Fetal alcohol spectrum disorder

Gideon Koren, Irena Nulman, Albert E. Chudley, Christine Loocke

Case

Ms. L, a 32-year-old G5 P2 A2 (gravida 5, para 2, abortions 2) woman, is admitted to hospital because of premature rupture of membranes at an estimated 34 weeks of gestation. She has had only intermittent prenatal care and no prenatal tests. This is an unplanned pregnancy, and she is not sure of the time of conception. Her 2 older children have been in foster care since birth, because child welfare authorities assessed her ability to parent as inadequate at the time; 1 child is in the process of adoption. Although child welfare authorities have documented a history of problem drinking, the woman denies any drinking during the current pregnancy. Her physical and neurologic examinations are unremarkable. Although she has sought routine prenatal care only periodically during her pregnancy, she describes developing a desire to parent this child in recent weeks. She denies any "recent" use of alcohol or cocaine, but will not be more specific. Informed consent for drug testing is obtained; no alcohol is detected in her blood, and a urine toxic screen is negative for cocaine, heroin, amphetamines and cannabinoids. Her hemoglobin level is 130 g/L, leukocyte count is 8.5 × 10^9/L, mean corpuscular volume is 82 fL, electrolytes and creatinine levels are normal, and gamma glutamyl transferase level is 75 (normally < 45) U/L. The woman's baby is delivered vaginally. His Apgar score is 8 at 1 minute and 10 at 5 minutes. His birth weight is 1.1 kg (below the third percentile for age) and head circumference 28.5 cm (fifth percentile for age). Findings from the physical and neurologic examinations of the baby are unremarkable, and he does not require assisted ventilation. Breastfeeding is started successfully.

What aspects of this case make you concerned that this child is at risk of fetal alcohol spectrum disorder (FASD)? What additional screens or laboratory tests might further indicate the possibility of FASD? What physical and neurodevelopmental deficits might present later in life if the child has FASD?

At least half of Canadian and American women drink socially[1] and half of all pregnancies are unplanned;[2] thus, an estimated quarter of all newborns (about 100 000 infants a year in Canada) are exposed to some alcohol during early gestation. Fetal alcohol syndrome (FAS) was originally described as intrauterine and postnatal growth retardation (below the third percentile); specific facial changes (short palpebral fissures [2 standard deviations below normal for age], smooth philtrum and thin vermilion border of the upper lip); and adverse brain effects (mainly mental retardation).[3,4] However, during the late 1970s and 1980s, it became apparent that this classic triad of symptoms was relatively uncommon in the offspring of heavy drinkers (occurring in only 4%–5%).[5] More often (in 30%–40% of children of heavy drinkers), the brain injury manifests as mild rather than severe cognitive dysfunction and a more subtle and complex pattern of neurobehavioural problems (Box 1) with or without physical features of classic FAS. The broader term "fetal alcohol spectrum disorder" (FASD) has been coined in recent years to encompass the wide range of adverse fetal effects of ethanol — from the classic FAS to its more partial presentations. Overall, it is estimated that FASD affects up to 9.1 of every 1000 babies born in the United States and Canada.[6,7]

Identifying pregnant women who are problem drinkers

Although safe alcohol intake levels during pregnancy are difficult to define, questionnaires can identify women who are at greater risk of having a child with FASD.[8] Two such questionnaires (TWEAK and T-ACE) can be used to screen all pregnant women to identify those at risk (Table 1).[9] The CAGE questionnaire is less appropriate for screening pregnant women, because it is less sensitive than TWEAK and T-ACE.[9,10] (Maternal and infant laboratory markers of possible antenatal alcohol use are discussed later.)

Defining the spectrum of disabilities

In 1996 the Institute of Medicine defined several categories of fetal alcohol pathology, from full-blown cases (i.e., history of maternal drinking, intrauterine and postnatal

Box 1: Common cognitive and behavioural problems in children with fetal alcohol spectrum disorder[4]

- Attention deficit hyperactivity disorder
- Inability to foresee consequences
- Inability to learn from previous experience
- Inappropriate or immature behaviour
- Lack of organization
- Learning difficulties
- Poor abstract thinking
- Poor adaptability
- Poor impulse control
- Poor judgement
- Speech, language and other communication problems

