

The Standardization of Diagnostic Criteria for Fetal Alcohol Spectrum Disorder (FASD): Implications for Research, Clinical Practice and Population Health

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La normalisation des critères diagnostiques du trouble du spectre de l'alcoolisation fœtale (TSAF) : implications pour la recherche, la pratique clinique et la santé de la population

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Abstract

Objective: Fetal Alcohol Spectrum Disorder (FASD) is a preventable disorder caused by maternal alcohol consumption and marked by a range of physical and mental disabilities. Although recognized by the scientific and medical community as a clinical disorder, no internationally standardized diagnostic tool yet exists for FASD.

Methods and Results: This review seeks to analyse the discrepancies in existing diagnostic tools for FASD, and the repercussions these differences have on research, public health, and government policy.

Conclusions: Disagreement on the adoption of a standardised tool is reflective of existing gaps in research on the conditions and factors that influence fetal vulnerability to damage from exposure. This discordance has led to variability in research findings, inconsistencies in government messaging, and misdiagnoses or missed diagnoses. The objective measurement of the timing and level of prenatal alcohol exposure is key to bridging these gaps; however, there is conflicting or limited evidence to support the use of existing measures.

Abrégé

Objectif : Le trouble du spectre de l'alcoolisation fœtale (TSAF) est un trouble évitable, marqué d'une série de déficiences physiques et mentales, qui est causé par la consommation d'alcool de la mère. Bien qu'il soit reconnu comme trouble clinique par la communauté scientifique et médicale, aucun instrument diagnostique internationalement normalisé n'existe encore pour le TSAF.

Méthodes et Résultats : Cette revue cherche à analyser les disparités des instruments diagnostiques existants pour le TSAF, et les répercussions de ces différences sur la recherche, la santé publique et les politiques du gouvernement.

Conclusions: La mésentente sur l'adoption d'un instrument normalisé reflète les lacunes existantes de la recherche sur les conditions et les facteurs qui influent sur la vulnérabilité fœtale aux dommages de l'exposition. Cette discordance a mené à la variabilité des résultats de recherche, à des messages incohérents du gouvernement, et à des diagnostics faussés ou ratés. La mesure objective de la chronologie et du niveau de l'exposition prénatale à l'alcool est essentielle pour combler ces lacunes, toutefois, les données probantes qui soutiennent l'utilisation des mesures existantes sont conflictuelles ou limitées.

Keywords

fetal alcohol spectrum disorder, fetal alcohol syndrome, diagnostic guidelines, diagnosis phenotypes

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Introduction

Fetal alcohol spectrum disorder (FASD) describes a range of physical and mental disabilities caused by alcohol consumption during pregnancy. ^{1,2} It is estimated that 630,000 children are born with FASD globally annually. ³ This figure, however, is based solely on published studies. As there is limited information available on the prevalence of FASD in many countries, the global prevalence rate may be significantly higher.

Since the first formal recognitions of FASD, ^{4,5} numerous diagnostic guidelines, criteria, and recommendations have been proposed. ^{2,6-17} Most are similar for the most severe form of FASD—fetal alcohol syndrome (FAS)—but differ in specificity of recommendations, criteria, clinical cut-offs and nomenclature for less severe forms. ^{6,7,12,13,18} This leads to uncertainty around the social and economic cost of this preventable disorder.

We review the development of existing diagnostic tools and examine the potential impact the lack of diagnostic standardization has on clinical practice, research, and population health.

Methodology

A search of the biomedical electronic database PubMed was conducted to identify primary studies and systematic reviews that analyzed, evaluated, and/or compared and contrasted diagnostic tools for FASD. Reference lists from retrieved articles, and grey references were used to identify additional studies. Grey references were obtained by a Google search. Non-English studies were largely excluded.

Overview of Diagnostic Tools

Institute of Medicine (IOM) Criteria for FASD Diagnosis

In 1996, the United States Congress mandated the Institute of Medicine (IOM) to conduct a study of FAS and related birth defects. In part, the objective was to develop diagnostic guidelines '... which could subsequently be used in epidemiologic, clinical, and basic research.' They included 4 subtypes of FASD; in order of severity, these are FAS, partial FAS (pFAS), alcohol-related neurodevelopmental disorder (ARND), and alcohol-related birth defects (ARBD). FAS is described as presenting '... with growth deficiency, with height or weight below the 10th percentile, facial characteristics (e.g., small eyes, smooth philtrum, and thin upper lip), CNS damage (structural, neurological, and/or functional impairment); pFAS presents with some but not all of the physiological symptoms of FAS. Patients with ARND do not present with any facial deformities but have symptoms of CNS damage associated with FAS. Patients with ARBD present with physical defects, such as malformations of the heart, bone, kidney, vision, or hearing systems.

