Appendix 1 (as supplied by the authors): Full-text version — Fetal Alcohol Spectrum Disorder (FASD): a guideline for diagnosis across the lifespan

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Abstract

Since *Fetal Alcohol Spectrum Disorder (FASD): Canadian Guidelines for Diagnosis* was published as a supplement to the Canadian Medical Association Journal in 2005, new evidence and recommendations have emerged necessitating an update and revision. A survey was sent to all diagnostic centres in Canada (between 2013-2014 to identify the strengths and weaknesses of the 2005 guidelines, and to highlight areas needing revision. The survey was developed and customized by the steering committee to ensure that the necessary information was collected to address the key questions identified for this project. Data supported the addition of sections pertaining to the approach for diagnosis in infants and young children, and adults, as well as improvements to the clarity, validity and implementation of both standardized anthropometric measures and neurodevelopmental assessment domains across the lifespan. A steering committee was tasked to review, analyze and integrate current approaches to diagnosis in an effort to achieve agreement on standard recommendations for best practices in FASD diagnoses using the AGREE II (Appraisal of Guidelines, Research and Evaluation instrument. The purpose of this paper is to present the updated set of diagnostic guidelines for FASD with recommendations on their application for individuals at risk for alcohol-related effects across the lifespan. The evidence-based guidelines and recommendations are based on widespread consultation with expert practitioners as well as research and community partners in the field and were developed using the Grading or Recommendations, Assessment, Development and Evaluation (GRADE system to describe both the strength of recommendations and quality of evidence. There was unanimous agreement that the diagnostic process should continue to involve a comprehensive, multidisciplinary

approach that includes a history, physical examination, and neurodevelopmental assessment.

Introduction

In 2005, the *Fetal Alcohol Spectrum Disorder (FASD): Canadian Guidelines for Diagnosis* [1] was published as a supplement to the Canadian Medical Association Journal. The field has since evolved and additional evidence, expertise, and experience are now available necessitating a revision of the 2005 guidelines with the objectives to address new knowledge, as well as specific gaps and inconsistencies in several key areas.

With the recent release of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), which includes proposed diagnostic criteria for FASD-related conditions in the Section III and references to FASD-related diagnoses under the section "Neurodevelopmental Disorders" [2], the need to clarify terminology is increasingly important.

Fetal Alcohol Spectrum Disorder (FASD): Canadian Guidelines for Diagnosis was published in 2005 and has since been widely adopted by Canadian FASD diagnostic clinics and, in part, by a number of other countries [3, 4]. The updated and revised version has attempted to address the identified limitations leading to improved clarity and consistency for FASD diagnoses.

As before, the complexities associated with FASD require a comprehensive, multidisciplinary assessment to provide an accurate diagnosis and appropriate recommendations for management. A multidisciplinary approach continues to be the standard for collecting precise data that will provide information about the incidence and prevalence of FASD. This information continues to be of paramount importance for informing prevention and intervention strategies and policy.

The 2005 Guidelines harmonized the Institute of Medicine nomenclature with the methodology of the 4-Digit Diagnostic Code [1]. We have provided examples of how the updated approach correlates to terminology in the Institute of Medicine [5], Standard protocol developed by the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (Hoyme [6], 4-Digit Diagnostic Code [7], International classification of diseases [8], the Centers for Disease and Prevention [9] and DSM-5's schema [2] (see Appendix A.

This updated document supercedes the 2005 guidelines and responds to an important clinical question, which is to provide current evidence-based recommendations for the diagnostic approach to disabilities associated with prenatal alcohol exposure, as well as clarifications related to diagnostic terminology.

These guidelines are neither exhaustive nor exclusively healthcare service-driven – rather they focus on the needs of the individual with FASD and on building recommendations for services and interventions that will be most beneficial. The guidelines will aid experienced teams in making an FASD diagnosis for individuals with suspected prenatal alcohol exposure across the lifespan. New team members should first acquire a solid grounding in FASD and work with experienced colleagues.

These guidelines were drafted with the aim to be sufficiently specific to guide the complex diagnostic process, but with enough flexibility for diagnostic centres to implement the principles and approaches in their own settings. These updated and revised guidelines represent the input and expertise of clinicians, researchers and policy-makers who have significant experience in the field.

These guidelines should not translate into the need for increased resources that would create barriers for patients; instead, they are intended to improve the diagnostic

process in general for existing multidisciplinary clinics, as well as future ones. Training workshops – both in person and online – are being widely developed to improve dissemination of these guidelines and to ensure extensive uptake.

Methods

Process of Guideline Development

The development of these guidelines followed the Appraisal of Guidelines, Research and Evaluation (AGREE II framework [10] (Appendix B. The AGREE II instrument is a tool used to assess the methodological quality of clinical practice guidelines. AGREE II, is comprised of 23-items organized into six domains, which are used to assess guideline quality: scope and purpose of the guidelines; stakeholder involvement; rigour of development; clarity of presentation; applicability and editorial independence.

The Steering Committee led the process, with input from all diagnostic centres across Canada and national and international experts. An in-depth survey was sent to all diagnostic clinics in Canada to determine specific areas of the 2005 Guidelines that required update and/or revision. A pan-Canadian consultation was held over two days to present updated evidence and to receive input and advice for recommendations.

Specific portions of the guidelines were delegated to groups of content experts within the Steering Committee, who used the systematic literature review to draft the recommendations. These evidence-based FASD diagnostic guidelines align with the expert advice and input from Canadian FASD diagnostic centres and leading national and international authorities, engaged during the development of these guidelines.

A 14-member steering committee was formed in September 2012. Committee members included: 4 clinical psychologists; 3 paediatricians; 3 researchers; 1 social

worker, 1 clinical geneticist, 1 clinic coordinator and 1 was a parent of individuals living with FASD.

The target audience for these guidelines are the members of a multidisciplinary team that diagnoses FASD. The referent setting was the Canadian health care system. These guidelines address the concerns and gaps identified by the larger FASD community, including experts from all facets of health and social service disciplines. An in-depth survey was administered to all FASD diagnostic centres in Canada to determine strengths and weaknesses of the 2005 Guidelines and to identify areas for update and revision. These data were used by the Steering Committee to determine topics for the literature review. An initial literature review was performed and provided to participants who were invited to participate in a two-day pan-Canadian face-to-face workshop in October 2013. The goal of the workshop was to provide input on the recommendations from a wide range of individuals involved in the FASD diagnostic process. Following this consultation, the literature review was refined and the recommendations for each section were graded. These guidelines will be re-evaluated when significant new evidence emerges.

Data Sources

The following data sources were searched since 2005 for all other topics, until September 2014: PUBMED, PSYCHLIT, MEDSCAPE, MEDLINE, the Canadian Institutes for Health funding database and Cochrane library. The search strategies are available in Appendix C.

Quality assessment and data abstraction

All committee members participated in the review of the evidence, and worked in groups according to their area of expertise. The following criteria were used for assessment: sample size, sample population, similarity of groups, measurement protocol, definitions of outcomes, and definitions of levels of prenatal alcohol exposure.

Development of recommendations

Recommendations were appraised by two experienced researchers, who assessed whether the assigned strength and quality of the recommendation based on the evidence synthesized and, reflected the existing literature, where the evidence was lacking, recommendations were based on clinical experience. Two committee members used the GRADE approach methodology for the recommendations [11] (see Appendix D. Recommendations were evaluated as either "strong" or "weak", based on the quality and quantity of supporting evidence. The Steering Committee is confident that the desirable effects outweigh the undesirable effects for the "Strong" recommendations and that most individuals will be best served by the course of action.

Desirable effects probably outweigh undesirable effects for the "Weak" recommendations, but there is uncertainty and clinical judgement is essential to determine the best course of action in each case. Evidence was also graded based on the potential impact of future research findings.

Whenever possible, an explicit link between the recommendation and supporting evidence has been made in the text. All recommendations were formulated based on the quality of evidence and input from experts in the field. All Steering Committee members and then external national and international experts (see the Acknowledgements Section)

reviewed three drafts of the guidelines. Each recommendation reflects the consensus of the Steering Committee, and there are no competing interests from members of the committee. The views of the funding body have not influenced the content of the guideline.

Tools and advice for their application are indicated, where available. The recommendations are presented in nine areas related to the diagnostic process:

1. Screening, Referral and Support
2. The Medical Assessment: Family History, Maternal Alcohol History, Physical Examination, and Differential Diagnosis
3. Sentinel Facial Features
4. The Neurodevelopmental Assessment
5. Nomenclature and Diagnostic Criteria
6. The Diagnostic Team
7. Special Considerations in the Neurodevelopmental Assessment of Infants and Young Children
8. Special Considerations in the Neurodevelopmental Assessment of Adolescents and Adults
9. Management and Follow-up

Guidelines for the Diagnosis of Fetal Alcohol Spectrum Disorder

1.0 Screening, Referral and Support

A critical part of the diagnostic process is screening individuals who may have FASD and then making the appropriate referrals for assessment. A number of tools are currently under development. Facial photographic assessment is the most accurate, but can only identify those with the facial features of FASD. Behavioural rating scales do not

demonstrate sufficient specificity for FASD (that is, to identify FASD but not other conditions) and should only be used if there is the possibility of a follow-up diagnostic assessment for those individuals screening positive. There are a number of measurement tools that can be used by trained individuals, including standardized questionnaires [12-14] and facial photographic assessment tools [15-17].

Primary care physicians and front-line service providers are ideally suited to screen pregnant women for problematic alcohol and substance use. It is imperative that they have appropriate training to feel comfortable and competent talking to pregnant women and screening for FASD. Psychosocial support for clients should be taken into careful consideration, to assist individuals and families through screening, referral and if indicated, diagnostic processes. Relevant practice guidelines have been developed and may better assist service providers to care for their clients [18, 19].

Recommendations

1.1 All pregnant and post-partum women should be screened for alcohol use with validated measurement tools by service providers who have received appropriate training in their use [18]. Women at risk for heavy alcohol use should receive early brief interventions (i.e., counselling and/or other services). (See Appendix E). (Strong, High|++++)

1.2 Referral of individuals for a possible FASD diagnosis should be made whenever there is evidence of or suspected prenatal alcohol exposure at levels associated with physical or developmental effects (see below for discussion on prenatal alcohol exposure). (Strong, Moderate|+++0)

1.3 Abstinence from alcohol should be recommended to all women during pregnancy to ensure the safest outcome for the fetus and appropriate support should be provided, as indicated (see Appendix E). (Strong, High|++++)

Comments

The purpose of screening for alcohol use during pregnancy is to identify and refer pregnant women, who may be placing their child at risk for FASD, for intervention services. Screening facilitates the implementation of appropriate interventions, at the earliest time point [20].

There is no known safe level of alcohol consumption during pregnancy. There is research to suggest that even low to moderate levels of prenatal alcohol exposure can negatively impact a fetus and these adverse consequences can persist into adulthood [21-24]. A reliable and accurate maternal alcohol history is the best screening tool for FASD.

There are a variety of factors that have been identified, which can impact a woman's consumption of alcohol during pregnancy [25], including a prior history of alcohol consumption [26, 27], a family background of alcohol use [5, 20], a history of inpatient treatment for problematic alcohol and/or substance use and/or a history of mental health problems [28, 29], the previous birth of a child with FASD [20, 30], a lack of contraception/unplanned pregnancy [28], a history of physical/emotional/sexual abuse [28], low income and/or limited access to health care [27-29]. It is therefore critical for service providers to effectively and appropriately determine alcohol use among *all* women of childbearing age.

A lack of access to accurate antenatal health records can be a significant barrier to diagnosis. It is critical for healthcare providers to discuss alcohol use during pregnancy,

to document concerns or suspicions and to ensure that appropriate follow-up care is provided. Although information about quantity, frequency and pattern of alcohol consumption during pregnancy is important, it is difficult to determine for a number of reasons, including under-reporting [31, 32].

