Fetal alcohol spectrum disorder – New diagnostic initiatives

Rachel Greenbaum MA, Gideon Koren MD

Of all forms of substance abuse, alcohol abuse is the most serious in pregnancy, whether judged by its frequency or capacity to harm the fetus (1). Prenatal alcohol exposure is the most prevalent, single cause of intellectual impairment in children in the western world (2,3).

Although alcohol's role in human teratogenicity was not systematically studied until the 1970s, adverse effects of alcohol consumption during pregnancy have been noted throughout history, dating back to the Bible and Greek history (4). The first scientific study of children of alcoholic mothers was conducted by a British physician, Dr William Sullivan, in 1899. However, until the past few decades, little attention was paid to the plausibility of alcohol being a teratogen. In 1968, an article in France by Lemoine and Lemoine (5) provided the first description in the medical literature of the effects of alcohol on the fetus. Jones and Smith (6) coined the term 'fetal alcohol syndrome' (FAS) in 1973, after recognizing a distinct dysmorphic syndrome associated with gestational alcoholism.

The criteria for the diagnosis of FAS is based on the presence of the following:

- evidence of excessive maternal drinking during pregnancy;
- characteristic facial dysmorphology (ie, microcephaly, poorly developed philtrum, thin upper lip and flattened maxillary area);
- pre- and/or postnatal growth retardation (weight, length and/or height below the 10th percentile); and
- central nervous system (CNS) damage (signs of neurological abnormality, developmental delay, intellectual impairment or neurobehavioural anomalies) (4).

However, very few alcohol-exposed children present with the full-blown syndrome, especially with all the facial features listed for FAS. Moreover, of the dysmorphic characteristics listed, most are not 'disfiguring', and in fact, many lead to appealing or attractive-looking faces. Further, these facial features often tend to fade with age and may become undetectable in adolescence (7,8), whereas the associated CNS damage is life-long and debilitating.

Full-blown FAS encompasses a relatively small proportion of children prenatally affected by alcohol (9,10). It is estimated that only 10% to 40% of the offspring of alcohol-abusing women meet the criteria necessary for a diagnosis of FAS (11). As a consequence, the term 'alcohol-related neurodevelopmental disorder' (ARND) is used to describe the large number of children affected by prenatal alcohol exposure who do not fit all of the criteria for a diagnosis of full-blown FAS (1).

The combined incidence of fetal alcohol-related abnormalities has been estimated to be about 0.91% in the general population and up to 10% to 20% of the population in some Native communities in which drinking in pregnancy is a common lifestyle activity (12). A slightly more conservative estimate of one to three children in a general obstetric population of 1000 was reported by Korkman et al (3) for European communities. The incidence of FAS appears to vary both within and between countries, and was reported to be more than 20 times higher in the United States than in other countries (13).

DIAGNOSING ARND

In 1996, the National Institute of Medicine, Washington, District of Columbia, formally established the diagnostic criteria for ARND (1). These criteria include a history of prenatal alcohol exposure in conjunction with the following.

- There is evidence of CNS neurodevelopmental abnormalities, including any of the following:
  - — decreased cranial size at birth;
  - — structural brain abnormalities (ie, microcephaly,

The Motherisk Program, Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children, University of Toronto, Toronto, Ontario

Correspondence: Dr Gideon Koren, Division of Clinical Pharmacology, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8. Telephone 416-813-5781, fax 416-813-7562, e-mail gkoren@sickkids.ca

partial or complete agenesis of the corpus callosum, cerebellar hypoplasia); and

— neurological hard or soft signs such as impaired fine motor skills, neurosensory hearing loss, poor tandem gait and poor eye-hand coordination.

- There is evidence of a complex pattern of behaviour or of cognitive abnormalities that are inconsistent with the child's developmental level, and they cannot be explained by familial background or by the environment alone. These factors include the following:

—learning difficulties and deficits in school performance;

—poor impulse control;

—problems in social perception;

—deficits in higher level receptive and expressive language;

—poor capacity for abstraction or metacognition;

—specific deficits in mathematical skills; and

—problems in memory, attention or judgment.