The IOM was criticized as lacking criteria for diagnostic categories and clinical definitions for ARBD and ARND, and the need for the documentation of family and genetic history. The Canadian guidelines (below) also criticized the definition IOM uses for partial FAS, claiming that 'using the term partial FAS in the absence of measurable brain deficits could be harmful for the individual because the diagnosis of partial FAS implies brain dysfunction.' 19

Hoyme and colleagues (2005 and 2016) provide greater clarification on clinical criteria, claiming to 'operationalize the IOM categories'. R,20 The amended criteria provide a more defined demarcation of 'documented' prenatal alcohol exposure (PAE), and better describes the neurobehavioural criteria for the diagnosis of FAS, pFAS, and ARND. Hoyme and colleagues also revised the diagnostic criteria for ARBD, provided an updated research dysmorphology scoring system, and a new lip/philtrum guide incorporating a 45-degree view.

CDC FAS: Guidelines for Referral and Diagnosis

In 2002, the U.S. Congress mandated the Centers for Disease Control (CDC) to develop guidelines for FAS diagnosis to be incorporated into medical guidelines and curricula, and be recognized by professional organizations and accrediting boards. ¹⁰ Guidelines only include criteria for FAS and do not include other subcategories of FASD. ¹⁶ The CDC reported that no existing criteria were uniformly accepted, and that the IOM criteria did not provide reliability and accuracy, nor take into consideration ethnic or differential diagnostic considerations.

4-Digit Diagnostic Code

The 4-Digit Diagnostic Code, the 'Washington Criteria', (1997, updated in 1999 and 2004) created a more sensitive diagnostic tool than the IOM, using 4 key common and accepted diagnostic features of FAS (growth deficiency, the FAS facial phenotype, CNS damage or dysfunction, and gestational exposure to alcohol), ranking each on a 4-point Likert Scale. ¹¹ Its purpose was to 'improve the ease, accuracy, and reproducibility of diagnoses across the full spectrum of FASD'. ²¹ This tool is currently used in clinics in the US and Canada. ¹²

Although developed to create a single, standardized diagnostic guideline, it was criticised for being impractical in real-world applications and not controlling for differential diagnosis, motivating Hoyme and colleagues to provide updated IOM guidelines in 2005.

Canadian Guidelines for Diagnosis

In 2005 (and later reviewed in 2015), a subcommittee of the Public Health Agency of Canada's National Advisory Committee on Fetal Alcohol Spectrum Disorder created a comprehensive guideline for the diagnosis of FASD, in

conjunction and consultation with the 2002 CDC guidelines. The purpose was to reach agreement on a Canadian standard for diagnosis. IOM Criteria and 4-Digit Diagnostic Code were harmonized: IOM terminology was used, and the 4-Digit approach to describing, assessing, and measuring features indicative of FAS was adopted. The guidelines recommend review by a multidisciplinary team, a neurobehavioural assessment, analysis and documentation of maternal alcohol history, and a differential diagnosis.² A significant number of Canadian clinics claim to use the 2005 Canadian guidelines.²²

The 2015 update to this guideline included several amendments: 12

- The use of fetal alcohol spectrum disorder (FASD) as a diagnostic term.
- The inclusion of special considerations for diagnosing FASD in infants, young children, and adults.
- The deletion of "growth" as a diagnostic criterion.
- The addition of a new "at-risk" category for FASD.
- Revision and refinement of brain domains evaluated in the neurodevelopmental assessment.

Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-5)

The DSM-5 diagnosis 'Neurodevelopmental Disorder Associated with Prenatal Alcohol Exposure" (ND-PAE)' describes the range of neuro-disabilities associated with prenatal alcohol exposure (PAE). ND-PAE can be diagnosed regardless of the presence or absence of the physical effects of PAE. ¹⁸ Confirmation of maternal alcohol consumption is required. Although ND-PAE is mentioned under 'other specified neurodevelopmental disorder', no diagnostic criteria or detailed description is provided in the DSM-5. ¹³ Further reference is made under 'conditions needing further study'. The proposed criteria for ND-PAE do not include criteria for recognizing facial deformities characteristic of more severe cases, nor do they recognize FASD subtypes.

