DIAGNOSTIC ISSUES AFFECTING THE EPIDEMIOLOGY OF FETAL ALCOHOL SPECTRUM DISORDERS

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ABSTRACT

Background
Epidemiological measures of the prevalence of fetal alcohol spectrum disorders (FASD) vary greatly in the literature. Irrespective of the methodology, the criteria to define a 'case' are set by the researchers. Hence, estimates of the prevalence of FASD primarily depend on the diagnostic criteria currently available. The problem lies therein - the aforementioned criteria are ill-defined.

Materials & Methods
A critical analysis of the diagnostic criteria from the Institute of Medicine, Hoyme, 4-Digit Diagnostic Code and Canadian guidelines was performed, with particular attention focused on the inconsistencies in specificities of the fetal alcohol syndrome (FAS) facial phenotype.

Results
To date, the Canadian guidelines represent the only guidelines that have pushed for a uniform diagnostic capacity through harmonizing the IoM and 4-Digit Diagnostic Code criteria. In the absence of a reliable biochemical marker of effect to confirm maternal drinking during pregnancy, the importance and dependence on diagnostic guidelines for FASD is understated. With the availability of four published guidelines for diagnoses across the spectrum of FASD, there is a need to reach a set standard globally. There are profound implications of relaxed and strict diagnostic approaches on FAS prevalence reporting in the literature.

Conclusions
This review exposes the clinical burden of diagnosing the range of FASD with disputing diagnostic criteria. Discrepancies in the criteria pose a danger to the validity of FASD diagnoses with respect to inaccurate estimates of incidence and prevalence. In turn, these discrepancies risk compromising the future healthcare of affected individuals with regards to intervention, counselling and treatment.

Key Words: *FAS, FASD, 4-Digit, Canadian, Hoyme, IoM*

Concerns about the teratogenic effects of fetal exposure to alcohol date back to Plato's dialogues,[1] which theorised that the "offspring then generated will in all probability be perverse and crooked in body and mind".[2] Today, maternal drinking during pregnancy is known to be responsible for the phenomenon of fetal alcohol spectrum disorders (FASD). The term, which bears no diagnostic value by itself,[3] broadly describes the range of pervasive conditions caused by prenatal alcohol exposure.

Fetal alcohol syndrome (FAS), "the most clinically recognisable form of FASD",[4] is a condition whereby individuals affected present with evidence of growth retardation, impaired neurocognition and a characteristic triplet of facial anomalies. Other diagnoses within FASD include partial FAS (PFAS), alcohol-related birth defects

(ARBD) and alcohol-related neurodevelopmental disorder (ARND).[4,5]

Epidemiological measures of the prevalence of FASD vary greatly in the literature.

Methods of active case ascertainment, passive surveillance and clinical-based studies have been pivotal in recording its occurrence in populations.[6,7] Irrespective of the methodology, the criteria to define a 'case' are set by the researchers.[6] Hence, estimates of the prevalence of FASD primarily depend on the diagnostic criteria and guidelines currently available. The problem lies therein – the aforementioned criteria are ill-defined.

METHODS

A critical analysis of the diagnostic criteria from the Institute of Medicine, Hoyme, 4-Digit Code and Canadian guidelines is fundamental to this discussion.[3,5,8,9] These guidelines enable health practitioners to consider diagnoses along the range of FASD. Divergent diagnostic practices and its implications on prevalence reporting will then be appraised. This review will also pay particular attention to inconsistencies in specificities of the FAS facial phenotype, with view of the consequences in an epidemiological context.

Institute of Medicine (IoM) Guidelines

The Institute of Medicine of the National Academies[5] published the first set of guidelines for the diagnosis of FAS (with confirmed or unknown prenatal alcohol exposure), PFAS, ARBD and ARND. With the exception of ARBD, there is considerable overlap between the diagnostic categories, which adds to the complexity of diagnosing children along the continuum of FASD. In comparison to other diagnostic guidelines currently available, the IoM criteria for the diagnosis of FAS are evidently undefined.

The lack of explicit parameters when assessing for evidence of growth deficits, facial abnormalities and CNS dysfunction is problematic. Ultimately, interpretation of 'low' and 'short' anthropometric measurements of growth and face will vary between clinicians. Interestingly, the CNS criteria also fail to account for cognitive impairment in the diagnosis of FAS, which is paradoxical given that it is arguably "the most disabling feature of FAS"[10] as aptly put by Astley. Stratton *et al.*[5] justifies its exclusion, emphasising that neurocognitive dysfunction is not specific to individuals with FAS. Such deficits can be correlated with variables independent of prenatal alcohol exposure, for instance, genetic-environmental interactions.[4,5] Whilst this is certainly true, ethanol teratogenesis induces apoptotic insults to neural progenitor cells.[11,12] Damage to these cell populations affects the neurogenesis, migration and differentiation of nerve cells in the developing embryo, which can result in the structural and functional manifestations of CNS damage seen in individuals with FAS. Prenatal exposure to alcohol clearly has implications for cognitive deficits in the full-blown syndrome, yet it only qualifies a diagnosis of PFAS or ARND according to the IoM criteria.[4,5,13]

Whilst the IoM guidelines duly address the need for clinicians to differentially diagnose conditions grouped under the term FASD, its diagnostic categories are too generalised and poorly defined, thus rendering it inappropriate for sole use in routine clinical practice today.