© 2003 Canadian Medical Association or its licensors

Table 1: Screening questionnaires for diagnosing problem drinking

TWEAK (score of 3 or more indicates heavy or problem drinker)	
T (tolerance)	How many drinks* does it take before you begin to feel the first effects of alcohol? (3 or more drinks = 2 points)
W (worried)	Have close friends or relatives worried or complained about your drinking in the past year? (Yes = 2 points)
E (eye-opener)	Do you sometimes take a drink in the morning when you first get up? (Yes = 1 point)
A (amnesia)	Has a friend or family member ever told you about things you said or did while you were drinking that you could not remember? (Yes = 1 point)
K (kut down)	Do you sometimes feel the need to cut down on your drinking? (Yes = 1 point)
T-ACE (score of 2 or more indicates heavy or problem drinker)	
T (tolerance)	How many drinks does it take to make you feel high? (3 or more drinks = 2 points)
A (annoyed)	Have people annoyed you by criticizing your drinking? (Yes = 1 point)
C (cut down)	Have you ever felt you ought to cut down on your drinking? (Yes = 1 point)
E (eye-opener)	Have you ever had a drink in the morning to steady your nerves or to get rid of a hangover? (Yes = 1 point)

Note: TWEAK has a sensitivity of 79% and a specificity of 83%; T-ACE has sensitivity of 70% and a specificity of 85%.[10]
*A standard drink is commonly defined as one containing 15 g of alcohol (e.g., 360 mL [12 oz.] of beer, 150 mL [5 oz.] of wine or 45 mL [1.5 oz.] of spirits).

growth retardation, typical facial changes and brain dysfunction) to cases in which there are neurodevelopmental effects but no physical changes.[11] The institute permits diagnosis of FAS only when there is evidence of maternal drinking, except when the pathognomonic facial changes are apparent, because other conditions do not elicit such changes. The institute's categories cover the range of so-called "primary disabilities" seen in children with FASD (Table 2).

Facial signs of FAS are most evident between 8 months and 8 years of age; hence, their vague appearance in the newborn should not be misinterpreted. For the same reason, when examining an adolescent or adult, earlier childhood pictures may be useful to uncover facial features that may have disappeared. It is also important to evaluate photographs taken when the child is not smiling, because smiling leads to narrowing of the upper lip and thinning of the philtrum. Other physical malformations may also occur in FASD, although the frequency and occurrence of these malformations is poorly defined (Table 3).

The complex neurobehavioural problems may manifest themselves insidiously. For example, attention deficit hyperactivity disorder (ADHD), diagnosed in about half of children with FASD, becomes apparent usually at or near school age. Frequently, these children exhibit impaired social adaptive ability and impaired executive functions, which reflect prefrontal cortex dysfunction. Secondary disabilities[9] are those believed to occur as a result of primary disabilities and are revealed as mental health problems, school dropout and trouble with the law (Table 4).

Coles and colleagues[12] found that, among the factors

Table 2: The Institute of Medicine's diagnostic criteria for fetal alcohol-related abnormalities[11]

Category 1	
FAS with confirmed maternal alcohol exposure	Patients in this category have the classic triad of growth retardation, characteristic facial dysmorphology and neurodevelopmental abnormalities. This is often defined as full-blown FAS
Category 2	
FAS without confirmed maternal alcohol exposure	If the triad described in category 1 is present, a diagnosis of FAS is possible even without confirmed maternal drinking
Category 3	
Partial FAS with confirmed maternal alcohol exposure	Such patients may have only some of the characteristic facial anomalies plus growth retardation or central nervous system neurodevelopmental abnormalities or behavioural/cognitive abnormalities
Category 4	
FAS with confirmed maternal alcohol exposure and alcohol-related birth defects	Patients in this category will have some congenital anomalies as a result of alcohol toxicity
Category 5	
FAS with confirmed maternal alcohol exposure and alcohol-related neurodevelopmental disorder	Patients in this category will have evidence of central nervous system neurodevelopmental abnormalities or a complex pattern of behavioural/cognitive abnormalities, or both, but not necessarily any obvious physical changes

Note: FAS = fetal alcohol syndrome.

protecting against severity of outcomes of FAS, the age of diagnosis is important. Early diagnosis leads to improved management of these children and, hence, decreases the burden of secondary disabilities. Although many children with extensive prenatal alcohol exposure appear normal at birth, they may later be identified with many subtle neurobehavioural deficits not apparent in their early years.