DSM-5 is believed to have incorporated new terminology and diagnostic criteria to remedy the lack in clarity and consistency across existing diagnostic systems around less severe forms of FASD. ¹⁸ The proposed criteria emphasize psychometric measurements over features that might arguably be attributed to familial genetics (e.g., head circumference, facial dysmorphic features, and body length and weight). ¹⁸ The DSM-5 criteria, although not yet validated, are widely used. ^{6,18}

ICD-10

According to the American Academy of Pediatrics, the following ICD-10 codes can be used for a primary diagnosis of FASD:^{10,23}

- P04.3 Newborn (suspected to be) affected by maternal use of alcohol (excludes FAS)
- Q86.0 FAS (dysmorphic) *no further description offered for this specific code.
- F06.30 Mood disorder due to known physiological condition, unspecified
- P00.4 Newborn (suspected to be) affected by maternal nutritional disorders
- P01.9 Newborn (suspected to be) affected by maternal complication of pregnancy, unspecified
- G93.4 Encephalopathy, other and unspecified (static)
- G96.8 Other specified disorders of central nervous system
- G96.9 Disorder of central nervous system, unspecified

Alcohol: Teratogenic Mechanisms of Prenatal Alcohol Exposures

The recognition of FASD as a clinical disorder is established. There is scientific evidence that CNS damage (structural, neurological, and/or functional impairment) linked to prenatal exposure to alcohol is characteristic of FASD in all subtypes, and recognized in all diagnostic tools. 6,12 The teratogenic mechanisms of alcohol on brain structure and function at a cellular level, described largely through animal studies, have demonstrated sensitivity of the brain to PAE and have resulted in successfully modelling select behavioural deficits associated with FASD.²⁴⁻²⁷ Basic studies of brain structure and function have shown that alcohol exposure may influence calcium signalling pathways,²⁸ and alter glutamate receptor function, 29 resulting in increased oxidative stress and neuronal damage due to hypoxia.²⁴ In addition to those processes related to apoptotic neurodegeneration,³⁰ there is evidence for genetic changes that may include epigenetic consequences: these include altering DNA methylation patterns, ^{31,32} inducing histone modification, enrichment of histone acetylation (H3K9 ac) and methylation (H3K27me2,3, and H3K9me2), and increased expression of histone acetyltransferases and methyltransferases.³³ The structural consequences include impairment of neuronal proliferation and migration, 24,34 including GABAergic inter-neuronal migration. 35 Evidence from these and other preclinical studies indicate clearly that alcoholinduced neuronal disruptions can lead to wide-spread structural and functional brain malformations, affecting cognitive performance and behaviour. 36-45

Longitudinal human studies have provided key evidence for the altered trajectory of brain development in children and adolescents diagnosed with FASD. Abnormalities were observed in cortical volume and thickness, varying depending on brain tissue type and region. Grey matter in healthy development follows an inverse U-shape trajectory, possibly reflecting the natural process of neural plasticity followed by refinement. Greater decreases in grey matter inversely correlated with increased IQ. Individuals with FASD,

however, exhibit a more linear downward trajectory, with greater decreases in grey matter correlating with decreased IQ. 50-52 White matter mean diffusivity increased earlier in childhood in healthy controls than in FASD groups, suggesting delayed neural refinement and axonal myelination in FASD groups. 52 There was a concentration of abnormalities observed in medial brain regions. 50-53 This may be reflective of prenatal disturbances to the midline tissues of the neural tube, which is particularly vulnerable to the teratogenic effects of alcohol exposure during embryogenesis.⁵⁴ Longitudinal studies also provide insight into brain activation differences between healthy controls and FASD groups, observing group differences in both neuronal recruitment patterns and functional MRI signal intensity over time (increased intensity in controls, decreased intensity for FASD groups).55

Ambiguity Leads to Discrepancy

Although there is conclusive evidence that alcohol is teratogenic, human studies have failed to elucidate the doseresponse relationship between alcohol and FASD.⁵⁶ There are 3 significant gaps that promote ambiguity. First, although it is now widely accepted that exposure to moderate to heavy concentrations of alcohol can be detrimental to the health of the developing embryo or foetus, studies examining the effects of low levels of exposure are inconclusive. 57-64 Second, there are gaps in knowledge about what impedes and/or facilitates the teratogenic vulnerability of a foetus. A foetus' susceptibility to FASD may be modified by genetic susceptibility, maternal health, 65,66 or maternal environment (socioeconomic status, availability of healthy food and vitamins, stress, among others). 67,68 Third, FASD can be misdiagnosed or underdiagnosed because children with FASD may not express the 'complete' phenotype or may present subtle physical symptoms (e.g., pFAS, ARBD, ARND), and the lack of adequate follow-up, communication, and consideration in diagnostic processes can lead to a failure in identification. 7,8,11,69,70 A 2015 study of 547 children who underwent a comprehensive diagnostic evaluation found a missed diagnosis rate of over 80% and a misdiagnosis rate of 6.4%.⁷¹ The consequence is that '... the majority of these cases go undetected until secondary disabilities develop and the child has begun their schooling.'72 Early diagnosis facilitates earlier developmental interventions and supports, potentially improving the child's quality of life and social functioning.

