

# Fetal alcohol spectrum disorder

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## 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  $8.5 \times 10^9/L$ , 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<sup>1</sup> and half of all pregnancies are unplanned;<sup>2</sup> 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).<sup>3,4</sup> 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%).<sup>5</sup> 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.<sup>6,7</sup>

## 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.<sup>8</sup> Two such questionnaires (TWEAK and T-ACE) can be used to screen all pregnant women to identify those at risk (Table 1).<sup>9</sup> The CAGE questionnaire is less appropriate for screening pregnant women, because it is less sensitive than TWEAK and T-ACE.<sup>9,10</sup> (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<sup>4</sup>

- 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

**Table 1: Screening questionnaires for diagnosing problem drinking**

<b>TWEAK</b> (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)
<b>T-ACE</b> (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%.<sup>10</sup>  
 \*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.<sup>11</sup> 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<sup>9</sup> 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<sup>12</sup> found that, among the factors

**Table 2: The Institute of Medicine's diagnostic criteria for fetal alcohol-related abnormalities<sup>11</sup>**

<b>Category 1</b>	
FAS with confirmed maternal alcohol exposure	Patients in this category have the classic triad of growth retardation, characteristic facial dysmorphism and neurodevelopmental abnormalities. This is often defined as full-blown FAS
<b>Category 2</b>	
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
<b>Category 3</b>	
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
<b>Category 4</b>	
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
<b>Category 5</b>	
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 neuro-behavioural 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.<sup>13</sup>

### 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.<sup>14</sup> Two recent meta-analyses failed to show adverse fetal effects after mild social drinking (up to several drinks a week) by nonalcoholic women.<sup>15,16</sup> 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.<sup>17</sup> 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.<sup>13</sup>

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.<sup>13</sup>

### 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<sup>18</sup> 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 3: Rare birth defects that may also be associated with FAS<sup>4</sup>**

<b>Cardiac</b>	Atrial septal defects
	Aberrant great vessels
	Ventricular septal defects
	Tetralogy of Fallot
	Hypoplastic nails
	Clinodactyly
	Shortened fifth digits
	Pectus excavatum and carniatum
<b>Skeletal</b>	Radioulnar synostosis
	Klippel–Feil syndrome
	Hemivertebrae
	Camptodactyly
<b>Renal</b>	Scoliosis
	Aplastic kidneys
	Dysplastic kidneys
	Ureteral duplications
	Hypoplastic kidneys
<b>Ocular</b>	Hydronephrosis
	Horseshoe kidneys
	Strabismus
<b>Auditory</b>	Refractive problems secondary to small globes
	Retinal vascular anomalies
<b>Auditory</b>	Conductive hearing loss
	Neurosensory hearing loss
<b>Other</b>	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.

**Table 4: Secondary disabilities associated with FASD<sup>4</sup>**

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.<sup>19</sup>

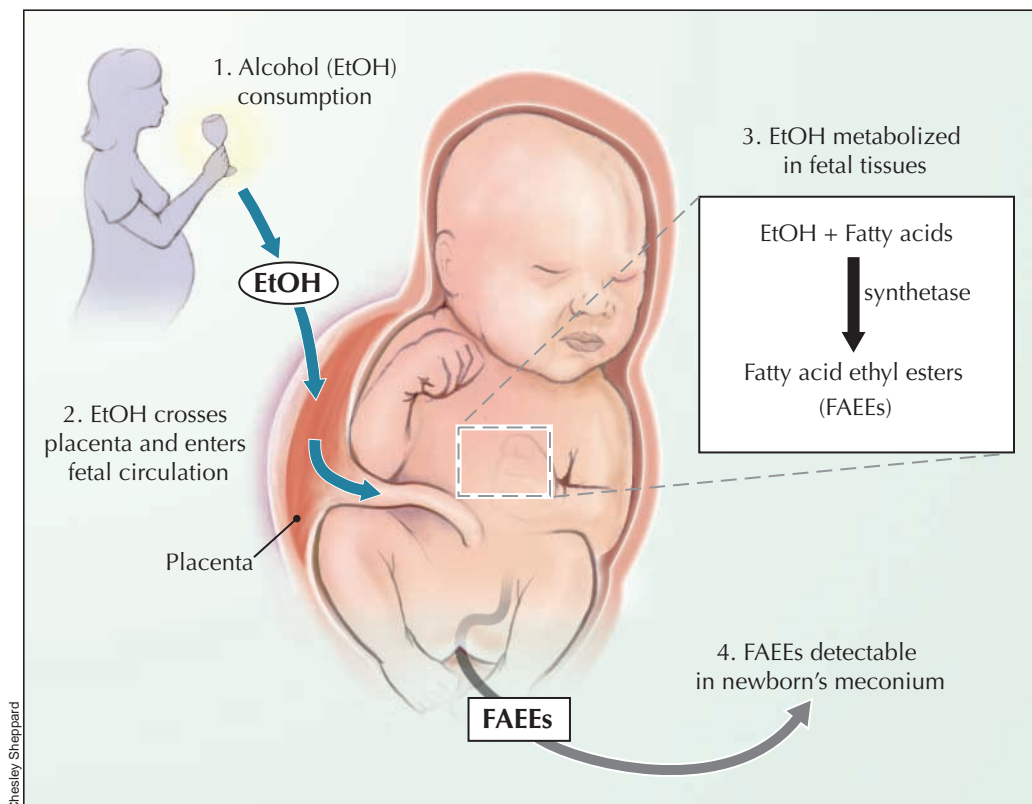
Although it is often in the best interests of the child to identify mothers who have addiction problems, informed consent is still required before testing the woman or her child. If the patient does not understand the potential ramifications of a positive test result, then informed consent has not been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

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.<sup>4</sup> 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).<sup>21,22</sup> 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.<sup>22</sup>

## 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<sup>22</sup>) 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.<sup>23</sup>

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.<sup>24</sup> 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,<sup>25</sup> 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.<sup>8</sup> Providing physicians with tools to diagnose and manage FASD can have an impact on the most preventable form of neurodevelopmental deficit in Canadian children.

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