Although overall rates of FASD among heavy drinkers may be relatively low, it is of substantial clinical importance that a woman who has given birth to an affected child has a high risk of having subsequent children also affected if she continues to drink.[13]

Counselling of pregnant women who are light drinkers

Counselling of women who drank small amounts of alcohol before realizing they had conceived is a complex but important task, because an estimated 25% of all pregnant Canadians fall into this group. About 90% of Canadian women know that alcohol "is not good for the unborn baby" and many believe that even brief and mild exposure to alcohol poses fetal risk.[14] Two recent meta-analyses failed to show adverse fetal effects after mild social drinking (up to several drinks a week) by nonalcoholic women.[15,16] In contrast, recent studies suggest significant differences in aggressive and externalized behaviour in 6-year-old children with prenatal exposure to as little as 1 alcoholic beverage a week compared with an unexposed control group.[17] It is clear, however, that substantial prenatal alcohol exposure — either heavy daily or weekend binge drinking — is the rule in children diagnosed with classic FAS.[13]

For physicians, it is a complex task to counsel women to abstain from any drinking during pregnancy while reassuring those who were inadvertently and mildly exposed that, although the threshold of ethanol embryopathy is unknown, there is currently no widely established evidence of fetal risk with such exposure. This "double message" is often poorly understood by the public. Nevertheless, it is unclear what, if any, threshold exists, and the best advice is against the use of alcohol during pregnancy. For women who appear disproportionately worried after having consumed only very small amounts of alcohol before realizing they were pregnant, it is important to remember that more than half the babies of heavy drinkers appear to be spared adverse effects. The reason why one child appears so dramatically affected and another, with similar exposure, appears unaffected is unknown, but it may be due to pharmacogenetic variability in ethanol metabolism, placental transfer or fetal handling of the molecule.[13]

Table 3: Rare birth defects that may also be associated with FAS[4]

Cardiac	Atrial septal defects
	Aberrant great vessels
	Ventricular septal defects
	Tetralogy of Fallot
	Hypoplastic nails
	Clinodactyly
	Shortened fifth digits
	Pectus excavatum and carniatum
Skeletal	Radioulnar synostosis
	Klippel–Feil syndrome
	Hemivertebrae
	Camptodactyly
	Scoliosis
Renal	Aplastic kidneys
	Dysplastic kidneys
	Ureteral duplications
	Hypoplastic kidneys
	Hydronephrosis
	Horseshoe kidneys
Ocular	Strabismus
	Refractive problems secondary to small globes
	Retinal vascular anomalies
Auditory	Conductive hearing loss
	Neurosensory hearing loss
Other	Numerous malformations have been found in some patients with FASD. The etiologic specificity of most of these anomalies to alcohol teratogenesis remains uncertain

Note: FASD = fetal alcohol spectrum disorder.

Laboratory markers of maternal drinking

Several laboratory tests can help to either support or refute the historical information obtained from screening questionnaires. Elevated liver enzymes (specifically isolated gamma glutamyl transferase [GGT] elevations) and a mean corpuscular volume of less than 98 fL may indicate chronic alcoholism.

In 1998 Stoler and colleagues[18] found that the most sensitive combination of laboratory test results predicting maternal alcohol dependence are an elevated GGT level, a mean corpuscular volume of less than 98 fL, a high carbohydrate-deficient transferrin level and a high whole-blood-associated acetaldehyde level.

Table 4: Secondary disabilities associated with FASD[4]

Problem	% of all cases of FASD
Mental health problems	90
Dependent living	80
Employment problems	80
Disruptive school experience	60
Trouble with law	60
Confinement	50
Inappropriate sexual behaviour	50
Alcohol or drug problems	30

Women who use other drugs (cocaine, heroin and barbiturates) while pregnant are at increased risk of also abusing alcohol; thus, testing women and infants for these drugs can also identify children at risk of FASD.[19]

Although it is often in the best interests of the child to identify mothers who have addiction problems, informed consent is still required before testing the woman or her child. If the patient does not understand the potential ramifications of a positive test result, then informed consent has not been obtained.[20]

Because of the short elimination time of many drugs of abuse, analysis of neonatal blood or urine is likely to miss most cases. The hair babies are born with develops during the last trimester, whereas meconium begins to develop in the second trimester of pregnancy. Studies have showed that neonatal hair and meconium are sensitive biologic markers of in utero exposure to cocaine and other drugs of abuse, including heroin, marijuana and barbiturates.[4] In addition to documenting in utero exposure late in pregnancy, a positive neonatal hair test result indicates drug abuse long after pregnancy was diagnosed and, hence, is a marker of maternal addiction. Because there is evidence of health risks for infants cared for by addicted mothers, such information is crucial in ensuring the safety of the infant and in mobilizing medical and social assistance.

