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Fetal Alcohol Spectrum Disorders (FASD)

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Synthesis

How important is it?

Alcohol consumption in women of childbearing age has maintained around 55% worldwide in the last 20 years, including roughly 11% of pregnant women who reported consuming alcohol in the previous month. Other research has found that 30% of women admit consuming alcohol at some point during pregnancy, and 8% report having had more than four drinks on one occasion. Although most women reduce their consumption once they find out they are expecting, many of them do not know about the pregnancy before the fourth or sixth week of gestation and continue drinking during that period. Although experts advice women to avoid alcohol during pregnancy or while trying to conceive, drinking continues to be reported by women perhaps due to persistent confusion about the effects of alcohol on fetal development.

Despite its entirely preventable nature, prenatal alcohol exposure (PAE) remains the leading cause of congenital abnormalities, intellectual impairment, and other developmental problems in children. Complications due to maternal alcohol consumption during pregnancy affect families and children from all ethnic and economic backgrounds.

One of the most severe birth defects caused by PAE is Fetal Alcohol Syndrome (FAS). FAS is an enduring and irreversible condition marked by a set of distinctive facial traits (e.g., small openings to the eyes, thin upper lip, flattened area above the upper lip) as well as growth deficits and central nervous system dysfunction. On average, approximately 1 - 3 per 1,000 viable infants are born with FAS, and these rates increase to 10 - 15 per 1,000 in at-risk groups such as the foster care population.

Given that most children exposed to alcohol during the prenatal period do not exhibit all of these defects, the term Fetal Alcohol Spectrum Disorders (FASDs) has been introduced in recent years to incorporate the range of deficits associated with PAE. The prevalence of FASDs in the general population is estimated at 5%[a].

Aside from the direct devastating effects prenatal alcohol exposure has on children and families, it also represents a significant financial burden for governments and communities. For instance, the lifetime cost for the care of one child with FAS is estimated at $2 million in special medical,

health and educational resources.

What do we know?

The severity of the adverse effects of PAE varies across children, and depends on a number of factors, including the extent of the PAE (amount, timing, incidence) and genetic predispositions. However, even a small amount of alcohol consumed during pregnancy can have lasting effects on offspring. As little as one alcoholic beverage per week in the first three months of pregnancy has been associated with psychiatric problems at age 4 and 8 in young girls, even after controlling for a variety of confounding factors.

Early childhood

Alcohol consumption during pregnancy has been associated with a wide range of negative outcomes throughout development. Infants and toddlers who have been exposed to alcohol in utero display dysfunctions in sleep, regulation, orientation, and habituation. They tend to be more irritable than unexposed children. Heavy alcohol consumption is also associated with more negative emotionality in infants, which in turn, can diminish the level of responsiveness, support and stimulation provided by the mother, and can ultimately exacerbate the negative impact of PAE on development. After controlling for age, ethnicity, and family income, prenatally alcohol-exposed children are much more likely to be classified with an insecure attachment or symptoms of depression than unexposed children.

Childhood

Disturbances in infancy often persist in childhood, where alcohol-exposed children show increased reactivity, irritability and activity level, and struggle with deficits in attention. Difficulties experienced by prenatally alcohol-exposed children are also noted in the neurobehavioural domain, and include impairments in intellectual, language, memory, visual-spatial problem-solving, and executive functioning. Children with FASDs are also more likely than unexposed children to be diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) and to display behaviour problems and poor adaptive skills even after controlling for intellectual functioning.

Adolescence and Adulthood

PAE continues to have an impact on adolescent and adult offspring. One of the most documented effects is the high incidence of mental health problems, such as mood and personality disorders in this population. Problem behaviours and delinquency are also more common among adolescents and adults with FASDs than among non-exposed individuals. These individuals engage in more illegal acts, antisocial conduct, inappropriate sexual behaviours, and are more frequently incarcerated. They are also more likely to experience socioemotional, occupational, and substance-related problems.

What can be done?

The most direct and obvious way to prevent FASDs is to eradicate alcohol consumption in women who are either pregnant, planning a pregnancy or who could become pregnant. However, despite health recommendations, the rates of alcohol consumption of women of childbearing age have remained stable. In addition, inconsistent information given to women and disputes about what is the safe amount of alcohol women should consume during pregnancy contribute to confusion. A clear consensus based on a systematic review of research on PAE is strongly needed, and should guide the recommendations and practice of professionals.