CHALLENGES FOR THE PAEDIATRICIAN

In the following section, some of the major challenges are reviewed that are related to the diagnosis of fetal alcohol spectrum disorder (FASD), and that are relevant to the context of paediatric medicine in Canada and other countries.

Despite the establishment of the Institute of Medicine guidelines, diagnostic issues are far from resolved. The absence of pathognomonic facial characteristics in the majority of fetal alcohol-affected children makes identification of the disorder extremely difficult. According to Sampson and colleagues (14),

> *The problem with the FAS face as an indicator of fetal alcohol affected individuals, is poor sensitivity; there are too many false negatives, that is, affected individuals without the FAS face characteristics who are thus often not identified.*

Without diagnoses, these individuals do not receive the services that they require (14), and this may exacerbate existing deficits.

Furthermore, a misconception exists that FAS is on the extreme negative end of a continuum, with ARND representing relatively less negative effects. However, this does not seem to be the case. A longitudinal analysis by Steinhausen et al (15) refuted earlier evidence (16), and showed no linear relationship between the degree of morphological damage and intelligence. This analysis suggests that ARND is a significant disorder in its own right, whether like or distinct from FAS. In a study comparing children with histories of heavy prenatal alcohol exposure who had defining physical dysmorphology, Mattson et al (17) found significant neuropsychological deficits in both groups, regardless of whether physical features were present. Recently, a number of studies have extended these findings to other cognitive domains, and to aspects of behavioural, adaptive and social functioning, confirming that the effects of prenatal alcohol exposure can be as devastating for children with ARND as for children with FAS (18).

In a recent physician survey conducted by the Motherisk Program, most physicians expressed a need to know more about diagnosing this disorder (19). In response to this need, a new national program has been developed to train and certify physicians in the detection and diagnosis of FASD. The program entails a 4-h course that delivers continuing medical education; certification is given after participants have submitted an analysis of two cases. An important pillar of this course was the development of the *Handbook for the Diagnosis of Fetal Alcohol Spectrum Disorder* (20).

In many remote areas of Canada, it is unrealistic to expect children to be mobilized to the few existing clinics in large cities to be given a diagnosis of FAS. The only realistic way to diagnose them is through telemedicine. Presently, the University of Manitoba operates a telediagnosis program with Thompson, Manitoba (Chudley A; personal communication, 2001). A telediagnosis program is being planned that will be based on the ability of physicians certified by the Motherisk program to send to us by mail, by web or through telemedicine all data needed for diagnosis, and the Motherisk team will interact and corroborate the diagnosis of FASD with the local teams across the country.

A critical prerequisite for the diagnosis of FAS is documentation of maternal drinking (1). Due to litiginous fears, fear of loosing a child, shame and embarrassment, women often refrain from reporting their drinking habits during pregnancy. This reality reinforces the need for a biological marker of maternal drinking that is independent of maternal reporting. Over the past few years, the Motherisk team has developed the use of fatty acid ethyl esters (FAEE) as markers of fetal exposure to alcohol. These esters are produced by enzymatic interaction between ethanol and circulating fatty acids, and have been shown to reflect heavy maternal drinking (21).

The Motherisk program is presently examining the feasibility of using meconium FAEE as a screening test for intrauterine exposure to ethanol (22). Because meconium begins to form at around 14 weeks' gestation, the presence of FAEE in meconium reflects maternal drinking taking place long after most mothers have become aware of their pregnancy, and hence, it shows alcohol dependence and a high probability for FASD.

ACKNOWLEDGEMENTS: These projects are supported by: Canadian Institutes of Health Research, Ottawa, Ontario; The Brewers' Association of Canada, Ottawa, Ontario; and The Research Leadership in Better Pharmacotherapy During Pregnancy and Lactation, Toronto, Ontario.