A novel meconium test developed at The Hospital for Sick Children, Toronto, makes it possible to detect maternal drinking in the second trimester of pregnancy (Fig. 1).[21,22] Although its exact clinical role is still being determined, this test can detect FAEEs in a sample of neonatal meconium obtained within the first 2–3 days of life. It has a sensitivity of 100% and a specificity of 98% for identifying children of heavy alcohol drinkers.[22]

The case revisited

There are several initial clues leading to the suspicion of Ms. L's problem drinking, including her previous history of drinking while pregnant. She has a positive TWEAK score (5 points). Her elevated GGT level and low-normal mean corpuscular volume may also be clues to a problem with chronic alcohol abuse. Although the results of her initial toxicology screen are negative, this is not surprising given the short elimination time of many of these substances in the body. Ms. L consents to additional testing of her baby after birth, including hair and meconium tests. Hair analysis reveals the metabolite of cocaine, benzoylecgonine, at 5 ng/g of hair (limit of detection 0.5 ng/g). The meconium test is positive for FAEEs at 40 nmol/g (a negative result is 2 nmol/g or less[22]) and for benzoylecgonine at 1.2 μg/g (de-

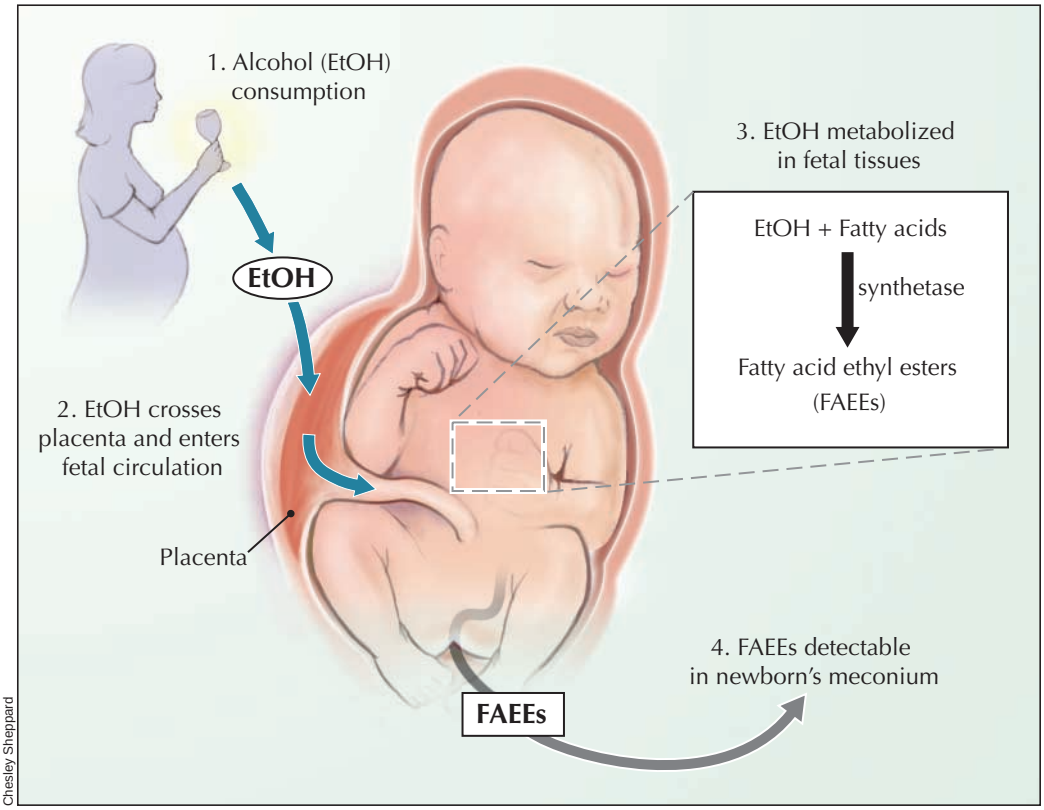

Fig. 1: Neonatal meconium assay for fatty acid ethyl esters (FAEEs). Most of the body's load of ethanol is eliminated after enzyme oxidation to acetaldehyde and water. However, ethanol is also esterified with fatty acids to FAEEs, which can be found in adult blood and tissue. It is now evident that FAEEs can be found in neonatal meconium and may reflect maternal drinking in pregnancy.

tection limit is 50 ng/g). Analysis of the mother's hair is positive for cocaine and its metabolites (cotinine 30 ng/g and benzoylecgonine 42 ng/g).