Hoyme Guidelines

A report by Hoyme et al.[8] attempts to amend the ambiguity of the IoM criteria. Measures of height, weight, head circumference and palpebral fissure length that fall at or below the 10th percentile provide quantitative means of fulfilling the criteria for FAS.[8] The Hoyme FAS criteria for facial dysmorphology and growth retardation, nonetheless, remain non-standardized for race. Normal reference ranges quoted within the guidelines are derived from white populations.[8] Hence, application of the Hoyme guidelines requires skill on behalf of the physician with respect to discriminating cases from various racial backgrounds.[8]

4-Digit Diagnostic Code

The 4-Digit Diagnostic Code[3] is the third diagnostic system relevant to this discussion. Currently in its third edition, the 2004 guidelines rank growth retardation, facial features, CNS

damage and prenatal alcohol exposure on a four-point Likert scale. Permutations range from 1111 to 4444, whereby 1111 is indicative of normal findings and 4444 advocates a categorical diagnosis of FAS with alcohol exposure. Each possible rank combination that falls within this array is allocated a diagnosis that falls under FASD.[3]

Unlike other diagnostic guidelines previously mentioned, the 4-Digit Diagnostic Code is adjusted to account for race when assessing a patient's upper lip, philtrum, palpebral fissure length and occipital frontal head circumference.[3] It should be noted, however, that the normal reference range cut-offs differ remarkably compared to those quoted in Hoyme's revised IoM guidelines. The implications of incongruent diagnostic methodologies, when ascertaining the true prevalence of FAS, will now be considered.

In a 2006 study by Astley[10], the 4-Digit Diagnostic Code and Hoyme guidelines established FAS prevalence rates of 3.7% and 4.1%, respectively. Whilst the difference may seem marginal from a superficial standpoint, the patients flagged with FAS were noticeably different amongst the two measures of prevalence. Ideally, both diagnostic guidelines ought to have identified the same individuals yet only 17 patients met the standards set by both the 4-Digit and Hoyme criteria to qualify for a diagnosis of FAS. This provides evidence to suggest that epidemiological measures of the incidence and prevalence of FAS are indeed influenced by discrepancies between the guidelines. Such inconsistencies in the specificities of the Hoyme and 4-Digit facial phenotypes may account for the different FAS prevalence rates reported in this study. An explanation of the cause of discordant specificities is now fundamental to this discussion.

For an individual to meet the FAS facial phenotype, the 4-Digit Code explicitly requires the simultaneous expression of three facial features whereas the Hoyme guidelines stipulate the need for the presence of at least two facial anomalies.[3,8] This is a matter of particular significance since the Hoyme guidelines essentially slacken its facial criteria, which potentially compromises the validity of its FAS diagnoses.

The dissimilarity in palpebral fissure length (PFL) cut-off values between the two diagnostic systems is another point of reference in this discussion. A length that falls more than or equal to two standard deviations ($\leq 2.5^{th}$ percentile) from the mean PFL will receive an ABC-Score of 'C' with the 4-Digit Diagnostic Code. This score is imperative in the diagnosis of FAS since the rank 4 facial phenotype can only be derived from a palpebral fissure - philtrum - lip ABC-Score combination of 'CCC'.[3] In contrast, the Hoyme guidelines only consider lengths that measure at or below the 10^{th} percentile.[8]

In addition to this, both guidelines incorporate different normal reference range cut-off values within the criteria for CNS damage. The 4-Digit and Hoyme CNS criteria operate 2.5^{th} and 10^{th} percentile fig 1 cut-offs, respectively, upon measurement of the occipital frontal circumference (OFC).[3,8,10] Whilst the 4-Digit Diagnostic Code also considers deficits in function that relate to behavioural, cognitive and learning domains, the Hoyme guidelines limit its domain definition of CNS damage to "deficient brain growth or abnormal morphogenesis".[3,8] Disagreement between the diagnostic criteria contributes toward explaining why the two systems produced variable outcomes of FAS diagnoses in the 2006 study by Astley, particularly with reference to the individuals identified.

Canadian Guidelines

The last diagnostic system of notable significance to this discussion is the Canadian guidelines, which were devised by an expert panel of the Public Health Agency of Canada's National Advisory Committee on FASD.[9] These guidelines recommend a multidisciplinary team-based approach in the diagnostic process and in fact harmonise the IoM and 4-Digit Code approaches, rectifying the aforementioned concerns and limitations raised surrounding the IoM criteria. The current recommendations integrate the nomenclature of the IoM criteria (with respect to describing the diagnosis) with the objectivity and scientific rigor underling the 4-Digit Code criteria,

setting a standard for brain and physical cut-off values.[9] In line with the 4-Digit Code criteria,[3] the Canadian guidelines use two standard deviations below the mean for the cut-off value when measuring PFL as part of the dysmorphology assessment in diagnosing the full-blown FAS phenotype. Using a normal distribution curve in a non-standardised population as an example, Fig. 1 illustrates a comparison of the PFL cut-off values between the Hoyme, 4-Digit and Canadian guidelines.

