cm sections to estimate her pattern of drug use over the course of gestation. Neonatal hair begins to grow in the third trimester and is not shed until 2 to 3 months after birth. Therefore, there is a wider window of opportunity for sample collection. However, hair testing has some disadvantages. Most newborns have very little hair and obtaining a sufficient sample may be difficult, especially when most parents are reluctant to have someone cut their newborns' hair. Thus, although hair sampling is technically noninvasive to the neonate, it may be perceived as an invasive test by parents.

Hair testing has been used to estimate the rates of drug use in various populations. A prevalence study of cocaine use during pregnancy was conducted by Forman and associates in three metropolitan Toronto hospitals. (41) Of 600 neonates tested, 6.25% were positive for cocaine. A study conducted by Ostrea and colleagues

Table 2. The Use of Meconium Screening in Different Populations to Estimate the Rate of Fetal Exposure to Common Drugs of Abuse

Study	Sample Size	Duration	Drug (% of All Positive Screens)	Comment (% Positive in Entire Study Population)
Bauer et al (30)	N = 8,627	2 y	Cocaine and opiates	Overall 10% positive
Maynard et al (31)	N = 28	Not specified	Cocaine (94.1%), opiates (5.8%), cannabis (5.8%)	Overall 61% positive; 1 neonate positive for both cocaine and opiates
Moriya et al (32)	N = 50	Not specified	Cocaine (61.5%), opiates (38.5%), PCP (7.7%), cocaine and opiates (7.7%)	Overall 26% positive
O'Connor et al (33)	N = 156	1 mo (universal)	Cannabis (50%), cocaine (25%), opiates (25%)	Overall 2.6% positive
	N = 85	3 mo (risk-based)	Cannabis (72.7%), cocaine (27.3%)	Overall 12.9% positive
Ostrea et al (34)	N = 3,010 (high-risk urban center)	1 y	Cocaine (30.7%), opiates (20.5%), cannabis (11.5%)	Overall 44.3% positive
Ostrea et al (35)	N = 81 (NICU)	Not specified	Cocaine (87.8%), opiates (22%)	Overall 50% positive
Ostrea et al (36)	N = 4,409 (4 centers)	Not specified	Cocaine (16.3%), opiates (3%), cannabis (1.3%)	Overall 19% positive (range of 1.8% to 38% from low- to high-risk centers); cocaine use most popular in high-risk centers; cannabis use predominated at low-risk centers
Ostrea et al (37)	N = 98	Not specified	Cocaine (10.2%), methadone (5.1%), morphine (4.1%), amphetamines (1%)	Overall 11% positive
Zenewicz and Kuhn (38)	N = 493	5 mo	Cannabis (86.4%), cocaine (13.6%), cocaine and cannabis (4.5%)	Overall 4.5% positive

PCP = phencyclidine; NICU = neonatal intensive care unit

(42) compared the differential sensitivities and specificities of maternal interview, maternal hair analysis, and meconium analysis. The authors concluded that meconium and hair analyses had the highest sensitivities in detecting the use of cocaine and opiates (80% to 100%), but not cannabis (20%). The most recent comparison of meconium and hair analysis in neonates was reported by Bar-Oz and coworkers. (43) Among 185 paired hair and meconium samples collected from newborns, 53 tested positive for cocaine or benzoylecgonine, 27 for opiates, and 55 for cannabis in either neonatal hair and/or meconium combined. Meconium was found to be marginally more sensitive than neonatal hair testing for cocaine (96% versus 84%), benzoylecgonine (95% versus 78%), and cannabis (98% versus 71%), but equally sensitive for testing opiates (87%). In all cases in which hair tested positive while meconium tested negative (n = 10), the samples were documented as transitional (ie, mixture of meconium and infant stool), which explains the lack of concordance in test results (ie, meconium needs to be pure to ensure high sensitivity).