Thus, according to the history and laboratory evidence, the baby meets many of the criteria for FASD: confirmed alcohol exposure and physical features of FASD, including intrauterine growth retardation, small head circumference and short palpebral fissure. FAS is diagnosed. The baby was also exposed in utero to cocaine, which is associated with potential teratogenic effects, including microencephaly.[23]

At delivery, it is too early to assess whether the baby has any neurodevelopmental effects of the prenatal alcohol exposure, unless these are heralded by gross structural brain anomalies (noted through diagnostic imaging) or severe neurologic impairment. He has an estimated 4%–5% risk of classic FAS (category 1 of the Institute of Medicine classification) and a 30%–40% chance of having an alcohol-related neurodevelopmental disorder (category 5 of the institute's classification). In addition to care by his primary care providers, this baby could benefit from close and frequent neurodevelopmental follow-up, optimally by a multidisciplinary team consisting of a developmental psychologist, a pediatrician and an occupational therapist (other professionals may include a speech and language pathologist and a physiotherapist). It is also important to address the mother's alcohol dependence by offering her care options, such as addiction treatment, mental health therapy and support.[24] While being sensitive to cultural, spiritual, religious and emotional needs of the mother, it is important to ensure that she is offered effective contraception while she is struggling with her addiction program.

Conclusion

Thirty-five years after FAS was first described,[25] the diagnosis of FASD continues to present major challenges, some of which are reflected in this practice review. There is often no history of maternal drinking, and when this is coupled with a lack of pathognomonic physical features or neurobehavioural information, many cases cannot be diagnosed with reasonable conviction. Moreover, among offspring of alcohol-dependent women, there is a well-defined clustering of neuropsychiatric morbidity, which may not necessarily reflect intrauterine effects of ethanol. Last, but not least, diagnostic services for FASD are scarce, and most physicians do not feel well informed or prepared to diagnose FASD.[8] Providing physicians with tools to diagnose and manage FASD can have an impact on the most preventable form of neurodevelopmental deficit in Canadian children.

This article has been peer reviewed.

From the Motherisk Program, Division of Clinical Pharmacology and Toxicology, Hospital for Sick Children and University of Toronto, Toronto, Ont. (Koren, Nulman); the Section of Genetics and Metabolism, Children's Hospital of Winnipeg and University of Manitoba, Winnipeg, Man. (Chudley); and the Department of Pediatrics, Women's and Children's Hospital of British Columbia and Sunny Hill Health Centre, Vancouver, BC (Loocke)

Competing interests: None declared.

Acknowledgements: Gideon Koren is a senior scientist of the Canadian Institutes for Health Research (CIHR). Some of the work presented here was supported by grants from the CIHR, the Hospital for Sick Children's Translational Research Competition and Physicians Services Inc., Toronto, Ont.