For adolescents and adults, there are a few screening tools that can help identify individuals who may have FASD. The Life History Screen [12] and the FASD Screening and Referral Form for Youth Probation Officers [33] are two of the most recommended. The Canadian Association of Paediatric Health Centres National FASD Screening Toolkit is also a good resource (http://www.caphc.org/fasd/fasd-national-screening-tool-kit) [13,14]. All positive screens for FASD should be referred for further investigation including a comprehensive diagnostic assessment. It is important to remember that *screening is not diagnosis.* New screening tools, such as the Neurobehavioural Screening Test (NST) [13, 34-36], are still being developed but are not yet at a stage where they can be confidently used in the pre-referral process.

2.0 The Medical Assessment: Family History, Maternal Alcohol History, Physical Examination, and Differential Diagnosis

Recommendations

2.1 The diagnostic process should include compiling a social and medical history and complete physical examination. (Strong, High|++++)

2.2 Confirmation of prenatal alcohol exposure requires documentation that the biological mother consumed alcohol during the index pregnancy based on: reliable clinical observation; self-report; reports by a reliable source; medical records documenting positive blood alcohol concentrations; alcohol treatment or other social, legal or

medical problems related to drinking during the pregnancy. The presence of all 3 facial features has such high specificity to alcohol exposure and FASD that confirmation of alcohol exposure is not required when they are present [71]. The presence of fewer than 3 facial features does not have the same degree of specificity and therefore requires other confirmation. (Strong, Moderate|+++0)

2.3 The number of type(s) of alcoholic beverages consumed (dose), the pattern of drinking and the frequency of drinking should all be documented, if possible. (Strong, High|++++)

2.4 Sources for confirmed prenatal alcohol history must be reliable and devoid of any conflict of interest. Unsubstantiated information, lifestyle alone, other drug use or history of alcohol exposure in previous pregnancies cannot, in isolation, confirm alcohol consumption in the index pregnancy. However, co-occurring disorders, significant psychosocial stressors and prenatal exposure to other substances (e.g., smoking, licit or illicit drugs) in the index and previous pregnancies should still be recorded, based on the known interactions of these substances and their effects on pregnancy outcomes for both the mother and her offspring. (Strong, Moderate|+++0)

Comments

It is critical that FASD is recognized as a medical and neurodevelopmental health condition that requires a thorough physical and mental assessment. The family history must be reviewed, and if possible, a three-generation family tree should be obtained. This allows the team to identify existing developmental disorders in the family and identify the potential of inheritable disorders, based on an occurrence in the parents, siblings or second or third generation relatives. Consanguinity in the parents may indicate a risk of

certain inherited disorders. The presence of FASD in other siblings is a risk factor for having another affected child [7, 30, 37-39].

As outlined in the 2005 Guidelines [1], the goal of the physical assessment is to distinguish the specific physical features associated with prenatal alcohol exposure from those that arise due to other causes. Several structural deficits and/or birth defects have been associated with FASD involving the ears, eyes, palmar creases, digits, elbow, joints and heart; children with FASD are also an increased risk for additional structural defects including congenital heart defects and oral facial clefts [40-42] . For diagnostic purposes, any signs of anomalies should be recorded when conducting the overall medical evaluation for each patient. Physical and neurological screening examinations should include measurements of growth and head size, and document the presence of physical anomalies (e.g., cleft palate, congenital heart defects, clinodactyly, palmar crease abnormalities etc.. Due to the fact that FASD can be a diagnosis by exclusion, this information is essential for determining the presence of a genetic disorder that may mimic FASD.

Prenatal Alcohol Exposure (PAE)

The evidence to support a recommendation of safe levels of prenatal alcohol exposure does not exist. The available literature is difficult to interpret based on the observation that differences in study design and methodology (e.g., binge vs. daily/weekly consumption; individual trimester exposure versus throughout gestation make it hard to compare outcomes. The units for PAE differ across studies and countries, including the definition for a standard unit of alcohol (see Appendix E, and there are many additional confounding variables that make it impossible to establish a threshold of PAE that would

be considered absolutely safe for pregnant women. Differences in gender, ethnicity, history and genetics [43-45] – to name a few – have all been shown to contribute to alcohol's effects, as has the timing, frequency and quantity of alcohol consumption. Although dose per occasion is likely more important than drinking frequency [46], binge drinking does occur in all types of prenatal alcohol consuming women – low/light, moderate and heavy [47]. As most of the published data related to drinking alcohol during pregnancy is collected from mothers either prospectively or retrospectively, it may be inherently flawed, as studies have shown that women tend to under-report (or not report their alcohol consumption during pregnancy [48-50]. This suggests that all published data needs to be interpreted with caution, and again underscores the difficulty in ascribing definitive threshold values for PAE. Since alcohol can affect CNS development at all stages, it is highly unlikely that a single mechanism could be responsible for all of the varied effects that have been observed due to PAE. Furthermore, if multiple mechanisms are involved, then it is almost certain that there is no single threshold for all fetal alcohol-induced damage [51]. In the context of alcohol-teratogenicity, the identification of thresholds of exposure depends fundamentally on the choice of measures for dose and subsequent outcomes – if the outcome were craniofacial dysmorphology then exposure during embryogenesis would be most critical [51]. Thus, the amount of alcohol needed to contribute to the observed deficits continues to be controversial and complicated.

Summary of PAE Literature

In 1976, an association was found between moderate alcohol consumption (1.5 oz AA/day) and lower birth weight [52]. Similarly, in a study of over 400,000 American

women, all of whom had consumed alcohol during pregnancy, researchers revealed that consumption of 15 drinks or more per week was associated with a reduction in birth weight [53]. As well, 7 standard drinks/week has been (cautiously suggested as a possible threshold by several researchers in the field [54, 55], and data to corroborate that 7 drinks/week can lead to structure and/or functional abnormalities has also been made [22, 54, 56-58]. As reviewed by Jacobson & Jacobson (1994, most measures of adverse outcomes correlated with a range of 7-28 standard drinks/week [59]. However, because few pregnant women drink every day, 7 standard drinks/week typically represents relatively heavy doses of alcohol on drinking days [60]. Most adverse neurodevelopmental effects have not yet been shown to occur with exposure below 7 standard drinks/week [59]. However, adverse neurodevelopmental effects have been shown to be related to episodes of binge drinking equivalent to 4-5 standard drinks/occasion [22, 50, 63-69] and there is evidence that even a single episode of binge drinking may have measurable neurodevelopmental effects in humans [69] and animals [61].

There is also evidence that exposure to alcohol early in pregnancy, before some women may know that they are pregnant, can affect physical and neurodevelopmental development [62-64]. For this reason, it is important to assess and consider alcohol exposure that occurred prior to pregnancy recognition. At this time, the threshold of alcohol exposure known to be associated with adverse neurodevelopmental effects is 7 or more standard drinks per week, or any episode of drinking 4 or more drinks on the same occasion [65]. Because the effect sizes seen with a single binge episode are relatively small, a threshold of 2 binge episodes is recommended as a minimum for

diagnosis. These recommendations are tentative, and may become outdated as more data becomes available.

Minimal drinking, below the threshold described above, has not been shown to be associated with neurodevelopmental effects, but also has not been studied thoroughly enough to be considered safe. There is no known safe amount of PAE, and public health agencies should advise women to abstain from alcohol while pregnant. A variety of maternal and fetal factors such as maternal age and weight, rate and pattern of alcohol consumption, levels of drinking prior to pregnancy, and nutrition status [66-68] can also mediate the impact of a given dose of alcohol on brain development.

Emerging data suggest that questions pertaining to behaviours *prior* to pregnancy (or pregnancy recognition may be more revealing and predictive of the current situation compared to direct questions about prenatal alcohol and drug use [31, 66, 69]. This preliminary evidence underlies the need for frontline healthcare workers to inquire about pre-pregnancy behaviours and provide accurate information to promote healthy pregnancies.

3.0 Sentinel Facial Features

The criteria for facial features as they were historically described and associated with prenatal alcohol exposure have not changed from the 2005 Guidelines. There is evidence to support the recommendation that the simultaneous presentation of the three characteristic facial features that discriminate individuals with PAE include short palpebral fissures, indistinct philtrum and thin upper lip [70, 71]. Based on the current evidence, it is apparent that other facial and/or physical birth defects may be associated with prenatal alcohol exposure. However, it remains to be further confirmed as to which

of these features are prognostic and specific to prenatal alcohol exposure. Importantly, it appears that the presence or absence of specific prenatal alcohol-related features (facial and physical differ across age ranges and populations (e.g., ethnicities [72-74], further complicating our ability to distinctly identify additional diagnostic features that would be unique to prenatal alcohol exposure.

Overview of the Evidence

In a longitudinal analysis that explored which facial measures were most predictive of prenatal alcohol exposure and whether the measurements changed with age, a set of 16 facial measurements were selected. The data revealed that measures of craniofacial width (minimal frontal, orbital width (palpebral fissure width and ear and mandibular measures (ear length and lower facial depth were consistently predictive of group membership across age groups (5 and 9 years old [75]. After evaluating a computational model that could be used to accurately identify children with FAS automatically using facial features from 3D scans, researchers found that prenatal alcohol exposure not only produced the specific dysmorphic features – short palpebral fissures, thin upper lip and flat philtrum – but also other more subtle features that made the overall gestalt of an FASD face [76]. Although variations in the facial features associated with prenatal alcohol exposure were found across different sample populations using computerized anthropometry, at least one measure involving the eye (e.g., shortened palpebral fissures, reduced outer canthal width, or reduced inner canthal width was apparent in all of them [73], suggesting that the palpebral fissure length measurement is particularly sensitive to PAE. Overall, the findings were consistent with the clinical description of facial features involving the orbital region (palpebral fissure size) and mid-

face (mid-facial hypoplasia and thin upper lip with flat philtrum as discriminating features of PAE. Using data from active case ascertainment studies of three distinct populations of children with PAE, similarities and differences in dysmorphology, growth, and unique physical features were explored [72]. After combining the populations, their model revealed that the following variables predict dysmorphology unambiguously: small palpebral fissures, narrow vermillion, smooth philtrum, flat nasal bridge, and fifth finger clinodactyly. Collectively, it is clear that there is emerging evidence to suggest the diagnostic utility of additional facial and/or physical features that in some (yet unspecified combination may be unique to prenatal alcohol exposure. However, the decision to reduce the number of facial features (to 2 of 3 required for the diagnosis of FASD with Sentinel Facial Feature did not appear sufficiently supported by evidence, and further investigation is needed before a formal recommendation can be made.

Assessing the Face

The University of Washington Lip-Philtrum Guides continue to be the standard for an objective evaluation of lip and philtrum development. As described by the FAS Diagnostic and Prevention Network (http://depts.washington.edu/fasdpn/htmls/lip-philtrum-guides.htm, the Lip-Philtrum Guides reflect the full range (or normal distribution of lip thickness and philtrum depth one would see in a general population. The Rank 3 picture reflects the population mean (or 50th percentile. Ranks 1 and 5 reflect the extreme ends of the normal curve (< 2.5th percentile and > 97.5th percentile. In practice, the Lip-Philtrum Guides have been described as a likert scale (i.e., which has often been misunderstood as an equal interval scale. When understood as a quasi-normal curve, the lip and philtrum rankings of "4" and "5" are understood as the extremes of

development, with "3" as the average range. For the purposes of an FASD evaluation, rankings of "4" and "5" are the critical values.

Since the publication of the 2005 Guidelines, research conducted in Canada has provided current norms for palpebral fissure length for children age six years and older [77]. The third facial feature, palpebral fissure length, can now be accurately evaluated for this age group. Standard deviation values can be conveniently computed using University of Washington software (http://depts.washington.edu/fasdpn/htmls/diagnostic-tools.htm#pfl).

