

Diagnosis of fetal alcohol spectrum disorder: current practices and future considerations¹

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Abstract: This paper discusses the current state of knowledge and practice for diagnosing fetal alcohol spectrum disorder (FASD). The strengths and challenges of different models of diagnosis are compared. Some models require a team approach for evaluation, while other approaches assume that a clinician in his or her office provides a diagnosis based on a review of the patient's medical and social history, behaviour, and physical examination. The author reviews the emergence of new information from recent advances in genetics, imaging, and electrophysiology that has the potential to lead to changes in practice and improved reliability of an FASD diagnosis.

Key words: guidelines, multidisciplinary team, imaging, genetics, epigenetics.

Résumé : Cet article présente l'état actuel des connaissances et des pratiques relatives au diagnostic des troubles du spectre de l'alcoolisation foetale (TSAF). Les forces et les défis des différents modèles de diagnostic sont comparés. Quelques modèles requièrent une approche par équipe, alors que d'autres assument qu'un clinicien ou une clinicienne dans son bureau peut poser un diagnostic sur la base de la synthèse de l'historique médicale et sociale de la patiente, de ses comportements et de l'examen physique. L'auteur passe en revue l'émergence d'une nouvelle information tirée des progrès récents sur le plan de la génétique, de l'imagerie et de l'électrophysiologie, qui ont le potentiel de mener à des changements dans les pratiques et à des améliorations dans la fiabilité du diagnostic des TSAF. [Traduit par la Rédaction]

Mots-clés : lignes directrices, équipe multidisciplinaire, imagerie, génétique, épigénétique.

Introduction and history

Since the first published description of the role of alcohol in adverse outcomes in children almost 50 years ago (Lemoine et al. 1968; Jones et al. 1973), and the first reference to the term fetal alcohol syndrome (FAS) by Jones and Smith (1973), the extent and variable consequences of prenatal alcohol effects (PAE) has subsequently expanded. The first recognized cases presented with developmental delay, growth impairment, birth defects, microcephaly, and the characteristic facial dysmorphic features (short palpebral fissures, smooth, poorly formed philtrum, and thin vermilion border of the upper lip). Subsequently cases of PAE without growth or facial dysmorphic features were identified and referred to as fetal alcohol effects (FAE) (Clarren and Smith 1978).

The classically affected child with the features of growth impairment, neurodevelopmental delay, and characteristic facial features have the designation of FAS. In those affected individuals with 2 of the 3 facial characteristics or those without growth impairment are designated as having partial FAS (pFAS), and the term alcohol related neurodevelopmental disorder (ARND) was designated for those children who presented with few or absent dysmorphic features, variable combinations of impairments in memory, expressive and receptive language, attention regulation, social adaptation, executive function, motor and sensory functions, cognitive abilities, and academic performance (Stratton et al. 1996). Subsequently, a research group in Washington State presented their method of FAS and related disorders utilizing the 4-digit code with objective measurements of the facial features

using photographic analysis software (Astley and Clarren 2000; Astley 2004). Recently the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), proposed trial diagnostic criteria for PAE and related conditions under the section "Neurodevelopmental Disorders" (American Psychiatric Association 2013). In addition, a revision (Cook et al. 2016) to the Canadian guidelines (Chudley et al. 2005) recommended that the term fetal alcohol spectrum disorder (FASD) be used as a diagnostic term. In the revised guidelines by Cook et al. (2016) FASD was grouped into 2 diagnostic categories: (FASD with sentinel facial findings [essentially FAS]; FASD without sentinel facial findings [essentially pFAS and ARND]). Although the majority of diagnostic guidelines were developed in North America, other countries such as Germany (Landgraf et al. 2013) and Australia (Watkins et al. 2013) have published their own versions of FASD diagnostic guidelines.

It is important to diagnose FASD. Earlier studies suggested that both primary prevention and prevention of secondary disabilities are possible (Streissguth et al. 1996; Astley 2014).