Other Matrices of Interest

The detection time of a drug and its metabolites in neonatal blood samples is governed by the same principles as drugs in urine (eg, time of last dose, pharmacokinetics). Because of the invasiveness of its collection and its relatively lower detection sensitivity, neonatal blood is not a preferred matrix. Amniotic fluid or neonatal gastric aspirate are other potential matrices of interest, but are limited in practice by the narrow time frame of collection (peripartum and immediately postpartum). Cocaine and its metabolites have been detected in amniotic fluid. (44) One case report of nail analysis as a potential method in the assessment of intrauterine drug exposure was published in 1997. (45) Cocaine was found in the nail clippings of a 3-month-old male infant who died of sudden infant death syndrome. Because nails reach the

Table 3. Comparison of Different Screening Matrices

Matrix	Advantages	Disadvantages
Amniotic fluid	• Concentrates drugs and metabolite	• Narrow timing of collection
Maternal blood/cord blood	• Large sample size • Noninvasive in mother (part of routine)	• Narrow time frame to collect cord blood • Recent exposure only
Maternal/neonatal hair	• Sectioning of maternal hair (detailed history of gestational drug use) • Fetal hair indicates exposure from third trimester • Timing of collection not critical	• Small sample size from most infants • Not favored by most parents
Maternal/neonatal urine	• Kidney concentrates drugs and metabolites (higher levels than blood)	• Difficult to collect in neonates • Recent exposure only
Neonatal meconium	• Easy, rapid, noninvasive sample collection directly from diaper • Matrix unique to fetus • Indicates fetal exposure from second trimester until delivery	• Availability within first 3 postnatal days
Neonatal nail	• Noninvasive sample collection • Indicates fetal exposure from mid-gestation	• Not validated (only one case report)

tips of fingers and toes of the fetus at the end of the eighth month of pregnancy, the authors concluded that the cocaine detected in the nail clippings three months after birth was associated with gestational usage. Table 3 summarizes the clinical applications of testing various matrices in the mother and neonate.

Proposed Scheme for Maternal-Neonatal Screening

A proposed scheme for toxicologic testing in the delivery ward or nursery is derived from the data presented and discussed herein (Figure). Both urine and meconium should be collected and stored to await further decision for which matrix to test. Although urine is less sensitive than meconium or hair in detecting prenatal drug exposure, it remains the first-line mass screening method for practical and economical reasons. A positive urine screening result generally precludes the need for other tests. A negative urine screening result does not equate to no further testing if clinical suspicion or case presentation (eg, neonatal complications) suggests otherwise. In such cases, testing of meconium or hair is warranted.

Novel Development in Detecting Prenatal Alcohol Exposure

Due to the rapid elimination of ethanol and its major metabolite, acetaldehyde, there has been intense search for more stable and reliable biologic markers. Fatty acid ethyl esters (FAEE) are a group of ethanol metabolites that result from the enzymatic conjugation of free fatty acids or fatty acyl-CoA to ethanol. FAEE have been proposed as markers of recent and chronic ethanol consumption in adult drinkers and in postmortem specimens. (46) As discussed previously, urine testing fails to identify the alcohol-exposed neonate in most cases because of the combined effect of low immunoassay sensitivity for ethanol and the agent's short circulation. In the past, detection of prenatal alcohol exposure often relied on maternal self-reports, which usually underestimated the actual exposure. Recently, the presence of FAEE in neonatal meconium samples has stimulated the development of an objective neonatal screening test for prenatal alcohol exposure.

Bearer and colleagues (47) examined the use of ethyl linoleate as a potential marker of prenatal alcohol exposure. Because linoleic acid is an essential acid that is not produced by the body and must be consumed from diet, the validity of using this FAEE alone remains questionable. Moore and associates (48) documented the use of an expanded profile of FAEE in estimating the rates of alcohol consumption in two different populations. The group demonstrated that an expanded screening profile increases the sensitivity of the test. An empiric analysis revealed a particular group that potentially was at high risk for alcohol-related effects because samples in this category contained levels of FAEE that were six- to 60-fold higher than the rest of the population. Although a correlation between different meconium FAEE concentrations and amount of gestational alcohol consumption has not been established, such a relationship has been documented for ethyl linoleate. (47)