Recommendations

3.1 The following three sentinel facial features must be present due to their specificity to prenatal alcohol exposure: (Strong, High|++++)

- Palpebral fissure length below the 3rd percentile or 2 standard deviations below the mean.
- Philtrum rated 4 or 5 on the 5-point scale of the University of Washington Lip-Philtrum Guides [16].
- Upper lip rated 4 or 5 on the 5-point scale of the University of Washington Lip-Philtrum Guides [16].

3.2 Associated features (abnormalities such as mid-face hypoplasia, micrognathia, abnormal position or formation of the ears, high arched palate, epicanthic folds, limb abnormalities, palmar crease abnormalities, short-upturned nose, etc.) should be recorded, but do not contribute to confirming or refuting an FASD diagnosis. (Weak, Moderate/+++0)

3.3 Clinicians should refer to the following references, which can be used for real time measurement as well as photographic analysis, to measure palpebral fissure length (Strong, High|++++):

- 29-32 weeks [78]
- 32-40 weeks [78, 79]
- 0-6 yrs [78]
- 6-16+ yrs [77, 78, 80]

Comments

Facial features should be assessed in all age groups [81]. If a patient's facial features change with age, the diagnosis of the facial features should be based on the point in time when the features were most clearly expressed. Measuring the sentinel facial features in adults is relevant and should be completed, if possible. However, this can be a challenge if clients have mustaches, beards and facial piercings. A repaired cleft lip and palate can also prevent accurate assessment of the lip and philtrum. It may be helpful to view childhood photographs in which non-smiling [16] views of the face could be informative.

The sentinel facial features associated with prenatal alcohol exposure have been clearly identified since the early 1970's. Measurement of the palpebral fissure length should be performed by an individual – usually the physician – who is trained to do so, or by photographic assessment using a standardized program [7, 71]. The norms for individuals at age 16 can be used for adults, since evidence indicates that palpebral fissure length matures by the age of 16 and no further changes are anticipated [82]. It is important to note, however, that there is a paucity of data related to head circumference in individuals beyond age 16. Other factors that need to be carefully considered when

evaluating facial features, especially for adult cases, include surgery, injury or trauma to the face, cleft palate/cleft palate repair, and facial hair.

Special Considerations for Infants and Young Children with Facial Features and Microcephaly

A review of the FASD diagnostic data [71] revealed that the presence of all 3 sentinel facial features *and* microcephaly (head circumference 2 or more standard deviations below the mean in children, who were old enough to undergo a complete neurodevelopmental assessment (i.e. over age 8, was always associated with significant neurodevelopmental impairment (as defined below. For this reason, infants and young children presenting with all 3 sentinel facial features *and* microcephaly may receive a formal diagnosis of *FASD with Sentinel Facial Features*, even if they have yet to meet the criteria for significant neurodevelopment impairment. However, an older child or adult who presents with all 3 facial features and microcephaly, but who does not show *any* signs of neurodevelopmental impairment should *not* receive a formal diagnosis of FASD (see below. It is expected that this would be very rare, based on the research [71].

4.0 The Neurodevelopmental Assessment

The neurodevelopmental deficits associated with FASD are complex and multifaceted. It is well established that learning disabilities [83], inattention [84], social [85] and executive function deficits [86] can occur regardless of facial dysmorphology. Consequently, there is no single neuropsychological measure, nor pattern of neuropsychological profiles that are specific to all individuals with FASD [1, 87-91]. It is presumed that differences in the dose and timing of exposure [66], as well as interacting genetic [92, 93] and environmental influences [94-96] on brain development

account for the variability in presentations. However, the most common neurodevelopmental disabilities include attention, executive function, spatial working memory, mathematics, communication, and adaptive behaviour [87, 97, 98].

Significant deficits in at least three CNS domains are required for an FASD diagnosis and this has not changed from the 2005 guidelines. The criterion for significant impairment also has not changed: scores on standard measures 2 or more standard deviations (SD below the mean indicate significant impairment. The committee considered comments that the 2 SD was a conservative cut-off for the FASD diagnosis and more stringent than other diagnostic schemes in the U.S. We acknowledge that children who are functioning below average (e.g., -1.5 SD but not -2 SD show significant difficulties in learning and behaviour compared to their peers and may have important deficits that need to be considered in the profile and planning but they do not meet the standard for FASD. The 2 SD cut-off is the standard for defining a severe level of deficit in other guidelines (i.e., for Intellectual disability in DSM-IV and 5.

Historically, there has been substantive consistency across different diagnostic systems as to the definition of severe or significant impairment. Using 2 SD as a clinical cut-off for severe deficits corresponds closely to the criteria used by the DSM-5 [2], ICD-10 [8], and the American Association for Intellectual and Developmental Disabilities [99]. As well, many commonly used scales, including the Wechsler and Stanford-Binet intelligence scales and the Vineland Adaptive Behavior Scales define 2 SD as significantly below the population average and in the range of severe impairment. As for all aspects of diagnosis, clinical training and judgment are required to interpret test results and experienced clinicians will evaluate scores within the context of a complete

assessment picture. A diagnosis of FASD implies that alcohol is a causative factor, not just "associated with" the deficits and there is no empirical data that would support relaxing the clinical cut-off to 1.5 SD. Statistical models of changes to a cut-off score on a battery of neuropsychological tests suggests that small changes in the threshold for diagnosis may have a very large effect on prevalence rates [100]. Finally, this would reflect a major change from the 2005 guidelines without sufficient data to support the change.

The list of brain domains to be evaluated has been updated and clarified to reflect current research.

Recommendations

4.1 A diagnosis of FASD is only made when there is evidence of pervasive brain dysfunction, which is defined by severe impairment in three or more of the following neurodevelopmental domains (Strong, High|++++):

- Motor Skills
- Neuroanatomy/Neurophysiology
- Cognition
- Language
- Academic Achievement
- Memory
- Attention
- Executive Function, including Impulse Control and Hyperactivity
- Affect Regulation
- Adaptive Behaviour, Social Skills, or Social Communication

4.2 Severe impairment is defined as a global score or a major subdomain score on a standardized neurodevelopmental measure that is 2 or more standard deviations (SD) below the mean with appropriate allowance for test error. Please see Appendix F for examples of neuropsychological tests. In some domains, large discrepancies among subdomain scores may be considered when a difference of this size occurs with a very low base rate in the population (≤ 3% of the population). Clinical assessment with converging evidence from multiple sources and DSM-5 diagnostic criteria [2] for certain disorders may also be considered in specific domains which are not easily assessed by standardized tests. Ffor example, in the affect regulation domain the following diagnoses may be taken as an indication of severe impairment: Major Depressive Disorder (with recurrent episodes), Persistent Depressive Disorder, Disruptive Mood Dysregulation Disorder (DMDD), Separation Anxiety Disorder, Selective Mutism, Social Anxiety Disorder, Panic Disorder, Agoraphobia, or Generalized Anxiety Disorder. These exceptions are specified in the domain-by-domain discussion below. (Strong, Moderate|+++0)

4.3 Direct standardized measures should be used to assess brain domains whenever possible and this is recommended for the majority of evidence for brain dysfunction. We recognize, however, that in some cases it is not possible to use direct measures. In these situations, indirect assessment methods such as informant ratings, clinical interview, or historical assessment through file review may be used. (Strong, High|++++)

4.4 If historical assessment, clinical interview, or file reviews are used for indirect assessment (e.g., assessing adaptive behaviour) deficits should be considered by the

team to be at a severity level equal to the clinical cut-off, which is defined as 2 standard deviations below the mean (Strong, Moderate|+++0)

4.5 When using indirect methods of assessment, clinicians should ensure that information comes from multiple sources rather than a single informant rating multiple domains of function. (Strong, High|++++)

Comments

Statements 4.3, 4.4 and 4.5 regarding the use of indirect assessments were the result of extensive discussions regarding the strengths and weaknesses of different sources of information. Direct testing refers to standardized testing or physical measurements. The advantages of direct testing include the relative objectivity and lack of observer biases. The disadvantage of direct testing may be the absence of ecological validity; the relative calm, structure, and lack of ambiguity in the testing situation may not translate to real world situations. Indirect assessment, in contrast, may offer more ecological validity, but also carries risk of subjective bias. There is precedent for such a joint approach in the routine assessment of other common neurodevelopmental disorders, such as intellectual disabilities, which combine direct assessment of cognition with indirect assessment of adaptive function (e.g., DSM-5, and in autism, in which a typical assessment may include a direct test (e.g., the Autism Diagnostic Observation Schedule [101] and an indirect measure (the Autism Diagnostic Interview-Revised [102].

Direct and Indirect Assessment

Not all domains can be assessed both directly and indirectly; many are better suited to one approach or the other. It is incumbent that the clinician conducting the neuropsychological assessment considers the contribution from both the clinical

interview and their clinical judgement as supporting evidence to confirm the significant brain impairment finding for domains that have fewer direct measurements.

As well, associated features that are not diagnostic should be routinely assessed due to high prevalence and importance in management planning. Some of these are listed in Table 1. It also is critical to document a history of adverse childhood experiences such as violence, neglect and abuse (e.g.,, trauma), as they can be contributing factors to cognitive and behavioural deficits. Finally, other diagnostically relevant information, such as confirmed genetic conditions, must be documented.

Table 1. Features Commonly Associated with FASD

Associated Features	***Symptoms***
Sleep Problems	Nightmares, Wakefulness, Inability to fall asleep and/or stay asleep
Sensory Sensitivities	Hypo/Hypersensitive to one or more of the five senses (i.e., sight, hearing, taste, smell and touch)
Physical Findings/Other Congenital Anomalies	Physical anomalies beyond the three sentinel facial features, both major (e.g. Alcohol Related Birth Defects [5]) or minor
Growth	Intrauterine growth restriction, small stature
Attachment	An aversion to touch and physical affection
Proprioception	Motor clumsiness, problems moderating

	grip (e.g., unintentionally breaks objects)
Vestibular	Balance problems, over/under reactive to head movement.

Domain-by-Domain Discussion

In all domains discussed the "clinical cut-off" is defined as 2 or more standard deviations below the mean.

1. **Motor Skills**

   Impairment in the motor domain is present when a composite score below the clinical cut-off or on multiple subtest scores is obtained on assessment of fine motor skills, gross motor skills, graphomotor skills, or visual-motor integration.

   Tone, reflexes, balance, coordination, strength and other abnormal findings on the neurological examination may be considered in combination with formal assessment of motor skills. Hyper-reflexia and increased tone in infancy is predictive of CNS dysfunction later in life.

2. **Neuroanatomy/Neurophysiology**

   Impairment in neuroanatomy or neurophysiology is present when orbitofrontal head circumference is below the clinical cut-off; when the individual has been diagnosed with a seizure disorder not due to known postnatal influences; or when brain imaging shows convincing evidence of structural brain abnormalities known to be associated with prenatal alcohol exposure and other etiologies have been excluded [103, 104]. Although, a MRI is not required or necessary as a standard

approach to assessing an individual suspected to have FASD, it may be an adjunct in determining the extent of effects on the brain or to rule out other disorders.

3. **Cognition**

   Impairment in cognition is present when standardized tests of cognition or intelligence show a composite score below the clinical cut-off, a major subdomain score (such as verbal, nonverbal, or fluid reasoning) below the clinical cut off, or a large discrepancy among major subdomain scores, with a base rate below 3% *and* the lower of the two discrepant scores is at least one standard deviation below the mean.

4. **Language**

   Impairment in language is present when a score below the clinical cut-off is obtained on a composite score assessing core language, receptive language, expressive language, or when multiple scores below the clinical cut off are seen on subtests assessing higher-level language skills (for example,, the integrative aspects of language such as narrative and complex comprehension abilities), or when there is a large discrepancy between receptive composite score and expressive composite score, with a base rate of less than 3% *and* the lower of the two discrepant scores is at least one standard deviation below the mean.