Alcohol probably acts through multiple mechanisms, and undoubtedly timing and degree of exposure (Paintner et al. 2012) and genetic and other environmental factors (Grossman et al. 2003; Zhang et al. 2005; Dick and Bierut 2006; Archer 2011; Ungerer et al. 2013) are important contributors to the variability in the phenotype. The expanded spectrum of effects has contributed to a broader understanding of PAE. However, this has further complicated the diagnostic approach. Because a solitary clinician cannot provide a comprehensive evaluation, the need for a multidisciplinary team assessment of experts became necessary. Although a

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¹This Invited Review is one of a selection of papers covering various aspects of fetal alcohol spectrum disorder (FASD).

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diagnosis is possible at any age, in practice, the common ages for assessment to occur is in school age children, because the diagnostic tools present challenges in diagnosis for both the very young and in adults (as outlined in [Cook et al. 2016](#)). Currently, the evaluation of a child or adult referred for evaluation of possible PAE may involve developmental pediatricians, psychologists, speech and language clinicians, occupational therapists, educational specialists, social workers, and sometimes psychiatrists, neurologists, and other professional disciplines. This complexity and comprehensive assessment has advantages and disadvantages. An important advantage is to have multiple specialists evaluating the child who will derive benefits with the assessment and resulting recommendations of care and intervention. A major disadvantage is the time and costs involved. A Canadian study estimated that an FASD evaluation requires 32 to 47 h for one individual to be screened, referred, admitted, and diagnosed with FASD. This equates to a total cost of \$3110 to \$4570 per person. The total cost of FASD diagnostic services in Canada ranges from \$3.6 to \$5.2 million (lower estimate), and up to \$5.0 to \$7.3 million (upper estimate) annually ([Popova et al. 2013](#)). Another Canadian study noted an extension of wait times for evaluation, which stretches a medical system that has limited capacity ([Clarren et al. 2011](#)).

The need for objective criteria for a diagnosis of the various manifestations of PAE is clear, but this has not been easy to achieve on a universal basis. The absence of a biological marker to confirm or refute a clinical diagnosis has also hampered our ability to accurately, efficiently, and cost-effectively diagnose FASD. Having a universal and reliable diagnostic method would improve the reliability of prevalence estimates, result in earlier diagnosis, improve strategies for prevention and intervention, enhance common training programs for team development internationally, and reduce the waiting lists of suspected cases that may screen negative for a key biomarker.

The first attempt to develop a method for diagnosis that would incorporate the nondysmorphic child was published by the US National Academy of Medicine (NAM) ([Stratton et al. 1996](#)). Many other methods soon followed ([Astley and Clarren 2000](#); [Bertrand et al. 2004](#); [Chudley et al. 2005](#); [Hoyme et al. 2005, 2016](#); [Coles et al. 2016](#); [Cook et al. 2016](#)). To date, several diagnostic methods have been developed, implemented, and utilized, with many similarities in the approach to diagnosis, but with some important differences ([Coles et al. 2016](#)). [Coles et al. \(2016\)](#) compared several systems of diagnosis but was unable to identify which study was the most reliable in the absence of a gold standard for diagnosis or a diagnostic biomarker. Most diagnostic services have been concentrated in the USA and Canada ([Peardon et al. 2008](#)). A comparison of features of the more commonly used diagnostic methods are outlined in [Table 1](#).

Differential diagnosis

Because a specific biological marker is not yet available to confirm a diagnosis of FASD, the current approach depends on a thorough assessment of the child and the exclusion of other disorders that might mimic FASD. The differential diagnosis for FASD is very broad, particularly when few or no classical dysmorphic features of FAS are evident. Reviews of this are available in several publications ([Stratton et al. 1996](#); [Chudley et al. 2005](#); [Leibson et al. 2014](#)).

There is also the concern of co-morbidities and FASD. A recent literature review and meta-analysis confirmed that over 400 co-morbidities spanning 18 of 22 International Classification of Diseases (ICD) chapters have been reported in children with FASD ([Popova et al. 2016](#)). The pooled prevalence of some co-morbidities were several times greater in the FAS population when compared with the general population. For example, sensorineural and conductive hearing loss was estimated to be 129 times more frequent in the FAS population than in the general population of the US.

Children with other genetic disorders or genetic syndromes associated with developmental delays or intellectual disabilities may also have had PAE. In most cases with PAE in which a genetic disorder has been confirmed by a clinical geneticist or genetic testing, it would be virtually impossible to determine whether those individuals meet the diagnostic criteria for FASD, in the absence of a biomarker of effect specific to FASD. In these cases the disability resulting from the genetic disorder or syndrome will likely mask and (or) over-ride the effects of PAE.