Diagnostic discrepancies between diagnostic tools lead to variability in research findings (e.g., prevalence rates), and inconsistencies in government messaging. Objective measurement of the timing and level of PAE is key to bridging these gaps.

Difficulty in Measuring PAE

Measurement of PAE may be based on maternal surveys and interviews, clinical observation, medical records, and/or the

examination and measurement of known biomarkers in fluids, such as maternal blood, sweat, oral fluid, hair, and placenta, and/or newborn blood, urine, hair, and meconium. ^{72,73} There is conflicting or limited evidence to support the use of these tools.

A systematic review found T-ACE and TWEAK questionnaires to have similar sensitivities and specificities, and were concluded to be '... efficient screening tools for identifying alcohol consumption during pregnancy.'^{74,75} But tools do not identify all at-risk individual, or provide a detailed account of PAE (e.g., frequency, concentration, and/or developmental stage of exposure). Self-report is not an accurate measure of alcohol consumption in pregnancy, due to factors like underreporting and recall bias.⁷⁶ The validity of patient response is influenced by the interview environment, context of the interviews, how questions are posed, among other reasons.⁷⁷ Some advocate for a combination of questionnaires and/or self-reporting and biomarker testing.^{78,79}

There is insufficient evidence to support the use of existing biomarkers for accurate PAE measurement in practice.⁷³ They provide minimal information about alcohol consumption, are cumbersome, and require repeated application. 73,79 Target population groups may avoid disclosing accurate information or participating in research or measuring maternal alcohol consumption through biomarker testing or interviews and surveys due to concerns of negative stereotyping, 80 fear of reprisals, 81 and a perceived lack of benefit of the detection of alcohol consumption and FAS diagnosis. 82 An assessment of the willingness of women at risk to participate in a meconium fatty acid ethyl ester (FAEE) screening program found low participation rates, and this was attributed to possible maternal, '... embarrassment, guilt, fears of stigmatization and child apprehension (despite assurance otherwise).'81

Discrepancies in Diagnostic Tools

In the absence of an objective test or biomarker that can reliably identify FASD, disagreement within diagnostic tools arises regarding what diagnostic criteria can definitively and reliably identify a child with FASD. Physical features are an area of contention in diagnostic systems. The 4-Digit diagnostic code, Canadian guidelines, and CDC Guidelines require 3 facial features for FAS diagnosis, and Hoyme requires 2 facial features. 8,10,12,83 Some sources argue that the physical pattern of malformation for FAS, '... remains the only substitute for a specific "biomarker" of exposure, '6 which argues that, 'the pattern of physical features of FAS is today considered specific enough that a diagnosis of FAS can be established in the absence of confirmation of prenatal alcohol exposure,' but acknowledge that physical features may only be found in the most severe subset of patients with FASD (FAS). Alternatively, DSM-5 criteria for ND-PAE emphasize the measurement or observation of neurocognitive impairments and do not consider the presence or absence of dysmorphic physical symptoms. ¹⁸

The DSM-5 requires confirmation of maternal alcohol consumption, specifically consumption that is, '...above "minimal" levels (>13 drinks/month and >2 drinks/occasion)'. This threshold was suggested in reflection of a high base rate of drinking amongst women of child-bearing years, as a minimum level, to avoid 'over-use of diagnosis.' Some tools, however, such as IOM/Hoyme, 7,8,20 do not require confirmation of PAE for FAS diagnosis.