REFERENCES

1. Institute of Medicine of the National Academy of Sciences Committee to study Fetal Alcohol Syndrome. Introduction. In: Stratton K, Howe C, Battaglia F, eds. Fetal Alcohol Syndrome Diagnosis, Epidemiology, Prevention, and Treatment. Washington: National Academy Press, 1996:17-32.
2. Kaemingk K, Paquette A. Effects of prenatal alcohol exposure on neuropsychological functioning. Developmental Neuropsychol 1999;15:111-40.
3. Korkman M, Autti-Ramo I, Koivulehto H, Granstrom M. Neuropsychological effects at early school age of fetal alcohol exposure of varying duration. Child Neuropsychol 1998;4:199-212.
4. Abel EL. Historical background. In: Abel EL, ed. Fetal alcohol Syndrome. New Jersey: Medical Exonomics Books, 1990:1-11.
5. Lemoine P, Lemoine PH. Avenir des enfants de meres alcoholiques (Etudes de 105 cas retrouves a l'age adulte) et quelques constatations d'interet prophylactique. Ann Ped (Paris) 1992;39:226-35.
6. Jones K, Smith D. Recognition of the fetal alcohol syndrome in early infancy. Lancet 1973;ii:999-1001.
7. Berg S, Kinsey K, Lutke J, Wheway D. A Layman's Guide to Fetal Alcohol Syndrome and Possible Fetal Alcohol Effects. Surrey: FAS/E Support Network, 1995.
8. Jacobson SW, Jacobson JL. Teratogenic insult and neurobehavioural function in infancy and childhood. In: Nelson CA, ed. The Effects of Early Adversity on Neurobehavioral Development: The Minnesota Symposia on Child Psychology, vol 31. New Jersey: Erlbaum, Lawrence, Assocs 2000:61-112.
9. Connor P, Streissguth A. Effects of prenatal exposure to alcohol across the lifespan. Alcohol Clin Exp Res 1996;3:148-57.
10. Hagerman R. Fetal alcohol syndrome. In: Hagerman R, ed. Neurodevelopmental Disorders: Diagnosis and Treatment. New York, Oxford: Oxford University Press, 1999:3-59.
11. Roebuck T, Mattson S, Riley E. Behavioural and psychosocial profiles of alcohol-exposed children. Alcohol Clin Exp Res 1999;23:1070-6.
12. Sampson P, Streissguth A, Bookstein F, et al. Incidence of FAS and prevalence of ARND. Teratology 1997;56:317-26.
13. Nulman I, O'Hayan B, Gladstone J, Koren G. The effects of alcohol on the fetal brain: The central nervous system tragedy. In: Chang LW, Slikker W, eds. Handbook of Developmental Neurotoxicology. San Diego: Academy Press, 1998:567-86.
14. Sampson P, Strissguth A, Bookstein F, Barr H. On Categorizations I Analyses of Alcohol Teratogenesis. Environl Health Perspect 2000;108:421-8.
15. Steinhausen H, Nestler V, Sphor H. Development and psychopathology of children with the fetal alcohol syndrome. J Dev Behav Pediatr 1982;3:49-54.
16. Sphor H, Williams J, Steinhausen H. Prenatal alcohol exposure and long-term developmental consequences. Lancet 1993;341:907-10.
17. Mattson S, Riley E, Gramlin L, Delis D, Jones K. Neuropsychological comparison of alcohol-exposed children with or without physical features of FAS. Neuropsychology 1998;12:146-53.
18. Connor P, Sampson P, Bookstein F, Barr H, Streissguth A. Direct and indirect effects of prenatal alcohol damage on executive function. Dev Neuropsychol 2000;18:331-54.
19. Einarson A, Koren G. A survey of physician knowledge regarding awareness of maternal alcohol use and the diagnosis of FAS. Bio Med Central (In Press).
20. Koren G, Nulman I. Handbook for the Diagnosis of Fetal Alcohol Spectrum Disorder. Toronto: Motherisk Program, 2002. <www.motherisk.org> (Version current at March 6, 2002).
21. Bearer E, Lee S, Salvator NE, et al. Ethyl livoleate in meconium: A biomarker for prenatal ethanol exposure. Alcohol Clin Exp Res 1999;23:487-93.
22. Klein J, Karoskovt T, Koren G. Fatty acid ethyl esters: A novel biological marker for heavy in utero exposure. Ther Drug Monit 1999;21:644-6.