The most successful prevention strategies have been screening for alcohol consumption by health care professionals accompanied by brief interventions or extended brief interventions with pregnant and non-pregnant women of childbearing age. The efficacy of these treatments is also enhanced by implicating the woman’s life partner in the intervention. Health providers must therefore be thoroughly informed and educated about the harmful effects of drinking during pregnancy, and how to conduct brief interventions with women.

For alcohol-exposed children, a classification of syndrome-specific profiles would facilitate diagnosis in the absence of distinct facial characteristics. This would also ensure early identification and intervention, which has been shown to predict positive outcomes in this population. Pediatricians, nurses, educators, and early childhood mental health consultants should all be trained in recognizing the different signs of PAE, and in asking about and keep accounts of maternal alcohol consumption during pregnancy.

Results from animal research also suggest that certain substances could attenuate the negative impact of alcohol on the fetus. For instance, while dietary deficiencies (e.g., low levels of zinc and iron) may worsen the adverse effects of alcohol on fetal development, taking certain

supplements (e.g., choline, zinc, vitamin C, E, and B-carotene) may protect against these effects. Exposure to other substances, such as lithium and neuroprotective peptides, has also been successful at reducing the severity of the effects of PAE in animals, but this has yet to be shown in humans.

Treatment

Different interventions on prenatally alcohol exposed rodents have been linked to positive outcomes, including neonatal handling, enriching environment and rehabilitation. In humans, social skills training, socio-cognitive programs focused on mathematics and behavioural regulation have been successful at improving the functioning of children with FASDs. Family interventions can also improve the well-being and daily adaptation of alcohol-exposed children while simultaneously assisting and supporting parents to provide stable and optimal care to their children.

One way to thoroughly trace and organize the types of services offered to children with FASDs is to strengthen cooperation and communication across different child care systems, including health care, child welfare, community centers, and Early Start and Head Start programs. This initiative can also guarantee that FASD does not go undetected.

Existing therapies for children with FASD include behavioural, language, occupational and physiological treatments. The success of those treatments could be improved by taking into consideration the deficits and needs specific of children with FASDs. For instance, although many children with a FASD are prescribed stimulants for ADHD symptoms, the negative side effects of these drugs appear to be particularly salient for children with FASDs, and should therefore be prescribed with caution. Given that the occurrence of FASDs is scattered across economic classes and ethnicities, the assistance provided to these children and their families should be adapted to meet different community and cultural needs.

[a] May PA, Baete A, Russo J, Elliott AJ, Blankenship J, Kalberg WO, Buckley D, Brooks M, Hasken J, Abdul-Rahman O, Adam MP, Robinson LK, Manning M, Hoyme HE. (2014). Prevalence and characteristics of fetal alcohol spectrum disorders. Pediatrics. 134(5):855-66. doi: 10.1542/peds.2013-3319.

Neurobehavioural Profiles of Individuals with Fetal Alcohol Spectrum Disorders

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Introduction

Prenatal exposure to alcohol is the leading preventable cause of birth defects, developmental disorders, and intellectual disabilities in children.[1] The prevalence of fetal alcohol spectrum disorders (FASD) is estimated to range between 1.1 and 5.0% in the United States,[2] and has been identified in all racial and ethnic groups.[3] Children prenatally exposed to alcohol can suffer from serious cognitive deficits and behavioural problems as well as alcohol-related changes in brain structure. Heavy prenatal alcohol exposure is associated with decreased intellectual functioning and deficits in learning, memory, and executive functioning. Additionally, alcohol exposure is associated with problem behaviours including hyperactivity, impulsivity, poor socialization and communication skills, and the development of substance use problems.