5. **Academic Achievement**

   Impairment in academic achievement is present when a score below the clinical cut-off is obtained on standardized measures of reading, math, and/or written expression, or when there is a large discrepancy between cognition and one of the above, with a base rate of less than 3% and an achievement score at least one

standard deviation below the mean. The clinical team must determine that the individual has had consistent exposure to academic instruction before a deficit can be recorded.

6. **Memory**

Impairment in memory is present when a score below the clinical cut-off is obtained on a composite measure of overall memory, verbal memory, or visual memory, or when there is a large discrepancy between verbal and nonverbal memory, with a base rate of less than 3% *and* the lower of the two discrepant scores is at least one standard deviation below the mean.

A deficit in working memory should be considered under executive function rather than memory.

7. **Attention**

In many definitions and theories of brain function, attention overlaps with some of the executive functions. In order to distinguish these domains for diagnostic purposes, attention is here defined as sustained or selective attention and resistance to distractions. Deficits in inhibition, impulse control or hyperactivity should be considered under executive function rather than attention.

Impairment in attention by direct assessment is present when multiple subtest scores below the clinical cut-off are obtained on continuous processing tests or other neuropsychological measures of attention.

Impairment in attention by indirect assessment is present when a clinical assessment provides converging evidence of impairment from multiple sources,

including clinical interview, questionnaire, file review and direct clinical observation during neurodevelopmental testing.

8. **Executive Function, including Impulse Control and Hyperactivity**

Executive function refers to a set of higher-level skills involved in organizing and controlling one's own thoughts and behaviours in order to meet long-term goals. Although there is some overlap between attention and executive function in many conceptualizations, it is here defined as impairments in working memory, inhibition/impulse control, hyperactivity, planning and problem solving, or shifting and cognitive flexibility.

Impairment in executive function by direct assessment is present when multiple subtest scores below the clinical cut-off are obtained on neuropsychological measures of executive function.

Impairment in executive function by indirect assessment is present when a clinical assessment provides converging evidence of impairment from multiple sources, including scores at or below the clinical cutoff on standardized rating scales and supporting evidence from clinical interview, file review and direct clinical observation during neurodevelopmental testing.

9. **Affect Regulation**

Impairment in affect regulation is present when an individual meets the DSM-5 criteria for Major Depressive Disorder (with recurrent episodes), Persistent Depressive Disorder, Disruptive Mood Dysregulation Disorder (DMDD), Separation Anxiety Disorder, Selective Mutism, Social Anxiety Disorder, Panic

Disorder, Agoraphobia, or Generalized Anxiety Disorder. For the purpose of FASD diagnoses, young children who meet criteria A to F for the DMDD may be counted in this domain, although they should not be diagnosed with DMDD because of the age restriction. It is expected that clinicians will formally ascertain that the individual meets criteria rather than assign a diagnosis on the basis of clinical impression or questionnaire data alone. Care should be taken to look for a longstanding problem of dysregulation rather than a short-term response to unfavourable life events or environmental conditions (e.g., multiple foster placements). (See below for further discussion).

10. **Adaptive behaviour, social skills, or social communication**

Impairment in social communication by direct assessment is present when a score below the clinical cut-off is obtained on the composite score from a measure of social language, social communication skills or pragmatic language skills.

Impairment in adaptive behaviour or social skills by indirect assessment is present when according to a standardized interview or rating scale completed by a key informant, a score below the clinical cut-off is obtained on the global composite score or a major subdomain score. For children and most adolescents standardized indirect measures (i.e., by caregiver ratings) should be used. It is only adults and some adolescents who have not had a consistent caregiver within the last two years that clinicians may need to consider other methods of interview and use of historical records to rate adaptive function. For social language development a direct measure with the client should be used if age-appropriate, in combination with reports and historical

information. Observations and ratings should be across environments where appropriate (i.e., parents report on experiences at home and teachers can report on behaviour at school). Scores are considered significant when they are below the clinical cut-off.

However, adaptive behaviour can be difficult to assess in older adolescents and adults because a suitable informant may not be available if they live alone or in an institutional setting. A formal adaptive behaviour measure is preferred wherever possible and may be required for eligibility for some services. However, in situations where there is no suitable informant, the following historical or current information, derived from a file review, may be used as a proxy:

- Documented inability to function in key aspects of independent living as manifested by chronic inability to manage money, maintain a household of reasonable safety and cleanliness, keep a job once obtained, uphold personal hygiene regimen, exhibit socialization/coping strategies, and/or care for children.

  and/or

- Documented difficulty in social competence as manifested by being financially victimized or unintentionally involved in criminal behaviour due to social gullibility and/or a chronic inability to participate successfully in group treatments and/or group home placements.

In the judgment of the clinician, these deficits should also be considered at a severity level equivalent to or below the clinical cut-off.

Care must be taken to consider adaptive function separate from the secondary effects of addictions and social circumstances. The deficits in adaptive function should be consistent with deficits in the other 9 domains. This domain is intended to function as an additional indicator of overall disability related to neurodevelopmental impairment.

We realize that in standard neuropsychological practice, 1.5 standard deviations below the mean may indicate some impairment. These more subtle findings are an important part of the individual's profile. For the purpose of diagnosis, however, and the certainty that the scores represent injury caused by alcohol, the more extreme cut-off of 2 or more standard deviations below the mean is recommended. The multidisciplinary team, reviewing the data and using experienced clinical judgment, is critical in making an accurate diagnosis, as qualitative aspects of performance are also important. The diagnostic profile is dynamic and may change over time; thus individuals affected by prenatal alcohol exposure, or suspected to be affected, may require several assessments over time. Services should not be based on the diagnosis itself, but rather on the profile of brain function-dysfunction.

Further Considerations

- Clinical judgment must be used to determine whether a true deficit is present in situations in which test data is inconsistent within a domain, or when a global score or major subdomain score is within the standard error of measurement for cut-off. In these situations, the decision should be supported by clinical observation and history. A domain should not be considered impaired on the basis of a single subtest score from one assessment measure.

- Where assessment is indirect, clinicians must do their best to ensure that ratings are accurate and free of bias. Multiple reports should be obtained where possible, and integrated with clinical observation and file review.
- Extensive direct assessment may be unnecessary when there is strong clinical evidence of normal function within a domain.
- As described in the 4-Digit Diagnostic Code system for FASD assessment [7], significant, global delays in which multiple domains are affected, can contain evidence for overall brain dysfunction. When an intellectual disability along with low adaptive functioning have already been established it may be appropriate to limit testing. Severe global delay is not commonly found in FASD and other diagnoses should be considered. However, the standard of three affected domains must still be met. The complete profile of strengths and deficits is important to explain the results to the client and to plan appropriate management.
- The domains should be assessed as though they were independent entities. Clinicians should not use a single test score as evidence of deficits in two domains, even when those domains are theoretically related. For example, it is inappropriate to use the functional communication score from the Vineland Adaptive Behaviour Scale, as a measure of both social communication and language. It is similarly inappropriate to use Verbal IQ as a measure of both language and cognition. However, there are many test batteries, which include subtests that apply to several different domains. For example, the NEPSY-II provides information about both memory and executive function. In such cases, sub-scores may be used as evidence across different domains.

- The list of domains is practical rather than theoretical and represents different sources of information rather than independent factors. For instance, microcephaly, low cognitive ability, and low adaptive behaviour may be different indicators of the same pervasive problem. The intent is to ensure that those receiving an FASD diagnosis have severe and pervasive deficits rather than three deficits that are strictly independent of one another.
- At the conclusion of the assessment, the team should be convinced that the overall presentation is one of severe and pervasive disability based on multiple convergent sources of evidence.
- Clinicians must consider the issue of differential diagnosis when providing an FASD diagnosis. AN FASD diagnosis is often complex due the presence of multiple risk factors and negative exposures that are significant contributors to the patient's symptoms. No neurodevelopmental deficits are considered pathognomonic for or specific to FASD. Each profile or deficit should be considered independently, as a result of other factors. In other words, can the specific deficit be better explained by a factor other than prenatal alcohol exposure? It is the task of a skilled team of clinicians to determine the best explanation for the presenting problems. There will be cases where an FASD diagnosis is not made, despite a confirmed prenatal alcohol history, when one or more other etiological factors provide a better explanation for the neurodevelopmental deficits or when another co-occurring condition is a better explanation for the observed effects. In many cases, multiple risk factors are present and have likely interacted to create a complex profile of dysfunction. In

such cases, an FASD diagnosis should be made but the other relevant risk factors need to be considered and documented.

- Clinicians should be conservative about attributing deficits to prenatal alcohol exposure when other possible causes are short term and may be reversible, as might be seen in the case of a child who has just been moved into a new home environment. The same consideration should be made with respect to co-occurring conditions.
- It is appropriate to make additional relevant DSM-5 diagnoses such as attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD) intellectual disability, impulsive control disorder, conduct disorder and specific learning disorder when the individual meets those criteria as well as the criteria for FASD. We note that these terms provide different levels of explanation: FASD describes overall severe and pervasive neurodevelopmental dysfunction that is associated with prenatal alcohol exposure, while other diagnoses describe particular patterns of symptoms that help to predict prognosis and treatment response.
- In addition to noting the domains that are significantly impaired, clinicians may wish to provide broad ratings of the results for domains that do not meet the cut-off.

Comments on changes from the previous guidelines

The domains in the current list are impacted by prenatal alcohol exposure, can be reliably measured and are not redundant or easily confused with one another.. The domain previously titled “Hard and Soft Neurological Signs” was renamed “Motor Skills” and redefined to

clarify that evidence in this domain must arise primarily from direct tests of motor skills, with additional supporting evidence from neurological examination.

The domain previously titled "Brain Structure" was renamed "Neuroanatomy/ Neurophysiology" and redefined to include seizure disorders, previously considered a hard neurological sign and included in the same domain as motor skills. It was felt that seizure disorders had little in common with poor motor functioning and fit better with other objective medical indicators of brain structure abnormalities, such as microcephaly and those revealed by brain scans.

The domain previously titled "Communication" was changed to "Language" based on the recommendation we received from the Speech Language Pathologists who were consulted. It was felt that the title change more appropriately reflected the assessments recommended in this domain

The domain previously titled "Attention Deficit/Hyperactivity" was renamed "Attention" and redefined. Clinicians using the previous guidelines had expressed difficulty separating the concepts of ADHD and executive function, since most definitions of executive function include inhibition, impulse control and hyperactivity, which are central to an ADHD-combined or ADHD-hyperactive and impulsive diagnosis.

The domain of "Affect Regulation" was added to these guidelines based on the clinical studies reporting the prevalence of mental health disorders in the FASD population [105-109] and on the animal research showing that prenatal alcohol exposure directly affects neurotransmitters involved in stress and mental health [110], which are implicated in anxiety and depression [110, 111]. Human research suggests high comorbidity between FASD and mood and anxiety disorder [105, 106, 112] and negative

emotionality or the intensity of negative moods is one of the earliest observable signs of PAE in infants [113, 114]. Further research will be needed to determine whether other mental health concerns, including some forms of psychosis, should eventually be included in this domain.

The question, of whether or not sensory processing should represent a separate domain or reside within an existing domain, was difficult to answer and continues to be debated in some groups. A number of occupational therapists (OT were consulted and the sensitivity and specificity of the tests designed to assess sensory processing and integration were explored. Although there is anecdotal and empirical evidence to suggest that many individuals with FASD have sensory deficits or low sensory registration that can be prominent and disabling [115-119], common measures of sensory processing are based on caregiver rating, and place a greater emphasis on regulation of sensory input. The committee considered that this was difficult to separate from the cognitive and behavioural self-regulation already captured in the executive function and affect regulation domains. The committee was also influenced by the recent review from the American Academy of Pediatrics (AAP [120], stating that although sensory issues seem to be common among children with other neurodevelopmental disorders such as ADHD and autism spectrum disorder, the evidence for sensory processing as an independent problem was weak, and empirical studies suggest that some sensory measures may over diagnose difficulties in typically developing children. In further support of the committee's position on this issue, was the American Occupational Therapy Association's (AOTA recent published summary of research opportunities to further the understanding of children and adolescents with challenges in sensory processing and

sensory integration [121]. Sensory processing and sensory integration interventions were identified as a "research priority area" indicating an agreement with the AAP's position on lack of sufficient evidence. However, the committee recommends the evaluation of sensory processing and sensory integration by a trained professional to further inform appropriate interventions for individuals with FASD. Sensory problems can be an important trigger for negative behaviours and may create safety and health concerns (e.g. in the case of high pain tolerance that require specific recommendations for management [115, 122].