FIG. 1 Comparison of PFL cut-off valves between the Hoyme, 4-Digit and Canadian guidelines

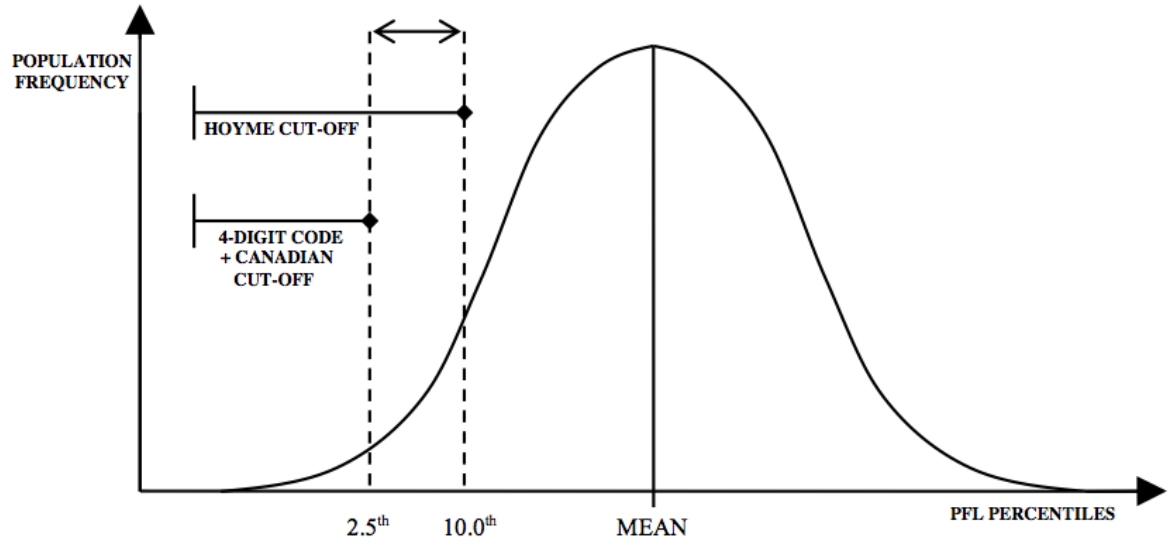

FIGURE 1 Legend: A normal distribution curve illustrating the range of palpebral fissure length values in a non-standardised population. Beaglehole *et al.*[14] affirm that the 95th percentile point separates normal and abnormal. Hence, the Hoyme PFL cut-off point enables individuals with a PFL within the normal range to be classified with the FAS facial phenotype. The area between the two arrows pointing in opposite directions depicts how over inclusive the Hoyme cut-off is in comparison to the 4-Digit Code and Canadian guidelines cut-off values. This serves to explain the lower specificity of the Hoyme facial criteria and the rationale behind the higher prevalence of FAS reported with the Hoyme guidelines.

CONCLUSION

This review has thoroughly considered the profound implications of relaxed and strict diagnostic approaches on FAS prevalence reporting in the literature. Currently available diagnostic methodologies incorporate different benchmark cut-off values in their criteria. A cut-off that tends to be more inclusive will flag all true positive cases of FAS, though at the expense of misclassifying normal subjects with FAS too. Likewise, a cut-off that is strict and more exclusive, whilst minimising false positives, may miss a diagnosis of FAS – thus maximising the incidence of false negatives.

To date, the Canadian guidelines represent the only guidelines that have pushed for a uniform diagnostic capacity through harmonising the IoM and 4-Digit Diagnostic Code criteria. The guidelines are currently used in

reports of population studies in Africa, Eastern Europe and North America and provide an invaluable source for clinicians and experts when considering diagnoses along the range of FASD. In the absence of a reliable biochemical marker of effect to confirm maternal drinking during pregnancy, the importance and dependence on diagnostic guidelines for FASD is understated. With the availability of four published guidelines for the diagnosis of FAS and its related disabilities, there is a need to reach a set standard globally. In clinical practice, diagnoses are variable from consultation to consultation amongst expert healthcare practitioners in the field. For example, some clinics are known to adopt the precision of the criteria set in the 4-Digit Diagnostic Code alongside the terminology from the IoM criteria in an attempt to produce a more desirable approach for diagnosis and treatment recommendations.[9]

This focus of this review was primarily to expose the clinical burden of diagnosing the range of FASD with disputing diagnostic criteria. Astley[10] states that professionals "…decide which guidelines are adopted into practice" yet this only serves to further compromise the accuracy of reported prevalence estimates. In an article by Mutch *et al*.,[15] the need for a uniform diagnostic capacity is stressed exhaustively - and rightly so. Discrepancies in the diagnostic criteria pose a danger to the validity of FASD diagnoses with respect to inaccurate estimates of incidence and prevalence. In turn, these discrepancies also risk compromising the future healthcare of affected individuals with regards to intervention, counselling and treatment.

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