Genetic testing is relevant to the diagnostic process for possible FASD in children who present with anomalies, are dysmorphic, or have more severe cognitive impairment (IQ < 60). Clinical geneticists are trained in dysmorphology, and pediatricians should involve geneticists in consultation for any child that is considered dysmorphic, whether or not PAE has been confirmed. A recent review of a genetics clinic experience in Manchester, England, determined that of 80 children referred for FAS assessment, only 20% were confirmed to have a diagnosis of FAS. ([Douzgou et al. 2012](#)) The most common alternate diagnosis was a chromosome anomaly (8.75%). Therefore, a genetic assessment was of particular value in excluding other diagnoses and providing accurate information to care givers.

In another study from Amsterdam, 27 children were evaluated in a genetics clinic for possible FAS ([Abdelmalik et al. 2013](#)). Two were identified as having a pathogenic microstructural chromosomal rearrangement. The authors cautioned that 22 of the children had other factors that may have affected their intellectual abilities, such as familial intellectual disability and social deprivation.

In those children with a suspected genetic disorder, select genetic testing to confirm a diagnosis is appropriate. In those children who do not present with a bona-fide recognizable genetic syndrome, a chromosome microarray analysis is indicated. In nondysmorphic children referred for FASD evaluation, in which there has been significant PAE and in which there is no obvious explanation in the family history or the child for the disability, genetic investigations probably have a limited value.

Maternal alcohol history

An important feature of the history is confirming PAE. Most guidelines require that reliable information on the timing, frequency, and amounts of alcohol ingested during the pregnancy is important to obtain, but often difficult, for several reasons.

Screening for alcohol use during pregnancy will identify at-risk pregnant women, who may be placing their child at risk for FASD. This would facilitate the implementation of appropriate interventions at the earliest time point ([Leonardson et al. 2007](#)). There is no known safe level of alcohol consumption during pregnancy. There is research to suggest that even low to moderate levels of PAE exposure can negatively impact a fetus, and these adverse consequences can persist into adulthood ([Olson et al. 1997](#); [Jacobson and Jacobson 2010](#); [Eckstrand et al. 2012](#); [Day et al. 2013](#)). A reliable and accurate history of maternal alcohol consumption is the best screening tool for FASD ([Cook et al. 2016](#)).

The following factors increase the risk for PAE ([Cook et al. 2016](#)): a woman's consumption of alcohol during pregnancy ([Abel and Hannigan 1995](#)); a prior history of alcohol consumption ([Bobo et al. 2007](#); [Anderson et al. 2013](#)); a family background of alcohol use ([Leonardson et al. 2007](#)); a history of in-patient treatment for problematic alcohol and (or) substance use and (or) a history of mental health problems ([Astley et al. 2000a, 2000b](#)); the previous birth of a child with FASD ([Astley et al. 2000a](#); [Kvigne et al. 2003](#)); a lack of contraception/unplanned pregnancy ([Astley et al. 2000a](#)); a history of physical/emotional/sexual abuse ([Astley et al. 2000a](#)); low income and (or) limited access to health care ([Astley et al. 2000a, 2000b](#); [Anderson et al. 2013](#)). It is therefore prudent for

Table 1. Comparison of common systems of diagnosis in North America.