The term "fetal alcohol syndrome" (FAS) was introduced in 1973[4] and is defined by three criteria: specific craniofacial features (short palpebral fissures, indistinct philtrum, and thin vermillion), pre- and/or postnatal growth deficits, and central nervous system (CNS) dysfunction.[5-7] Recent updates to the diagnostic criteria now recommend evidence of both abnormal structural CNS development (head circumference ≤ 10th percentile, structural irregularities, and/or nonfebrile seizures) and functional CNS impairment (cognitive and/or behavioural).[5] While examination of the consensus between diagnostic criteria is at the forefront of current research,[8] it is clear that children with confirmed prenatal alcohol exposure may not meet all diagnostic criteria while still exhibiting significant neurobehavioural impairments and neuroanatomical abnormalities.[9-11] The non-diagnostic umbrella term fetal alcohol spectrum disorders has been adopted to capture the spectrum of consequences of alcohol exposure.[5]

Subject

The development of a neurobehavioural profile for FASD can aid in the identification of children affected by prenatal alcohol exposure that otherwise would be quite difficult to discern. In addition to improving the identification of affected individuals, a neurobehavioural profile also will aid in improving intervention tools and early treatment options, as well as increasing the accuracy of incidence rates of the disorder.

Problems

The identification of children with heavy prenatal alcohol exposure is impeded by the fact that along the continuum of FASD, only diagnoses on the severe end of the spectrum (i.e. FAS and partial FAS) are characterized by physical facial features.[5] The majority of alcohol-affected children lack some or all of these physical markers and are therefore more difficult to identify, especially if a clear history of alcohol exposure is unavailable. Despite the presence of significant neurobehavioural impairments, many children are missed (80.1%) or misdiagnosed (6.4%).[12] While research over the last four decades has documented diverse and significant neurobehavioural deficits in children with FASD,[13] it is not clear whether one or more profiles of neurocognitive function exist and if so, whether these profiles are specific to this population.

Research Context

In order to determine the deficits associated with heavy prenatal alcohol exposure, researchers typically compare the performance of children with FASD to non-exposed controls on a wide range of neuropsychological tasks. Additionally, in order to improve upon the specificity of the neurobehavioural profile, comparisons are made with other clinical groups of children who display an overlap in neuropsychological performance to alcohol-affected children.[14] The majority of these comparisons are focused on individuals with low IQ scores and those with attention-deficit/hyperactivity disorder (ADHD).

Key Research Questions

Recent research has addressed whether children with FASD exhibit a unique neurobehavioural profile. The identification of a syndrome-specific profile would improve the diagnosis of children with FASD and inform interventions for all children affected by heavy prenatal alcohol exposure.

Recent Research Results

Summary of neurobehavioural deficits in children with heavy prenatal alcohol exposure. FASD is associated with a number of neurobehavioural impairments including lower overall intelligence and deficits in executive functioning, learning and memory, language, visual-spatial functioning, and attention.[13] Additionally, children with heavy prenatal alcohol exposure are at a high risk for developing maladaptive and problematic behaviours.[15,16] Children with and without the facial dysmorphia associated with FAS display similar deficits in many of these domains, as described below.

Overall intelligence. Compared to their non-exposed peers, children with heavy prenatal alcohol exposure have diminished intellectual functioning. The IQ scores for these individuals typically fall in the borderline to low average range, with reductions in both verbal and performance (nonverbal) IQ.[9] Such deficits are persistent and stable.[17-19] Among those with FASD, lower intellectual ability levels are reported for those on the severe end of the spectrum (i.e. FAS),[20] however, children with and without the facial dysmorphology display intellectual impairment.[9] In addition, FAS is thought to be the leading known cause of intellectual disability (i.e. IQ less than 70) in the United States, although the majority of children with FAS are not intellectually disabled.[1]

Executive function. Global executive functioning deficits are present across the spectrum of FASD.[21] Children with FASD display deficits on measures of verbal and nonverbal fluency,[22] problem solving and planning,[23] concept formation, and set-shifting.[24] Although deficits are also observed in working memory and response inhibition domains, results are inconsistent and further research is necessary.[25-27]

Learning and memory. Children with FASD display deficits in learning and memory, including deficits in the acquisition and recall of both verbal and non-verbal information.[28,29] These impairments are present even when compared to IQ-matched samples.[30] However, overall memory function is complex and may not be globally affected by prenatal exposure to alcohol. For example, while learning and recall are impaired, retention of verbal (but not nonverbal) material appears to be spared in most studies.[29,31] Deficits are also found with spatial learning and memory, primarily using animal models.[32]