5.0 Nomenclature and Terminology

FASD as a Diagnostic Term

In the 2005 guidelines, it was stipulated that FASD was *not* to be used as a diagnosis. However, based on advice from clinicians, researchers and other experts, we are recommending the adoption of FASD as a diagnostic term, with sub-categories that refer to the presence or absence of sentinel facial features. While the diagnostic features associated with FASD represent a spectrum of effects, they do not fall along a continuum in which the neurodevelopmental deficits range from mild to severe depending on the diagnosis.

The first reference to alcohol teratogenicity was published in 1968 [123], followed by similar observations from Jones and colleagues [124, 125]. Since the first descriptions of Fetal Alcohol Syndrome (FAS, a number of different terminologies have been introduced and revised, including Fetal Alcohol Effects (FAE, Partial Fetal Alcohol Syndrome (pFAS, Alcohol-Related Neurodevelopmental Disorder (ARND, Alcohol-Related Birth Defects (ARBD) and the 4-Digit Diagnostic Code nomenclature [1, 5-7, 9,

126]. The term FASD was originally coined as an umbrella term to encompass these diagnoses and the breadth of disabilities associated with prenatal alcohol exposure [1].

With the evolution of FASD-related language within different professions, it is critical to adopt standardized terminology wherever appropriate and possible. Standard terminology and definitions are important for comparing data across different geographical settings. Finally, we have considered the wisdom of expert practice [5] and clinical researchers in an effort to complement the current and most commonly used international approaches for diagnosing FASD-related conditions [3, 6, 7, 127].

Recommendations

5.1 A diagnosis of FASD may be made if an individual meets **either** of the two sets of criteria outlined below: (Strong, High|++++)

Diagnostic Criteria

5.1.1 FASD with Sentinel Facial Features

- Simultaneous presentation of the 3 sentinel facial features (short palpebral fissures, smooth philtrum and thin upper lip) **AND**
- Prenatal alcohol exposure (PAE) confirmed or unknown. This diagnosis should not be made when PAE is confirmed absent or at a level definitely below that known to be associated with physical and/or developmental effects (see section on PAE). **AND**
- Evidence of impairment in **3 or more** of the identified neurodevelopmental domains (see The Neurodevelopmental Assessment Section), or, in infants and young children, evidence of microcephaly.

- Growth impairment and other alcohol-related birth defects should be documented if present.
- Hereditary, prenatal and postnatal factors that may influence developmental outcome should be recorded.

OR

5.1.2 FASD without Sentinel Facial Features

- Evidence of impairment in **3 or more** of the identified neurodevelopmental domains (see the Neurodevelopmental Assessment Section). **AND**
- Confirmation of prenatal alcohol exposure, with the estimated dose at a level known to be associated with neurodevelopmental effects (see section on PAE).
- Growth impairment and other alcohol-related birth defects should be documented if present.
- Hereditary, prenatal and postnatal factors that may influence developmental outcome should be recorded.

5.2 At Risk for Neurodevelopmental Disorder and FASD, Associated with Prenatal Alcohol Exposure

5.2.1 This is not a diagnosis; this is a designation that should be given to individuals when:

- There is confirmation of prenatal alcohol exposure, with the estimated dose at a level known to be associated with neurodevelopmental effects (see section on PAE);
- CNS Criteria 5.1.1 and 5.1.2 are not met;

- There is some indication of neurodevelopmental disorder in combination with a plausible explanation as to why the neurodevelopmental assessment results failed to meet the criteria for significant impairment (e.g., patient was too young; assessment was incomplete etc.);
- Growth impairment and other alcohol-related birth defects should be documented if present;
- Hereditary, prenatal and postnatal factors that may influence developmental outcome should be recorded.

5.2.2 This designation may also be considered for individuals with all 3 sentinel facial features of FASD as described in 5.1.1, who do not yet have documentation or evidence for the requisite 3 or more neurodevelopmental domain criteria or true microcephaly. (See Section 4.0 and recommendation 4.2). This designation should never be considered when PAE is confirmed absent.

5.3 FASD should now be used as a diagnostic term when prenatal alcohol exposure is considered to be a significant contributor to observed deficits that cannot be fully explained by other etiologies. Because the observed deficits are recognized as being multifactorial in origin, all other known relevant contributors (e.g., trauma, known genetic anomalies) should be documented with the FASD diagnosis as they have significant impact on the functional and neurological challenges of the affected individuals. (Weak, Low|+000)

The reason that the individual's assessment is considered inconclusive should be recorded. Extra care and attention must be given in the wording used to describe the

results of the assessment such that the report is not misinterpreted. For this designation, an individual still may have FASD, but it cannot be determined at this time. A full re-assessment, including the neurodevelopmental assessment*, must* be performed at a later date, as appropriate.

Individuals in this category should receive the same services as those with a diagnosis of FASD, as required to address their current needs. An "At Risk" designation can be withdrawn if the individual does not show a true neurodevelopmental disorder in later years. It is important to emphasize that an "At Risk" designation must not be a holding pattern; appropriate services to address current and emerging needs should be recommended and accessed.

Comments

Since FAS was first described in the English literature 40 years ago, the essential criteria of sentinel facial features and central nervous system dysfunction associated with significant prenatal exposure to alcohol has not changed. However, the terminology used to describe the constellation of features has evolved.

After several long consultations among specialists in related developmental and mental health practices, a number of new and refined terms have recently emerged with the release of the DSM-5 [2]. These terms were developed specifically for mental health practitioners such as psychiatrists, who render behavioural (or phenomenogical diagnoses often without access to the multi-disciplinary assessment teams, which are required for the diagnosis of FASD. These terms should encourage ongoing engagement and support from the broader mental healthcare community in efforts to consider the

implications of prenatal alcohol exposure when making both functional and etiologic diagnoses.

Growth

In North America, FAS was "discovered" because a group of children were referred to a clinic for growth deficiency, and later found to have the other features of what is now known as FAS. At that time, growth deficiency became one of the defining features of FAS. Since then, the importance of growth in the overall presentation of alcohol-related effects has been debated. The predictive value of growth deficiency especially in the absence of documented prenatal alcohol exposure has been queried. Recent evidence [128], plus clinical experience suggest that growth is neither sensitive nor sufficiently specific to indicate an FASD diagnosis. Other contemporary diagnostic approaches have relaxed the criterion for growth deficiency in making the diagnosis, although not removing it entirely. Following an analysis of historical clinical reports, basic science, and clinical research, the committee supported the recommendation to remove growth as a diagnostic criterion.

However, growth parameters for both weight and height (or length in infants should be recorded, and confounding variables such as parental size, accuracy of gestational dates, genetics and associated conditions (e.g., gestational diabetes, nutritional status, illness should be considered. When growth restriction is present, it is relevant to development and should be monitored. The growth curves produced by the Canadian Paediatric Endocrinology Group (CPEG that are based on the 2010 World Health Organization (WHO curves (with some modifications are recommended. These growth curves have been endorsed by the Canadian Paediatric Society [129]. The WHO charts

growth up to 19 years of age, at which point adult growth is stable and could be plotted at the top end of the chart, as needed.

Terminology

The terminology associated with FASD has evolved over the years and has generated some challenges. The recommended adoption of FASD as a diagnostic term reflects an attempt to focus more on the effects of prenatal alcohol exposure on brain and behaviour (neurodevelopment and to simplify the nomenclature.

A diagnosis of *FASD with Sentinel Facial Features* is made when all three sentinel facial features are present along with CNS dysfunction. This diagnostic category has replaced the term Fetal Alcohol Syndrome ("FAS" as described in the 2005 diagnostic guidelines. Although, this diagnosis can be made in the absence of confirmed prenatal alcohol exposure due to the high specificity of the facial features, an accurate and reliable maternal alcohol history is still the recommended standard.

FASD without Sentinel Facial Features describes the majority of individuals with FASD – those without all three sentinel facial features, but with significant brain impairment due to prenatal alcohol exposure. For this category, there must be evidence of prenatal alcohol exposure at levels known to be associated with physical and developmental effects. This diagnostic category has replaced the terms partial Fetal Alcohol Syndrome ("pFAS" and Alcohol Related Neurodevelopmental Disorder ("ARND" as described in the 2005 Guidelines. The change to delete the pFAS category was made to address the concern that the Canadian criteria for pFAS differed from that of the 4-Digit Diagnostic Code [7]. Examples of how existing FASD diagnostic systems could be applied to the recommended diagnoses are illustrated in Appendix A.

The designation of *At Risk for Neurodevelopmental Disorder and FASD, Associated with Prenatal Alcohol Exposure* is a new category that was created to describe those individuals who have confirmed prenatal alcohol exposure and some indication of neurodevelopmental concerns, but who do not meet the criteria for either of the FASD diagnostic categories. It is especially germane for young children. Research [71] and clinical observation suggest that some individuals who have been prenatally exposed to alcohol may develop normally at younger ages or show only mild deficits. Later, when re-assessed, significant impairments become evident as they fail to develop the higher level thinking skills that are the norm for their age. At the older ages a more comprehensive assessment can be conducted to complete a possible FASD diagnosis. The designation of "At Risk" when they are younger is important and may enable them to access services and supports, with the recommendation that a follow-up assessment in the future be done to confirm FASD or not. Postnatal factors that may influence developmental outcome (e.g., nutrition, stress, trauma must always be considered and recorded.

In the adolescent and adult population, the individual may not be able to fully attend or participate in the assessment process due to social or other issues. While prenatal alcohol exposure may be confirmed and a strong indication of FASD is present based on poor adaptive function and mental health issues, the neuropsychological assessment may be incomplete and an FASD diagnosis cannot be confirmed. A designation of *At Risk for Neurodevelopmental Disorder and FASD, Associated with Prenatal Alcohol Exposure* should be rendered with the recommendation for reassessment when the individual's social situation is more stable and they are better able

to complete a full assessment. It must be noted that this is NOT a diagnostic category. It is simply a designation to identify individuals who may have FASD but require further assessment.

6.0 The Diagnostic Team

Because of the complexity of the outcomes related to prenatal alcohol exposure, a multidisciplinary team is essential for an accurate and comprehensive diagnosis and subsequent management recommendations. The multidisciplinary diagnostic team can be regional or virtual; satellite clinics and telemedicine have been created to meet the needs of referrals from distant communities.

The core team will vary according to the specific context and the age of the individuals being diagnosed. The clinicians should possess the necessary expertise to conduct all aspects of the assessment and have updated knowledge about FASD. New members of a FASD diagnostic team must receive appropriate training. Core team members are outlined below and should always consist of professionals with appropriate qualifications, who have received appropriate training around obtaining sensitive information from birth families, especially when acquiring the prenatal alcohol exposure history.