Diagnostic guideline	Clinical terms	Origin of system	Utility	Strengths	Challenges
Institute of Medicine (IOM) ^a	FAS, partial FAS, ARND	National-expert clinicians and researchers from the USA	Prototype for Hoyme and Canadian Guidelines	A prototype that has evolved and adopted to varying degrees by other guidelines	Historical use; does not provide any details of non-dysmorphic forms of FASD
Four-digit code ^b	FAS; partial FAS; static encephalopathy–alcohol exposed; neurobehavioural disorder–alcohol exposed; a total of 22 diagnostic categories	Regional-expert researchers and clinicians in the State of Washington	Used by many USA Centres and internationally	Detailed, objective and evidence based; categorizes physical features and brain impairments in graded manner	Very complex diagnostic terms and categories; some terms only accepted in the State of Washington for funding purposes
Centre for Disease Control (CDC) ^c	FAS	National	Used in USA	Re-iterates many features of the IOM	Does not provide any details of nondysmorphic forms of FASD
Hoyme ^{d,e}	FAS, partial FAS, ARND	A large research collaboration of clinicians and researchers in USA	Used by many Centres in USA and internationally	Details issues of dysmorphology and good explanation of alcohol exposure risks	Used in many published papers internationally and excludes individuals without dysmorphic features or normal growth
Canadian ^f	FAS, partial FAS, ARND	National-pan-Canadian	Used by most FASD clinics in Canada and several centres internationally	National collaboration with harmonization of terms from IOM and 4-digit code; more specific definition of brain domains	Uses term ARND which has some limitations with less acceptability amongst some experts
Canadian ^g	FASD with sentinel facial features; FASD without sentinel facial features	National-pan-Canadian	Used by most FASD Centres in Canada. Discusses special issues of diagnosis relevant to very young children and adults	Defines levels of evidence for recommendations and reduces the diagnostic categories to 2; presence of facial features or growth impairments not required in diagnostic category 2; redefines and clarifies brain domains	Currently undergoing “trials” and being phased in several Canadian clinics
Diagnostic and Statistical Manual 5th edition (DSM-5) ^h	ND-PAE	Psychiatric and psychology professionals	Mental health specialists; placed in section of DSM-5 for conditions for further study	Facilitates recognition of the treatment needs of individuals negatively impacted by PAE who may or may not have the physical effects of PAE	Concern that this may move diagnosis away from a comprehensive multidisciplinary team approach to a diagnosis in a mental health professional’s office

Note: FASD, fetal alcohol syndrome disorder; ARND, alcohol related neurodevelopmental disorder; IOM, Institute of Medicine; ND-PAE, neurobehavioral disorders associated with prenatal alcohol exposure; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition.

^aStratton et al. 1996.

^bAstley 2004.

^cBertrand et al. 2004.

^{d,e}Hoyme et al. 2005, 2016.

^fChudley et al. 2005.

^gCook et al. 2016.

^hAmerican Psychiatric Association 2013.

service providers to determine alcohol use among all women of childbearing age.

There are those who question the role of PAE and the diagnosis of FASD in children without growth abnormalities and (or) without sentinel facial features of FAS. This is a complex issue of attribution of causation, with the need to carefully exclude other genetic or environmental circumstances that might also cause the developmental delays and behavioural issues.

Genetic and epigenetic findings as biomarkers in FASD

Cynthia Bearer (Bearer 2001) has defined the different categories of biomarkers. She stated that

“The three categories of biomarkers are: biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility. The markers fall along the spectrum from exposure (e.g., prenatal exposure to alcohol) to disease (e.g., fetal alcohol syndrome). Biomarkers of exposure are designed to detect exposure rather than the effect of exposure. Conversely, biomarkers of effect are designed to detect the effect of exposure or the development of disease. Biomarkers of susceptibility can mark increased vulnerability at any of the steps between exposure and clinical disease”.

The search for a reliable biomarker of effect would clearly enhance the diagnostic process. Biomarkers of exposure would help to define those who have been exposed in utero, and therefore are at risk for developing clinical effects such as FASD, as has been seen, in part, with the altered free fatty acid ethyl ester ratios found in meconium from exposed fetuses. (Bearer et al. 2004–2005).

FASD is a classic example of a multifactorial condition in which causation is the result of genetic and environmental factors (Reynolds et al. 2011). Notwithstanding the important direct toxic effects of ethanol and its metabolically derived break down products, other environmental modifiers include maternal stress, nutritional status, and age. Numerous studies have shown that the genes involved in the oxidative reduction of ethanol can be protective or could increase the susceptibility of the exposed fetus, depending on the polymorphic variants that are inherited (Warren and Li 2005; Chudley 2011; Liyanage et al. 2017). The enzymes alcohol dehydrogenase (ADH) within the cytosol, aldehyde dehydrogenase (ALDH) within peroxisomes, and cytochrome P450 2E1 (CYP2E1) in the endoplasmic reticulum are key in the metabolism of ethanol. All of these enzymes genes have polymorphic variants, and some of these variants can lead to further cellular damage to cells involved in early development of the fetus. The by-products of ethanol metabolism include acetaldehyde, acetate, and oxygen free radicals, all of which can alter cell metabolism or directly damage cells. The harmful effects of acetaldehyde-DNA adducts that activate DNA damage pathways may also be involved in altering DNA replication or gene expression (Liyanage et al. 2017).