Language. Children with heavy prenatal alcohol exposure display deficits in various basic language skills including speech production,[33] phonological processing (e.g., pseudoword reading), articulation,[34] word ordering, and grammatical understanding.[35] Furthermore, children

with FASD make more grammatical errors compared to controls; grammatical error rate measures could be a potential biomarker that can significantly aid in the identification of those with FASD.[36] Overall, receptive and expressive language skills are impaired in alcohol-exposed children, although expressive abilities may be affected to a greater degree, and both types of deficits may be secondary to diminished intellectual functioning.[37]

Visual-spatial function. Children with heavy prenatal alcohol exposure have also been shown to have a variety of visual-spatial deficits, although these are not as well studied. Deficits include problems with basic figure copying,[38] spatial learning,[18] spatial working memory,[23] spatial recall,[39] visual-spatial reasoning,[40] visual-perceptual matching (e.g., matching complex geometric shapes),[41] and sustained visual attention.[42]

Attention. Attention deficits are well documented in children with FASD, specifically in the establishing and sustaining aspects of attention.[43] Within the area of sustaining attention, increased omission errors,[42] decreased accuracy rates, and slower reaction times are observed.[44] Additionally, attending to visual information appears to be more severely impaired compared to auditory information.[42,44]

Behaviour problems and psychiatric disorders. Children prenatally exposed to alcohol are at a high risk for problem behaviours that can interfere with their home, school and social environments. This includes an increased risk for psychiatric disorders,[15,45,46] trouble with the law, alcohol and drug abuse, and other maladaptive behaviours.[16] Additionally, they are more likely than non-exposed children to be rated as hyperactive, impulsive, or delinquent,[11,47] and frequently meet the diagnostic criteria for ADHD.[15,46,48] Further, children prenatally exposed to alcohol exhibit poor adaptive skills and are less likely to live independently.[49,50]

Specificity of neurobehavioural deficits in children with heavy prenatal alcohol exposure. Studies comparing children with FASD to non-exposed children with ADHD or low IQ scores lend support for a specific neurobehavioural profile associated with prenatal alcohol exposure. On measures of executive functioning, both alcohol-exposed children and non-exposed children with ADHD demonstrate deficits on sorting tasks and letter vs. category fluency, but only the alcohol-exposed group display overall deficits on letter fluency and letter-number switching.[51] Other studies comparing children with FASD and ADHD demonstrate that alcohol-exposed children display greater difficulty on tasks of visual-spatial reasoning, problem solving, and encoding and shifting aspects of attention,[52] as well as weaker social cognition and facial emotion processing

abilities.[53] Additionally, children with FASD display greater deficits in working memory, fluency, planning, and set-shifting compared to children with ADHD.[54] Both clinical groups have deficits in delayed recall of verbal information, but only children with FASD display deficits in the recognition of material, whereas children with ADHD are more impaired in the retention of learned material.[28] On measures of communication and socialization skills, children with FASD display an arrest in the development of adaptive abilities, whereas non-exposed children with ADHD are delayed in adaptive skills, as abilities tend to improve with age.[50] When comparing overall neuropsychological performance, children with alcohol exposure are more impaired compared to those with an ADHD diagnosis, however no differences are found between alcohol exposed children with and without ADHD.[55] Although the concurrent presence of FASD and ADHD does not appear to further affect cognitive functioning, the comorbidity does have an exacerbating effect on communication skills[56] and an increased rate of psychiatric disorders.[57] In summary, existing research suggests that children with FASD and children with ADHD have overlapping profiles of deficits, but with varying patterns and degrees of impairment, which are compounded by their comorbidity. Therefore, more research is needed to clarify the similarities and differences between these two diagnoses, and to further refine a neurobehavioural profile for FASD.

Children with FASD are similar to IQ-matched, non-exposed peers on measures of internalizing behaviour,[11] fine motor skills,[58] sustained attention, retention of verbal material, and expressive and receptive language skills.[36] However, children with FASD have more externalizing behaviour problems,[11] impaired adaptive skills,[59] and verbal learning deficits compared to IQ-matched controls.[58] Thus, common comorbidities, like low IQ and ADHD, do not entirely account for the neurobehavioural deficits reported in FASD, and other co-occurring factors need to be studied.