Recommendations

6.1 Core Team Members Across the Lifespan (Strong, High|++++):

Infants (<18 months):

- Paediatrician/Physician

- Child development specialist who has the skill set to conduct physical and functional assessments (i.e., Speech-Language Pathologist, Physiotherapist, Occupational Therapist, Clinical Psychologist)

Preschoolers (18 months-5 yrs)

- Paediatrician/Physician
- Occupational Therapist
- Speech-Language Pathologist
- Psychologist

School –Aged Children (6 yrs-age of majority)

- Paediatrician/Physician with expertise in FASD and differential diagnosis
- Occupational Therapist
- Speech-Language Pathologist
- Psychologist

Adults

- Physician
- Psychologist
- Speech-Language Pathologist/Psychologist with expertise in language assessment

6.2 Additional individuals who can provide valuable input into the diagnostic process may include addiction counsellors, childcare workers, cultural interpreters, mental health professionals, parents or caregivers, advocates, mentors, probation officers, psychiatrists, teachers, vocational counselors, nurses, clinical geneticists or dysmorphologists, neuropsychologists, social workers, nurse practitioners and family therapists. (Strong, High|++++)

7.0 Special Considerations in the Neurodevelopmental Assessment of Infants and Young Children

Since publication of the 2005 Guidelines, more evidence has become available that informs the FASD diagnostic assessment of infants and young children. Research has suggested that measures of infant state regulation [130] and negative temperament [131] are important indicators of FASD. Other symptoms and signs include poor eating, poor sleeping, poor alertness and irritability. Traditional tests of development in various domains are also available. However, the reliability of these tests tends to increase gradually with age, to a point where they become sufficiently reliable for decision-making purposes. Unfortunately, these "thresholds of confidence" occur at different ages for different tests, and often exist as unwritten rules rather than published practice guidelines. A working group of clinicians experienced in the diagnosis of infants and young children with FASD provided suggestions about when tests might be treated with high and low confidence. Their recommendations were integrated with feedback from other experts in this area. Please see Appendix F for examples of neurodevelopmental tests across the lifespan. Tests marked with an asterisk were viewed as having low confidence.

Although a number of references comment on the challenges of diagnosing FASD in infants and young children [132-139], there are several suggestions on how they can be addressed. The following approach is currently recommended:

Recommendations

7.1 Infants and young children with all 3 sentinel facial features and microcephaly should be diagnosed with ***FASD with Sentinel Facial Features***; these children have a high risk of neurodevelopmental disorder [71, 107]. They should also be referred to a clinical geneticist. (Strong, High|++++)

7.2 Infants and young children with all 3 facial features may be diagnosed with ***FASD with Sentinel Facial Features***, if they undergo a comprehensive neurodevelopmental assessment and demonstrate deficits in 3 or more brain domains. Infants and young children with confirmed prenatal alcohol exposure may be diagnosed with ***FASD without Sentinel Facial Features*** if they undergo a comprehensive neurodevelopmental assessment and demonstrate deficits in 3 or more brain domains. (Strong, Moderate|+++0)

7.3 Infants and young children with confirmed prenatal alcohol exposure, but who do not meet the criteria for FASD should be designated as ***At Risk for Neurodevelopmental Disorder and FASD, Associated with Prenatal Alcohol Exposure.*** Those with all 3 facial features, but no microcephaly, should be referred to a clinical geneticist. (Strong, High|++++)

7.4 A complete neurodevelopmental assessment should be recommended at an age-appropriate time for all infants and young children with confirmed prenatal alcohol exposure and/or all 3 facial features. (Strong, High|++++)

Comments

Differential diagnoses must also be considered first before giving an FASD diagnosis to a child under the age 6 years, especially given the inability to conduct a comprehensive

neuropsychological assessment. It is therefore important that these children receive appropriate investigations to exclude any underlying structural brain malformation or a genetic/metabolic disorder that may have similar symptoms to FASD.

In all cases, any signs of other congenital anomalies should be recorded. While microcephaly was historically noted as a characteristic feature of FAS in the first descriptions, it is now considered as evidence of impairment in the "Neuroanatomy/Neurophysiology" brain domain. The finding of true microcephaly (2 or more standard deviations below the mean predicts severe CNS dysfunction among infants/young children (≤ 6 years who present with all three sentinel facial features [71]. In these situations *FASD: with Sentinel Facial Features* diagnosis is appropriate. Postponing an FASD diagnosis in children with microcephaly and all three sentinel facial features simply because of the inability to complete a comprehensive neurodevelopmental assessment could lead to missed opportunities for early interventions.

When new tests or new research about familiar tests become available, clinicians must review the evidence and make a professional judgment about whether the reliability and validity warrants low confidence or high confidence.

8.0 Special Considerations in the Neurodevelopmental Assessment of Adolescents and Adults

Assessment and diagnosis of adults (adults are defined as age of majority and onwards require special considerations to address the many challenges and barriers that often present, including limited family support, poverty, homelessness, mental health, addiction, legal problems, and parenting challenges. Referrals for the assessment may be

initiated by a variety of sources including the individual, their family, community service agencies, medical service providers, and government departments and ministries such as Mental Health and Addictions Services, Justice and Children's Services. The referral source is often an indicator of the type of challenges or secondary disabilities the individual is currently experiencing or can be a reflection of their life stage, such as a youth transitioning to adulthood or an adult with aging parents and can provide important information for the management plan to ensure maximum success.

Frequently, the underlying purpose of a referral by social services agencies is that an FASD diagnosis may lead to stability for the individual by helping them obtain disability income which in turn can lead to secure and stable housing, and the means to meet their basic needs. Caregivers may initiate an assessment when they are struggling with their child's transition from youth to adulthood, seeking information about the individual's ability to live independently or to access needed supports. They may also have concerns about the care their adult child may receive when they are no longer able to assist and this can be extremely stressful for aging parents.

Recommendations

8.1 The diagnostic criteria for FASD are the same for adults as for younger individuals. (Strong, Moderate|+++0)

8.2 When it is not possible to obtain a formal adaptive behaviour measure or when there is no suitable informant, historical or current information, derived from a file review may be used as a proxy. (Weak, Low|++00)

8.3 The length and structure of the assessment must accommodate the individual's needs and capacity. It is important to recognize, for example, if the client gets frustrated or tires easily; situational factors could invalidate the assessment. (Strong, Low|++00)

8.4 Recommendations following the assessment must address basic and immediate needs of the client, and assist them in accessing required resources. (Strong, Moderate|+++0)

8.5 The core principles of bioethics, including autonomy and consent, confidentiality, beneficence, and non-maleficence must be carefully considered, especially when dealing with adults [140]. (Strong, Moderate|+++0).

Comments

The assessment of adaptive function in adults can be challenging. Those who have been well supported in their family or school systems may not appear to have significant deficits at the time of the FASD assessment. Adaptive function deficits may become apparent once these supports are removed, and especially when individuals are transitioning from youth to adulthood. Adaptive scales may not always be sufficiently sensitive to identify the difficulties the individual experiences in day-to-day situations once they attempt to live independently. Additionally, individuals may be estranged from their family and/or without a reliable person who can provide information about their historical and current adaptive function. A self-report by the person with FASD may be unreliable. It is necessary to obtain an in-depth and comprehensive history to accurately determine whether the patterns of adaptive function needed to support a diagnosis are present.

Frequently, adults have experienced early neglect or trauma, abuse, and unstable home environments. Complications of chronic alcohol or substance abuse, head injury, and mental health issues are also common. Given the many possible medical concerns, a complete physical examination at the time of the FASD assessment is critical. Accessing the necessary historical records regarding birth, early development, and schooling can be difficult because they may have been destroyed, they may be found under a different surname, or the individual may not have the capacity to provide the information needed to find the records (which may be located in various provinces and/or territories.

An individual's social circumstances, such as homelessness, can present a significant challenge to the assessment process, especially their ability to attend appointments. They may also experience limited sleep and alcohol and substance abuse, which may affect the test results. A client-centered approach is needed such that the length of the assessment is tailored to the individual's needs and capacity. They may have low frustration tolerance and become tired easily, and may not attend all the assessment sessions needed. It is especially important to access any recent assessments so that the usual test battery can be modified. When asking about previous testing, individuals and their caregivers often do not realize that some of the same tests are used in a school assessment or a forensic assessment as in the FASD assessment. Pregnancy, breastfeeding, and childcare responsibilities are stressors that can impact test results and attendance. A chronic state of crisis or mental health involvement may mean that there is never an ideal time to be assessed but the clinical team must be confident that a reliable assessment can be obtained. An FASD diagnosis based on unreliable data is not a valid diagnosis.

The assessment and diagnosis of FASD can help the individual, their family, and service providers to understand the challenges associated with a life-long disability that requires accommodations and supports to maximize success [141]. An FASD diagnosis may help them access interventions and supports that address their bio-psycho-social needs with recommendations for basic supports, general, physical and mental health.

Client- and family-centered approaches that are based on strengths, and sufficiently flexible to account for individual barriers should be best practices for supporting adults with FASD. Prevention education must be incorporated into the assessment process when working with adolescents and adults to address issues of sexual health, birth control, and pregnancy. Modifications to the service delivery model, including team composition and accommodations, may be needed to support individuals throughout the assessment process and implementation of their management plan [142]. The multidisciplinary team provides recommendations to address the basic and immediate needs of the client, and aims to assist the individual and their family in accessing the needed supports and services.

9.0 Management and Follow-Up

The results of the assessment should be presented to the family of the person being assessed (if a minor and to the individual, if an adult. A decision by the clinical team should be made with regard to whether and how to present the findings to an adolescent. The results should be presented in a written report that documents the social history, medical findings, results of the neurodevelopmental assessment, and diagnoses. FASD is a medical diagnosis, and as such, there is unavoidable terminology that may not easily be understood by the individual and/or his family. The clinical team should do its best to

simplify the findings when presented to the family and be available later to answer questions that may arise from the written report. The recommendations in the report should include services that might be available.

Recommendations

9.1 Education about the impact of FASD and support for the patient and those involved with their care is recommended. The potential psychosocial issues that might be expected to develop as a result of receiving the FASD diagnosis should also be discussed. It is important that this information is communicated in a culturally sensitive manner using appropriate language. (Strong, High|++++)

9.2 A member of the diagnostic team should follow-up within a reasonable length of time to ensure that the recommendations have been addressed and to provide further support, if needed. (Strong, Low|++00)

9.3 Individuals with FASD and their caregivers should be linked to resources that can improve outcomes. However, just because availability of services is limited, an individual should not be denied an assessment and management plan. Often the diagnosis is the impetus that leads to the developmental of resources. (Strong, Low|++00)

9.4 When young adults are transitioning to independent living situations, it may require that they undergo a re-assessment to identify any changes in their adaptive function scores and to make any subsequent adjustments to their management plan. (Strong, Low|++00)

Comments

Management plans [143] for affected individuals and those that care for them are important to improve outcomes. Individuals with FASD experience a wide variety of complex physical, mental and behavioural health-related challenges that require a multifaceted approach to diagnosis and management. The complexity and persistence of FASD symptoms across the lifespan necessitates a long-term plan for management. The types of recommended services and supports will differ based on individual needs, and will often depend on where patients obtain their diagnosis. Diagnostic clinics may consider implementing staged management plans across the lifespan, with the opportunity to review a patient's current situation and anticipate upcoming problems at predetermined time intervals.

Conclusion

The updated guidelines for the diagnosis of FASD address issues pertaining to the diagnostic process, including special considerations for diagnosing infants, young children, and adults (Appendix G: diagnostic algorithm. Providing an accurate and timely diagnosis to any individual at risk for FASD continues to be a major clinical challenge, both nationally and internationally. These recommendations for FASD diagnostic guidelines across the lifespan have been developed with an additional goal to inform diagnostic practice beyond the Canadian context. We hope they will form the foundation of guidelines used by other groups, although the specific details related to practice might differ based on variations in population anthropometrics and in healthcare delivery systems. Research in this field continues to evolve and reveal novel discoveries

that will help improve the technologies that are available for screening, diagnosis, and management.