A study examining 5 diagnostic tools (IOM/Hoyme, 4-Digit Diagnosis, Canadian guidelines, CDC guidelines, Emory) used on 1,581 patients applying for multidisciplinary evaluations found, 'there were substantial differences among systems in how physical features were identified and in the definition of neurobehavioural deficits.'16 For example, although the Canadian guidelines and CDC were in almost complete agreement on the physical features, the 4-digit code and IOM/Hoyme diagnostic tools were not. Concordance was greater between systems when the lesssevere forms of FASD (pFAS, ARND, ARBD) were amalgamated into one category (FASD v. no FASD diagnosis). Growth also showed a high degree of concordance between systems. 16 Disagreement between systems was attributed to differences in disciplines that led to the development of individual tools, with different levels of specificity in the definition of FASD, and through the use of different reference data for 'normal' physical measurement. 16 It has been stated that '... these 5 systems employ a wide variety of measures and thresholds in meeting the neurobehavioral criterion and there is inconsistency among them.'16

Discordance in Research

The lack of standardization of diagnostic criteria weakens accuracy, objectivity, and reproducibility, and limits the ability to compare results between FASD investigations. For example, international FASD prevalence rates vary considerably, from 7.7 per 1,000 population in some studies³ to 0.2 to 5 per 1,000 population in others. Variation is suggested to stem from, '...differences in FASD case definition and diagnostic methods, as well as geographical and population factors...'

Inappropriate Patient Care and Inconsistent Government Messaging

A lack of standardization of diagnostic tools causes clinical ambiguity, which can lead to 'inappropriate patient care, increased risk of secondary disabilities, missed opportunities for prevention and inaccurate estimates for incidence and prevalence.' A Canadian study examined multidisciplinary FASD diagnostic teams and found that just over 15% of individuals diagnosed with FASD had discrepancies between their diagnosis and the identified clinical description used to justify the diagnosis. It was acknowledged that

there is the occasional need for clinicians to make judgement calls in the process of diagnosis but cautioned that this rate of non-standard cases in their study seemed high. 'This raises the possibility that clinicians misunderstand or misremember the stated diagnostic rules or routinely stretched them to cover borderline cases.' To further complicate matters, in the 1980s, the Fetal Alcohol Study Group of the Research Society on Alcoholism proposed the term fetal alcohol effects (FAE) be used to refer to any symptom(s) thought to be a caused by prenatal alcohol consumption. This diagnostic imprecision and oversimplification, '…led clinicians either to disregard alcohol as a contributing factor for any children's problems or to over diagnose the contribution of alcohol to such problems, which hampered efforts to determine the actual magnitude of FASD.' 8,84

The gap in conclusive evidence of what level of alcohol, if any, is safe to consume during pregnancy led the Government of Canada to recommend that 'the safest option during pregnancy or when planning to become pregnant is to not drink alcohol at all.' Regardless, the maternal alcohol consumption rate in Canada is approximately 10%, with 3% of women engaging in at least one binge drinking episode during pregnancy. Additionally, most pregnancies in Canada and the US are unplanned, and women, on average, do not know they are pregnant until 4 to 6 weeks after conception. In a cross-sectional survey, 45% of surveyed women reported consuming alcohol in the 3 months before they discovered they were pregnant, 60% of whom did not learn they were pregnant until after the fourth week of gestation.

This divergence between government messaging and public behaviours may reflect the contentious history of the recognition of FASD, maintained by the ambiguity around the dose-response relationship between alcohol exposure and FASD. FASD was first recognized in 1973, but it took several supportive studies and 4 additional years before the American FDA released their first public awareness warning via the June 1st, 1977 Drug Bulletin, followed by the NIAAA recommending safe consumption of 2 drinks per day to a maximum of 6 drinks a day for pregnant women. Subsequently, the American Academy of Pediatrics endorsed the advisories, followed by the March of Dimes, American Medical Association and American Society of Addiction Medicine and eventually the American Congress of Obstetricians and Gynecologists. 88

Conclusion

FASD is recognized by the scientific and medical community as a preventable, clinical disorder, and alcohol as teratogenic. Ambiguity around exposure thresholds and the impeding or facilitating factors for teratogenic prenatal vulnerability lead to discrepancies between diagnostic tools and variability in research findings. These, in turn, lead to inconsistencies in government messaging, misdiagnoses or missed diagnoses, increased risk of secondary disabilities, inappropriate patient care, and imprecision around the true social

and economic cost of FASD. The objective measurement of the timing and level of PAE is a key to bridging these gaps; however, there is conflicting or limited evidence to support the use of existing tools. The implementation and support of successful prevention interventions, including those to support maternal psychiatric health before, during, and after pregnancy could yield an increase in positive pregnancy outcomes as well as significant public sector financial gain. According to Thanh and colleagues, the lifetime incremental cost per case with FASD is approximately \$800,000. Significant opportunity exists for researchers and policy makers to bridge these remaining gaps, and mould future public discourse, behaviours and perhaps even social culture around alcohol consumption during pregnancy.

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