Recent studies have focused on the role of epigenetic changes due to PAE and their role in altering gene expression, particularly genes that are involved in neurodevelopmental processes (Haycock 2009; Kobor and Weinberg 2011; McCarthy and Eberhart 2014; Portales-Casamar et al. 2016). Early evidence suggested that a characteristic epigenetic “signature” of both prenatal alcohol exposure and effect may be present in children with FASD when compared with children who have not been exposed prenatally to alcohol (Laufer et al. 2015; Portales-Casamar et al. 2016). More research to validate this possibility is required in larger research samples from diverse populations of individuals with FASD. The identification of a reliable signature based on genetic and epigenetic changes would aid tremendously in the early identification, diagnosis, and intervention for children with FASD.

Advances in imaging and neuroelectrophysiology in the diagnosis of FASD

At present, the use of neuroimaging such as magnetic resonance imaging (MRI), functional MRI (fMRI), diffusion tensor imaging (DTI) (white matter tractography), and positron emission tomography (PET) has identified interesting differences in FASD individuals when compared with controls (Norman et al. 2009; Maliszka et al. 2012; Donald et al. 2015; O’Conaill et al. 2015).

Many studies of FASD have reported smaller total brain volume and smaller volume of white and grey matter in specific cortical regions (Donald et al. 2015; Treit et al. 2016). Structural MRI findings often show altered shape and volume of the corpus callosum, the basal ganglia, and hippocampus. DTI studies show lower fractional anisotropy in the corpus callosum. Altered neurometabolic profiles were found in the frontal and parietal cortex, thalamus, and dentate nuclei. fMRI studies revealed reduced functional connectivity between cortical and deep grey matter structures (Donald et al. 2015). Clearly more studies are needed to determine how these technologies may be integrated into the diagnostic process. Currently, these technologies are limited to select individuals presenting with neurological changes associated with FASD, or for research purposes, to better understand and elucidate the harmful effects of alcohol on neurodevelopment as well as brain structure and function.

Electrophysiological investigations to assess saccadic eye movements and oculomotor function have revealed interesting findings in FASD children (Green et al. 2007; Reynolds et al. 2011; Paolozza et al. 2014). FASD children had elongated reaction times, excessive direction errors, and no express saccades. These results reflect deficits in executive function and motor control, and are consistent with dysfunction of the frontal lobes, possibly due to disrupted inhibitory mechanisms (Green et al. 2007). Green et al. (2009) demonstrated that eye tracking can be used as an objective measure of brain injury in FASD, revealing behavioral deficits in all three diagnostic subgroups independent of facial dysmorphism. Paolozza et al. (2014) assessed response inhibition deficits in children with FASD/PAE. Their results showed FASD children had difficulty controlling saccadic eye movements, which may point to overlapping brain regions damaged by prenatal alcohol exposure. Their study demonstrated that eye movement control tasks directly relate to outcome measures obtained with psychometric tests and may lead to earlier identification of children who would benefit from a FASD multidisciplinary diagnostic assessment.

Future consideration for FASD diagnosis

The diagnosis of FASD requires a multidisciplinary team with review of social, medical, educational, and birth records. Documenting alcohol exposure is essential, particularly when the child does not present with the sentinel facial features. Detailed assessments of the child with attention to behaviour and evaluation for dysmorphic features are key. Unfortunately, there are many methods for diagnosis, each with their own merits, but too many discrepancies exist. This leads to difficulty in validating a diagnosis, reduces the reliability of prevalence estimates, and hampers the evaluation of intervention strategies for therapy and prevention. Ideally, an international body of researchers and clinicians could consider developing a global consensus for FASD diagnosis using evidence-based criteria.

With recent advances in technology for assessing brain function through imaging, electrophysiological studies, and genetic and epigenetic investigations using reliable, validated biomarkers of exposure and effect, the reliability of a FASD diagnosis may be further enhanced.

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