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Appendix A

Examples of the interface with other diagnostic systems

	FASD with Sentinel Facial Features	FASD without Sentinel Facial Features	At Risk for Neurodevelopmental Disorder and FASD, Associated with Prenatal Alcohol Exposure
2005 Canadian Diagnostic Guidelines	FAS	pFAS ARND	
Institute of Medicine (IOM)	FAS pFAS	ARND	
4-Digit Diagnostic Code (4DDC)	Growth 2, 3, or 4 Face 4 Brain 3 or 4 PAE 2, 3 or 4 FAS	Face 1, 2 or 3 Brain 3 or 4 PAE 3 or 4 ~SE-AE or Sentinel Physical Findings SE-AE	Face 1, 2, 3 or 4 Brain 2 (or untestable at time of assessment) PAE 2 (For Face 4 ~NB-AE), 3 or 4
Standard protocol developed by the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (Hoyme)	FAS with/without Confirmed Maternal Alcohol Exposure	Partial FAS with/ without Confirmed Maternal Alcohol Exposure ARND	
Diagnostic and Statistical Manual of Mental Disorders – 5 (DSM-5)	315.8 Neurodevelopmental Disorder, associated with Prenatal Alcohol Exposure Neurobehavioral Disorder, associated with Prenatal Alcohol Exposure (Appendix 3[§])	315.8 Neurodevelopmental Disorder associated with, Prenatal Alcohol Exposure Neurobehavioral Disorder, associated with Prenatal Alcohol Exposure (Appendix 3[§])	
International Classification of Diseases-10 (ICD-10)	Q86.0*	Q86.8** Q86.99***	Q86.8** Q86.99***
Centers for Disease Control and Prevention (CDC)	FAS		

ARND: Alcohol-Related Neurodevelopmental Disorder; FASD: Fetal Alcohol Spectrum Disorder; FAS: Fetal Alcohol Syndrome; pFAS: partial Fetal Alcohol Syndrome; NB-AE: Neurobehavioral Disorder – Alcohol Exposed; SE-AE: Static Encephalopathy – Alcohol Exposed.

§ The DSM-5 stipulates that this is considered a condition for future study and not a current diagnosis.

*Q86.0: Fetal Alcohol Syndrome dysmorphic.
**Q86.8 Other congenital malformation syndromes due to known exogenous causes.
***Alternate Canadian Institute for Health Information code for partial FAS or other variants and Q86(p) for non-dysmorphic FASD.

APPENDIX B

Appraisal of Guidelines, Research and Evaluation (AGREE II) Instrument [10]

AGREE II Item	***Criteria Met***
Domain 1: Scope and Purpose	
1. The overall objective(s) of the guideline is (are) specifically described.	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply are specifically described.	Yes
Domain 2: Stakeholder involvement	
4. The guideline development group includes individuals from all the relevant professional groups.	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes
6. The target users of the guideline are clearly defined.	Yes
Domain 3: Rigour of development	
7. Systematic methods were used to search for evidence.	Yes
8. The criteria for selecting the evidence are clearly described.	Yes
9. The strengths and limitations of the body of evidence are clearly described.	Yes
10. The methods for formulating the recommendations are clearly described.	Yes
11. The health benefits, side effects and risks have been considered in formulating the recommendations.	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes

13. The guideline has been externally reviewed by experts prior to its publication.	Yes
14. A procedure of updating the guideline is provided.	Yes
Domain 4: Clarity of presentation	
15. The recommendations are specific and unambiguous.	Yes
16. The different options for management of the condition or health condition are clearly presented.	Yes
17. Key recommendations are easily identifiable.	Yes
Domain 5: Applicability	
18. The guideline describes facilitators of and barriers to its application	Yes
19. The guideline provides advice or tools on how the recommendations can be put into practice.	Yes
20. The potential resource implications of applying the recommendations have been considered.	Yes
21. The guideline presents monitoring or auditing criteria.	Yes
Domain 6: Editorial independence	
22. The views of the funding body have not influenced the content of the guideline.	Yes
23. Competing interests of members of the guidelines development group have recorded and addressed.	Yes

APPENDIX C

Search Strategies – only relevant retrievals included

PubMed

Search Terms	Retrievals
Date Publication: "2005-present" Title/Abstract: "fetal alcohol" Title/Abstract: "diagnosis"	138
Date Publication: "2005-present" Title/Abstract: "fetal alcohol" Title/Abstract: "diagnostic*"	138
Date Publication: "2005-present" Title/Abstract: "fetal alcohol" Title/Abstract: "diagnosis" Title/Abstract: "infant*"	10
Date Publication: "2005-present" Title/Abstract: "prenatal alcohol" Title/Abstract: "diagnosis"	56
Date Publication: "2005-present" Title/Abstract: "prenatal alcohol" Title/Abstract: "diagnosis" Title/Abstract: "infant"	2
Date Publication: "2005-present" Title/Abstract: "fetal alcohol" Title/Abstract: "diagnosis" Title/Abstract: "adult"	7
Date Publication: "2005-present" Title/Abstract: "prenatal alcohol" Title/Abstract: "diagnosis" Title/Abstract: "adult"	5
Date Publication: "2005-present" Title/Abstract: "prenatal alcohol" Title/Abstract: "infant"	36
Date Publication: "2005-present" Title/Abstract: "prenatal alcohol" Title/Abstract: "adult"	40

PSYCHLIT

Search Terms	Retrievals
Date Publication: "2005-present" Abstract: "fetal alcohol"	9
Date Publication: "2005-present" Abstract: "prenatal alcohol"	7
Date Publication: "2005-present" All fields: "fetal alcohol"	12

MEDSCAPE

Search Terms	Retrievals
Date Publication: "2005-present" Abstract: "fetal alcohol"	9
Date Publication: "2005-present" Abstract: "prenatal alcohol"	7
Date Publication: "2005-present" All fields: "fetal alcohol"	12

OVID-MEDLINE

Search Terms	Retrievals
Date Publication: "2005-present" Keywords: "fetal alcohol" AND "infant*" and "diagnosis"	60
Date Publication: "2005-present" Keywords: "fetal alcohol" AND "adult*" and "diagnosis"	7

APPENDIX D
Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Approach to Practice Guidelines [11, 144, 145]

Strength of the Recommendation	***Definition***
Strong	Highly confident of the balance between desirable and undesirable consequences (i.e., desirable consequences outweigh the undesirable consequences; or undesirable consequences outweigh the desirable consequences).
Weak*	Less confident of the balance between desirable and undesirable consequences.
Quality level of a body of evidence	***Definition***
High|++++	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate|+++0	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low|++00	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very Low|+000	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

***Weak recommendations should not be misinterpreted as weak evidence or uncertainty of the recommendation.*

Examples:

Strong, Moderate|+++0: Strong Recommendation, Moderate Quality of Evidence

Weak, Low|++00: Weak Recommendation, Low Quality of Evidence

APPENDIX E
Alcohol Use in Pregnancy

A. Society of Obstetricians and Gynaecologists of Canada: Alcohol use and pregnancy consensus clinical guidelines [19].

SUMMARY STATEMENTS

1. There is evidence that alcohol consumption in pregnancy can cause fetal harm. There is insufficient evidence regarding fetal safety or harm at low levels of alcohol consumption in pregnancy.
2. There is insufficient evidence to define any threshold for low-level drinking in pregnancy.
3. Abstinence is the prudent choice for a woman who is or might become pregnant.
4. Intensive culture-, gender-, and family-appropriate interventions need to be available and accessible for women with problematic drinking and/or alcohol dependence.

RECOMMENDATIONS

1. Universal screening for alcohol consumption should be done periodically for all pregnant women and women of child-bearing age. Ideally, at risk drinking could be identified before pregnancy, allowing for change.
2. Health care providers should create a safe environment for women to report alcohol consumption.
3. The public should be informed that alcohol screening and support for women at risk is part of routine women's health care.
4. Health care providers should be aware of the risk factors associated with alcohol use in women of reproductive age.
5. Brief interventions are effective and should be provided by health care providers for women with at-risk drinking.
6. If a woman continues to use alcohol during pregnancy, harm reduction/treatment strategies should be encouraged.
7. Pregnant women should be given priority access to withdrawal management and treatment.
8. Health care providers should advise women that low-level consumption of alcohol in early pregnancy is not an indication for termination of pregnancy.

B. Standard Drink and Binge Definitions

In Canada

- 1 Standard Drink = 13.6 g alcohol
    - = 341 mL = 12 oz of 5% alcohol beer
    - = 142 mL = 5 oz of 12% wine
    - = 43 mL = 1.5 oz of 40% distilled liquor
        - = ~0.5 oz AA

- 2 Standard Drinks = 1 oz AA

Standard Alcohol Units*

**International Center for Alcohol Policies-* *http://www.icap.org/PolicyTools/ICAPBlueBook/ - Module 20. Standard Drinks.*

Standard Drink (grams of ethanol)	***Country***
8	UK
9.9	Netherlands
10	Australia, Austria, France, Ireland, New Zealand, Poland, Spain
11	Finland
12	Denmark, Italy, South Africa
13.6	Canada
14	Portugal, USA

4-Digit Diagnostic Code Definition of "High" PAE

- >100mg/dL weekly alcohol (6-8 beers in a 55 kg woman) =6-8 standard drinks = (81.6-108.8g alcohol)

DSM-5 Definitions

- Criteria "A" is 'more than minimal exposure to alcohol during gestation, including prior to pregnancy recognition'
- Minimal drinking is up to 13 drinks a month, with no more than 2 drinks on the same occasion (pg. 799)

Binge Definitions

- Generally 4-5 drinks/occasion
- Centre for Addiction and Mental Health; Canadian Centre on Substance Abuse and Statistics Canada (CAN):
    - Binge for women: 4 or more drinks
    - Binge for men: 5 or more drinks
- National Institute on Alcohol Abuse and Alcoholism (USA):
    - Blood Alcohol Concentration at or over 0.08% (For the typical woman, this translates to roughly 3 ½ to 4 standard drinks in 2 hours)

APPENDIX F
Examples of Neurodevelopmental Tests[§]

([§]These tests are appropriate when English is the dominant language)

Notes

1. In all domains discussed, the "clinical cut-off" is defined as the 3rd percentile or 2 standard deviations below the mean. Please refer to the **Neurodevelopmental Assessment** section for more information.
2. Tests below are suggestions for most common situations but need to be considered in the context of each patient (i.e., hearing impaired, English as a second language etc.).
3. Standardized assessment results should be corroborated by informal observations and parent report.