However, because the human gut produces varying

amounts of ethanol as a normal byproduct of metabolism, the amount of FAEE that are produced endogenously must be standardized before establishing this approach as a neonatal screening test. The first population baseline of meconium FAEE was reported by Chan and associates, (49) who found that certain FAEE (ethyl laurate and myristate) are detectable in the meconium of neonates born to nondrinking mothers at low levels. The mean total cumulative FAEE level in their meconium samples was at least fivefold lower than levels detected in neonates born to confirmed heavy drinkers. It was concluded that with a positive cutoff of 2 nmol/g of meconium, the cumulative FAEE screening test yields the highest sensitivity (100%) and specificity (98%). The group currently is exploring the use of a meconium FAEE screening test in estimating the rate of heavy drinking among mothers of infants in whom polydrug exposure in utero is suspected. A similar analytic method using neonatal hair also is under development. (50) In the near future, the combined use of hair and meconium FAEE screening has the potential to help physicians confirm prenatal alcohol exposure and the diagnosis of fetal alcohol spectrum disorder.

Conclusion

The use of common drugs of abuse during pregnancy is a significant public health concern. Prenatal exposure to many substances can have direct consequences on both the mother and the developing fetus. Although some women admit to using drugs while pregnant, most deny any exposure due to obvious medical-legal concerns. It is, therefore, the front-line caregiver's responsibility (eg, nurse, physician, social worker) to observe for addiction disorders among pregnant women and to make an informed choice in selecting the most appropriate toxicologic screening method that can detect objectively exposure(s) that are suspected clinically. Early identification of an exposed and potentially affected child is crucial in the obstetrical-neonatal care setting.

References

1. Buchi KF. The drug-exposed infant in the well-baby nursery. *Clin Perinatol*. 1998;25:335–350
2. Klein D, Zahnd E. Perspectives of pregnant substance-using women: findings from the California Perinatal Needs Assessment. *J Psychoactive Drugs*. 1997;29:55–66
3. Reinarz SE, Ecord JS. Drug-of-abuse testing in the neonate. *Neonatal Netw*. 1999;18:55–61
4. Gupman AE, Svikis D, McCaul ME, Anderson J, Santora PB. Detection of alcohol and drug problems in an urban gynecology clinic. *J Reprod Med*. 2002;47:404–410
5. Kemper KJ, Greteman A, Bennett E, Babonis TR. Screening mothers of young children for substance abuse. *J Dev Behav Pediatr*. 1993;14:308–312
6. Szeto HH. Kinetics of drug transfer to the fetus. *Clin Obstet Gynecol*. 1993;36:246–254
7. Vandevenne M, Vandenbussche H, Verstraete A. Detection time of drugs of abuse in urine. *Acta Clin Belg*. 2000;55:323–333
8. Agarwal P, Rajadurai VS, Bhavani S, Tan KW. Perinatal drug abuse in KK Women's and Children's Hospital. *Ann Acad Med Singapore*. 1999;28:795–799
9. Berenson AB, Wilkinson GS, Lopez LA. Substance use during pregnancy and peripartum complications in a triethnic population. *Int J Addict*. 1995;30:135–145
10. Bosio P, Keenan E, Gleeson R, et al. The prevalence of chemical substance and alcohol abuse in an obstetric population in Dublin. *Irish Med J*. 1997;90:149–150
11. Buchi KF, Varner MW, Chase RA. The prevalence of substance abuse among pregnant women in Utah. *Obstet Gynecol*. 1993;81:239–242
12. Chasnoff IJ, Landress HJ, Barrett ME. The prevalence of illicit-drug or alcohol use during pregnancy and discrepancies in mandatory reporting in Pinellas County, Florida. *N Engl J Med*. 1990;322:1202–1206
13. Christmas JT, Knisely JS, Dawson KS, Dinsmoor MJ, Weber SE, Schnoll SH. Comparison of questionnaire screening and urine toxicology for detection of pregnancy complicated by substance use. *Obstet Gynecol*. 1992;80:750–754
14. Horrigan TJ, Piazza NJ, Weinstein L. The substance abuse subtle screening inventory is more cost effective and has better selectivity than urine toxicology for the detection of substance abuse in pregnancy. *J Perinatol*. 1996;16:326–330
15. Jacob J, Harrison H Jr, Tigert AT. Prevalence of alcohol and illicit drug use by expectant mothers. *Alaska Med*. 1995;37:83–87
16. Land DB, Kushner R. Drug abuse during pregnancy in an inner-city hospital: prevalence and patterns. *J Am Osteopath Assoc*. 1990;90:421–426
17. Martinez Crespo JM, Antolin E, Comas C, et al. The prevalence of cocaine abuse during pregnancy in Barcelona. *Eur J Obstet Gynecol Reprod Biol*. 1994;56:165–167
18. Ney JA, Dooley SL, Keith LG, Chasnoff IJ, Socol ML. The prevalence of substance abuse in patients with suspected preterm labor. *Am J Obstet Gynecol*. 1990;162:1562–1565
19. Noble A, Vega WA, Kolody B, et al. Prenatal substance abuse in California: findings from the Perinatal Substance Exposure Study. *J Psychoactive Drugs*. 1997;29:43–53
20. Pegues DA, Engelgau MM, Woernle CH. Prevalence of illicit drugs detected in the urine of women of childbearing age in Alabama public health clinics. *Public Health Rep*. 1994;109:530–538
21. Schulman M, Morel M, Karmen A, Chazotte C. Perinatal screening for drugs of abuse: reassessment of current practice in a high-risk area. *Am J Perinatol*. 1993;10:374–377
22. Sloan LB, Gay JW, Snyder SW, Bales WR. Substance abuse during pregnancy in a rural population. *Obstet Gynecol*. 1992;79:245–248
23. Ware S, Liguori R, Jamerson P, Weiner V, Joubert-Jackson C. Prevalence study of substance abuse in a midwestern city. *J Pediatr Nurs*. 1993;8:152–158
24. Hattab EM, Goldberger BA, Johannsen LM, et al. Modification of screening immunoassays to detect sub-threshold concentrations of cocaine, cannabinoids, and opiates in urine: use for detect-