References

1. Floyd RL, Decoufle P, Hungerford DW. Alcohol use prior to pregnancy recognition. *Am J Prev Med* 1999;17(2):101-7.
2. Martin JA, Park MM, Sutton PD: Births: preliminary data for 2001. *Natl Vital Stat Rep* 2002;50(10):1-20.
3. Jones KL, Smith DW. Recognition of the fetal alcohol syndrome in early infancy. *Lancet* 1973;2:999-1001.
4. Koren G, Nulman I. *The Motherisk guide to diagnosing fetal alcohol spectrum disorder*. Toronto: The Hospital for Sick Children; 2002.
5. Alcohol use among women of childbearing age — United States, 1991–1999. *MMWR Morb Mortal Wkly Rep* 2002;51(13):273-6.
6. Williams RJ, Odaibo FS, McGee JM. Incidence of fetal alcohol syndrome in northeastern Manitoba. *Can J Public Health* 1999;90(3):192-4.
7. Sampson PD, Streissguth AP, Bookstein FL, Little RE, Clarren SK, Dehaene P, et al. Incidence of fetal alcohol syndrome and prevalence of alcohol related neurodevelopmental disorder. *Teratology* 1997;56(5):317-26.
8. Nevin AC, Parshuram C, Nulman I, Koren G, Einarson A. A survey of physicians' knowledge regarding awareness of maternal alcohol use and the diagnosis of FAS. *BMC Fam Pract* 2001;3(1):2.
9. Bradley KA, Boyd-Wickizer J, Powell SH, Burman ML. Alcohol screening questionnaires in women: a critical review. *JAMA* 1998;280(2):166-71.
10. Chang G, Wilkins-Haug L, Berman S, Goetz MA, Behr H, Hiley A. Alcohol use and pregnancy: improving identification. *Obstet Gynecol* 1998;91(6):892-8.
11. Committee to Study Fetal Alcohol Syndrome, Division of Biobehavioral Sciences and Mental Disorders, Institute of Medicine. *Fetal alcohol syndrome: diagnosis, epidemiology, prevention, and treatment*. Washington: National Academy Press; 1996.
12. Coles CD, Kable JA, Drews-Botsch C, Falek A. Early identification of risk for effects of prenatal alcohol exposure. *J Stud Alcohol* 2000;61(4):607-16.
13. Abel EL. *Fetal alcohol abuse syndrome*. New York: Plenum Press; 1998.
14. Koren G, Koren T, Gladstone J. Mild maternal drinking and pregnancy outcome: preceived versus true risks. *Clin Chim Acta* 1996;246(1-2):155-62.
15. Polygenis D, Wharton S, Malmberg C, Sherman N, Kennedy D, Koren G, et al. Moderate alcohol consumption during pregnancy and the incidence of fetal malformations: a meta-analysis. *Neurotoxicol Teratol* 1998;20(1):61-7.
16. Makarechian N, Agro K, Devlin J, Trepanier E, Koren G, Einarson T. The association between moderate alcohol consumption during pregnancy and spontaneous abortion, stillbirth and premature birth: a meta-analysis. *Can J Clin Pharmacol* 1998;5:169-76.
17. Sood B, Delaney-Black V, Covington C, Nordstrom-Klee B, Ager J, Templin T, et al. Prenatal alcohol exposure and childhood behaviour at age 6 to 7 years: I. dose-response effect. *Pediatrics* 2001;108(2):E34.
18. Stoler JM, Huntington KS, Peterson CM, Peterson KP, Daniel P, Aboagye KK, et al. The prenatal detection of significant alcohol exposure with maternal blood markers. *J Pediatr* 1998;133(3):346-52.
19. Klein J, Chan D, Karaskov T, Koren G. Prevalence of prenatal alcohol and illicit substance exposure in neonates — assessment by meconium analysis [abstract]. *Ther Drug Monit* 2003;25(4):490.
20. Etchells E, Sharpe G, Walsh P, Williams JR, Singer PA. Bioethics for clinicians: 1. Consent. *CMAJ* 1996;155(2):177-80.
21. Bearer CF, Lee S, Salvator AE, Minnes S, Swick A, Yamashita T, et al. Ethyl linoleate in meconium: a biomarker for prenatal ethanol exposure. *Alcohol Clin Exp Res* 1999;23(3):487-93.
22. Chan D, Bar-Oz B, Pellerin B, Paciorek C, Klein J, Kapur B, et al. Population baseline of meconium fatty acid ethyl esters among infants of nondrinking women in Jerusalem and Toronto. *Ther Drug Monit* 2003;25(3):271-8.
23. Addis A, Moretti ME, Ahmed Syed F, Einarson TR, Koren G. Fetal effects of cocaine; an updated meta-analysis. *Reprod Toxicol* 2001;15(4):341-69.
24. Grant TM, Ernst CC, Streissguth AP. An intervention with high-risk mothers who abuse alcohol and drugs: the Seattle Advocacy Model. *Am J Public Health* 1996;86(12):1816-7.
25. Lemoine P. The history of alcoholic fetopathies. *J FAS Int* 2003;1:e2.

Correspondence to: *Dr. Gideon Koren, Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children, 555 University Ave., Toronto ON M5G 1X8; fax 416 813-7562; gkoren@sickkids.ca*