	0-3 months	**3-18 months**	**18-36 months**	**36 months- 6 years**	**7-18 years**	**18+ years**
Motor Skills	-AIMS -Neuro-logical examination*	-AIMS -Neuro-logical examination*	-PDMS-2 -M-FUN -Neuro-logical examination*	-M-FUN -BOT-2 -BEERY VMI	-Abnormal neurological signs (e.g., motor tone, reflexes)* -Movement-ABC-2 -BOT-2 -BEERY VMI -RCFT -PDMS-2	-Abnormal neurological signs (e.g., motor tone, reflexes)* -BEERY VMI -Grip strength -Grooved pegboard -Finger Tapping -RCFT

Neuroanatomy / Neurophysiology	-Micro-cephaly -Abnormal structure seen on brain imaging -Seizure Disorder	-Micro-cephaly -Abnormal structure seen on brain imaging -Seizure Disorder	-Micro-cephaly -Abnormal structure seen on brain Imaging -Seizure Disorder	-Micro-cephaly -Abnormal structure seen on brain Imaging -Seizure Disorder	-Micro-cephaly -Abnormal structure seen on brain Imaging -Seizure Disorder	-Micro-cephaly -Abnormal structure seen on brain Imaging -Seizure Disorder
Cognition	-Bayley-III*	-Bayley-III*	-Bayley-III*	-WPPSI-IV -DAS-II	-WISC-IV/V -DAS-II	-WAIS-IV
Language	-PLS-5* -REEL-3*	-PLS-5* -REEL-3*	-PLS-5 -REEL-3*	-PLS-5 -CELF-5 -PPVT-4 -EVT-2 -RBS -Language Usage Sample Analysis	-PLS-5 -CELF-5 -PPVT-4 -EVT-2 -TNL -Language Usage Sample Analysis	-CELF-5 -PPVT-4 -EVT-2 -Language Usage Sample Analysis
Academic Achievement	N/A	N/A	N/A	-BBCS -WIAT-3 -DAS-2: School	-DAS-2 -WIAT-3 -WJ III ACH	-WIAT-3 -WRAT-IV -WJ III ACH

				Readiness Battery		
Memory	N/A	N/A	N/A	-NEPSY-II -DAS-2 -KABC-II	- CMS -WRAML-2 -NEPSY-II -CVLT-C -RCFT	-WMS-IV -WRAML -CVLT-2 -RCFT
Attention	N/A	N/A	N/A	-Parent and teacher questionnaires and interviews (e.g., CBCL, BASC-2, SNAP-IV*), plus clinical observation -CPT *With other clinical evidence	-Parent and teacher questionnaires and interviews (e.g., CBCL, BASC-2, SNAP-IV*), plus clinical observation -CPT -TEACH *With other clinical evidence	-Parent questionnaires (e.g., SNAP-IV) -Clinical judgement and observation -CPT
Executive function	N/A	N/A	-N/A	-NEPSY-II (5+ years)	-RCFT -Clinical	-BADS -BRIEF

				-Clinical assessment including clinical interviews, file reviews and parent/teacher rating scales (e.g., BRIEF) -CEFI (5-18 years) -WCST	observations -TOPS-3E -TOPS-2A -SLDT-E -SLDT-A -D-KEFS -CEFI (5-18 years) -BRIEF -WCST -NEPSY-II -Working memory scales from WISC-IV/V or WRAML-2	-WCST -D-KEFS -RCFT -Working memory scales from WAIS-IV or WRAML-2
Affect Regulation	-CTS*	-CTS*	CTS* ITSEA*	-Dx of anxiety and/or depression disorder	-Dx of anxiety and/or depression disorder	-Dx of anxiety and/or depression disorder

				-CTS* -Clinical Interview -BASC-2 -CBCL	-Clinical Interview -Self-Report Questionnaires (BDI-II, BAI, MASC 2, CDI 2)	-Clinical Interview -Self-Report Questionnaires (BDI-II, BAI, MASC 2)
Adaptive behaviour, social skills OR social communication	-ABAS-II -VABS-II	-ABAS-II -VABS-II	-ABAS-II -VABS-II	-ABAS-II -VABS-II	-ABAS-II -VABS-II -SLDT-E -SLDT-A	-ABAS-II -VABS-II

**Measures marked with an asterisk are considered to have lower reliability in a given age category and are only to be used towards diagnosis when all three sentinel facial features and confirmed prenatal alcohol exposure are both present or when delays in this domain are considered so profound as to overcome the poor reliability of the measure.*

Key to Acronyms

ABAS-II: Adaptive Behavior Assessment System, Second Edition[1]
AIMS: Alberta Infant Motor Scale[2]
BADS: Behavioral Assessment of the Dysexecutive Syndrome[3]

[1] Harrison P, Oakland T. *Adaptive Behavior Assessment System, Second Edition*. Pearson: 2003.
[2] Piper M, Darrah J. *Motor Assessment of the Developing Infant*. Philadelphia, PE: WB Saunders; 1994.
[3] Wilson BA, Emslie H, Evans JJ, Alderman N, Burgess PW. *Behavioral Assessment of the Dysexecutive Syndrome (BADS)*. Pearson; 1996.

BAI: Beck Anxiety Inventory[4]
BASC-2: Behavior Assessment For Children, Second Edition[5]
Bayley-III: Bayley Scales of Infant and Toddle r Development, Third Edition[6]
BBCS-3: R: Bracken Basic Concept Scale, Third Edition: Receptive[7]
BDI-II: Beck Depression Inventory[8]
BEERY-VMI: Beery Buktenica Developmental Test of Visual-Motor Integration[9]
BOT-2: Bruininks-Oseretsky Test of Motor Proficiency, Second Edition[10]
BRIEF: Behavior Rating Inventory of Executive Function[11]
CBCL: Child Behavior Checklist[12]
CDI 2: Children's Depression Inventory 2[13]
CEFI: Comprehensive Executive Function Inventory[14]
CELF-5: Clinical Evaluation of Language Fundamentals, Fifth Edition[15]
CMS: Children's Memory Scale[16]
Conners CPT 3: Conners Continuous Performance Test, Third Edition[17]
CTS: Carey Temperament Scales[18]
CVLT-C: California Verbal Learning Test – Children's Version[19]

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[16] Cohen M. *Children's Memory Scale*. Pearson, 1997.
[17] Conners CK. *Conners Continuous Performance Test 3*. MHS Assessments; 2014.
[18] Carey WB, MacDevitt SC & Associates. *Carey Temperament Scales*. 2007.
[19] Delis DC, Kramer JH, Kaplan E, Ober BA. *California Verbal Learning Test – Children's Version*. Pearson; 1994.

DAS-II: Differential Ability Scales, Second Edition[20]
D-KEFS: Delis-Kaplan Executive Function System[21]
EVT-2: Expressive Vocabulary Test, Second Edition[22]
ITSEA: Infant Toddler Social Emotional Assessment[23]
KABC-II: Kaufman Assessment Battery for Children, Second Edition[24]
MASC 2: Multidimensional Anxiety Scale for Children, Second Edition[25]
Movement-ABC-2: Movement Assessment Battery for Children, Second Edition[26]
M-FUN: Miller Function and Participation Scales[27]
NEPSY-II: NEPSY, Second Edition[28]
PDMS-2: Peabody Developmental Motor Scales, Second Edition[29]
PLS-5: Preschool Language Scales, Fifth Edition[30]
PPVT-4: Peabody Picture Vocabulary Test, Fourth Edition[31]
RBS: Renfrew Bus Story[32]
RCFT: Rey Complex Figure Test and Recognition Trial[33]
REEL-3: Receptive Expressive Emergent Language Scale, Third Edition[34]

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[20] Elliott CD. *Differential Ability Scales, Second Edition*. Pearson; 2007.
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SLDT-A: The Social Language Development Test - Adolescent[35]
SLDT-E: The Social Language Development Test - Elementary[36]
SNAP-IV: Swanson, Nolan, and Pelham-IV Parent and Teacher Rating Scales[37]
TEA-Ch: Test of Everyday Attention for Children[38]
TNL: Test of Narrative Language[39]
TOPS-2A: Test of Problem Solving - Adolescent, Second Edition[40]
TOPS-3E: Test of Problem Solving - Adolescent, Third Edition[41]
VABS-II: Vineland Adaptive Behavior Scales[42]
WAIS-IV: Wechsler Adult Intelligence Scale, Fourth Edition[43]
WCST: Wisconsin Card Sorting Task[44]
WIAT-III: Wechsler Individual Achievement Test, Third Edition[45]
WISC-IV/V: Wechsler Intelligence Scales for Children, Fourth/Fifth Edition[46]
WJ III ACH: Woodcock-Johnson III Tests of Achievement[47]
WMS-IV: Wechsler Memory Scales, Fourth Edition[48]
WPPSI-IV: Wechsler Preschool and Primary Scales of Intelligence, Fourth Edition[49]
WRAML-2: Wide Range Assessment of Memory and Learning, Second Edition[50]

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WRAT-4: Wide Range Achievement Test, Fourth Edition[51]

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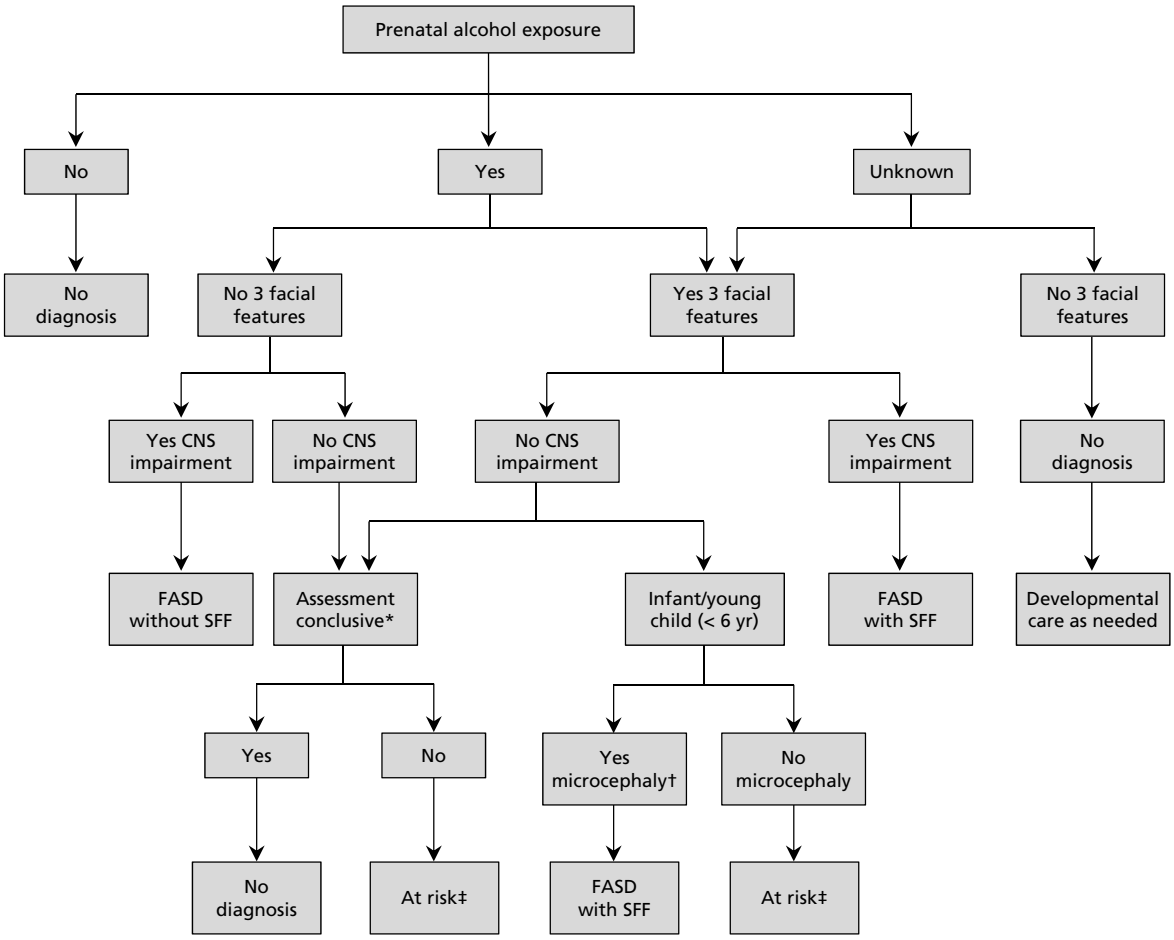
Appendix G: Diagnostic Algorithm for FASD



*Assessment conclusive = clinician conducting the neurodevelopmental assessment is satisfied that the session was a true representation of the person's ability and that any deficits reported were not due to extenuating circumstances. Assessments may be inconclusive for children under six years of age, because some domains cannot be assessed with confidence until the person is older or because of other confounding factors, such as temporary life stress or illness; see the text for more information.
†Microcephaly is not the only pathway to diagnosis for infants and young children; these individuals may also receive other FASD diagnoses, as specified elsewhere in the algorithm, if they show three areas of substantial impairment on neurodevelopmental tests.
‡At risk for neurodevelopmental disorder and FASD, associated with prenatal alcohol exposure. An at-risk designation includes situations where a full neurodevelopmental assessment is not conclusive because of age or situational factors; therefore, FASD may not be the diagnosis. Clinical judgment is recommended.
Note: CNS = central nervous system (yes/no impairment in ≥ 3 brain domains), SFF = sentinel facial features.8

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