ing maternal and neonatal drug exposures. *Ann Clin Lab Sci*. 2000;30:85–91
25. Ostrea EM Jr. Testing for exposure to illicit drugs and other agents in the neonate: a review of laboratory methods and the role of meconium analysis. *Curr Probl Pediatr*. 1999;29:37–56
26. Ostrea EM Jr. Understanding drug testing in the neonate and the role of meconium analysis. *J Perinat Neonatal Nurs*. 2001;14:61–82
27. ElSohly MA, Kopycki W, Feng S, Murphy TP. Identification and analysis of the major metabolites of cocaine in meconium. *J Anal Toxicol*. 1999;23:446–451
28. ElSohly MA, Stanford DF, Murphy TP, et al. Immunoassay and GC-MS procedures for the analysis of drugs of abuse in meconium. *J Anal Toxicol*. 1999;23:436–445
29. Moore C, Negrusz A, Lewis D. Determination of drugs of abuse in meconium. *J Chromatogr B Biomed Sci Appl*. 1998;713:137–146
30. Bauer CR, Shankaran S, Bada HS, et al. The Maternal Lifestyle Study: drug exposure during pregnancy and short-term maternal outcomes. *Am J Obstet Gynecol*. 2002;186:487–495
31. Maynard EC, Amoruso LP, Oh W. Meconium for drug testing. *Am J Dis Child*. 1991;145:650–652
32. Moriya F, Chan KM, Noguchi TT, Wu PY. Testing for drugs of abuse in meconium of newborn infants. *J Anal Toxicol*. 1994;18:41–45
33. O'Connor TA, Bondurant HH, Siddiqui J. Targeted perinatal drug screening in a rural population. *J Matern Fetal Med*. 1997;6:108–110
34. Ostrea EM Jr, Brady M, Gause S, Raymundo AL, Stevens M. Drug screening of newborns by meconium analysis: a large-scale, prospective, epidemiologic study. *Pediatrics*. 1992;89:107–113
35. Ostrea EM, Lizardo E, Tanafranca M. The prevalence of illicit drug exposure in infants in the NICU as determined by meconium drug screen. *Pediatr Res*. 1992;31:215A.
36. Ostrea EM Jr, Romero A, Yee H. Adaptation of the meconium drug test for mass screening. *J Pediatr*. 1993;122:152–154
37. Ostrea EM Jr, Matias O, Keane C, et al. Spectrum of gestational exposure to illicit drugs and other xenobiotic agents in newborn infants by meconium analysis. *J Pediatr*. 1998;133:513–515
38. Zenewicz D, Kuhn PJ. Routine meconium screening versus drug screening per physician order: detecting the true incidence of drug-exposed infants. *Pediatr Nurs*. 1998;24:543–546, 553
39. Spiehler V. Hair analysis by immunological methods from the beginning to 2000. *Forensic Sci Int*. 2000;107:249–259
40. Klein J, Karaskov T, Koren G. Clinical applications of hair testing for drugs of abuse–the Canadian experience. *Forensic Sci Int*. 2000;107:281–288
41. Forman R, Klein J, Meta D, Barks J, Greenwald M, Koren G. Maternal and neonatal characteristics following exposure to cocaine in Toronto. *Reprod Toxicol*. 1993;7:619–622
42. Ostrea EM Jr, Knapp DK, Tannenbaum L, et al. Estimates of illicit drug use during pregnancy by maternal interview, hair analysis, and meconium analysis. *J Pediatr*. 2001;138:344–348
43. Bar-Oz B, Klein J, Karaskov T, Koren G. Comparison of meconium and neonatal hair analysis for detection of gestational exposure to drugs of abuse. *Arch Dis Child Fetal Neonatal Ed*. 2003;88:F98–F100
44. Ripple MG, Goldberger BA, Caplan YH, Blitzer MG, Schwartz S. Detection of cocaine and its metabolites in human amniotic fluid. *J Anal Toxicol*. 1992;16:328–331
45. Skopp G, Potsch L. A case report on drug screening of nail clippings to detect prenatal drug exposure. *Ther Drug Monit*. 1997;19:386–389
46. Laposata M. Fatty acid ethyl esters: nonoxidative ethanol metabolites with emerging biological and clinical significance. *Lipids*. 1999;34(suppl):S281–S285
47. Bearer CF, Lee S, Salvator AE, et al. Ethyl linoleate in meconium: a biomarker for prenatal ethanol exposure. *Alcohol Clin Exp Res*. 1999;23:487–493
48. Moore C, Jones J, Lewis D, Buchi K. Prevalence of fatty acid ethyl esters in meconium specimens. *Clin Chem*. 2003;49:133–136
49. Chan D, Bar-Oz B, Pellerin B, et al. Population baseline of meconium fatty acid ethyl esters among infants of non-drinking women in Jerusalem and Toronto. *Ther Drug Monitor*. 2003;25:291–298
50. Klein J, Chan D, Koren G. Neonatal hair analysis as a biomarker for in utero alcohol exposure. *N Engl J Med*. 2002;347:2086

NeoReviews Quiz

5. The duration of time for detecting a drug of abuse in the maternal urine varies, depending on the time of intake, dose and mode of administration, and metabolism of the drug. Of the following, the duration of time after birth for the detection of a drug of abuse in the maternal urine is *longest* for:

   A. Amphetamine.
   B. Benzodiazepine.
   C. Methadone.
   D. Opiate.
   E. Phencyclidine.

6. Testing of neonatal meconium for a drug of abuse depends on deposition of the drug into the meconium that begins at the commencement of fetal swallowing and continues until after delivery. Of the following, the *earliest* gestational age at which exposure to cocaine has been detected in meconium in a fetus is:

   A. 12 weeks.
   B. 16 weeks.
   C. 20 weeks.
   D. 24 weeks.
   E. 28 weeks.

7. Various matrices for the detection of fetal exposure to drugs of abuse have been developed and tested for their sensitivities and specificities. Of the following, the matrix that is *most* sensitive for the detection of fetal exposure to benzoylecgonine is neonatal:

   A. Blood.
   B. Gastric aspirate.
   C. Hair.
   D. Meconium.
   E. Urine.

New Methods for Neonatal Drug Screening

Daphne Chan, Julia Klein and Gideon Koren

Neoreviews 2003;4;e236
DOI: 10.1542/neo.4-9-e236