Several studies have demonstrated the potential usefulness of a neurobehavioral profile in the identification of children with FASD. Performance on various neurobehavioural measures were successful in distinguishing between children with prenatal alcohol exposure and non-exposed controls with overall classification accuracy rates ranging between 71.5% - 92%.[60-62] Furthermore, when differentiating between alcohol-exposed and ADHD children, the neurobehavioral profile had an overall classification accuracy rate of 73.9%.[61] Executive function and spatial processing measures,[60] as well as measures of attention[62] are particularly sensitive to the detection of prenatal alcohol exposure.

Research Gaps

The use of a neuropsychological profile in the aid of the diagnosis of FASD has been shown to be useful and increase success rates compared to relying on the presence of dysmorphological characteristics alone. Additional research is necessary to further define this neurobehavioural profile, as well as to continue to identify deficits in various areas including working memory, response inhibition, and visual-spatial function, as impairments in these areas are less well understood, as discussed above. Additionally, the identification of risk and resiliency factors is imperative in the development of preventative measures. Improving identification techniques will aid in earlier diagnosis, enhance targeted interventions, and ultimately lead toward better outcomes for affected individuals.[49]

Conclusions

Prenatal exposure to alcohol affects 1.1 to 5.0% of the population and leads to a spectrum of neurobehavioural consequences, including decreased overall intelligence and specific deficits in executive functioning, learning, memory, language, visual-spatial skills, and attention. Children with FASD display deficits in daily living skills and are at a higher risk for problem behaviours. These abnormalities have been documented in children both with and without the facial dysmorphology required for a diagnosis of FAS. Although there is some overlap in the deficits observed of non-alcohol exposed children with ADHD or low IQ, children with FASD display a specific pattern in areas including adaptive skills, problematic behaviours, and some neuropsychological domains. The potential clinical utility of a neurobehavioural profile in the aid of differential diagnosis has been shown, yet further research is necessary to continue to refine and increase classification accuracy.

Implications

The identification of a syndrome-specific profile would improve diagnosis of children with heavy prenatal exposure to alcohol, especially for the majority of children with FASD who do not display the facial dysmorphology. Additionally, further refinement of a neurobehavioural profile for FASD would inform treatments and interventions for children along the spectrum. The effects of alcohol on the developing central nervous system are permanent and irreversible. Treatments are currently symptom-based and are aimed at addressing the cognitive and behavioural consequences of prenatal exposure to alcohol. Current treatments include those targeted toward improving attention, self-regulation, social skills, and adaptive abilities.[63] Furthermore, given the array of cognitive impairments associated with prenatal alcohol exposure, many affected

individuals experience trouble in academic and learning environments.[64] Interventions using modified teaching strategies that focus on improving language, literacy, and mathematic abilities have been successful.[65] Finally, parent-focused interventions that provide parents with effective parenting strategies not only show advancements for the child, but also reduce parent stress and improve upon the parent-child relationship.[63,65] Existing interventions have been shown to have a positive effect for children with FASD, thus greater clarity of the neurobehavioural profile exhibited by affected children could further direct clinicians in the development of rational treatments that are specific to the disorder.

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Clinical Assessment of Individuals with Fetal Alcohol Spectrum Disorders (FASD)

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Introduction

Fetal Alcohol Syndrome (FAS) is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. The condition is characterized by growth deficiency, a unique cluster of minor facial anomalies and central nervous system (CNS) abnormalities.[1] The prevalence of FAS is estimated to be 1-3/1,000 live-births[1] in the general population, and as high as 10-15/1,000 in high-risk populations like foster care.[2] Not all individuals exposed and damaged by alcohol have FAS. Most present neuropsychological impairments without the physical findings. The condition is now recognized as a spectrum of disorders, FASD. Diagnoses like FAS, Partial FAS (PFAS), Alcohol-Related Neurodevelopmental Disorder (ARND), Static Encephalopathy/Alcohol -Exposed (SE/AE) and Neurobehavioural Disorder/Alcohol-Exposed (ND/AE) fall under the umbrella of FASD.[1,3]

Subject

Although reference to the harmful effects of maternal drinking on infant outcome date back to biblical times,[4,5,6] the term FAS was not coined until 1973.[7-9,10,11] Diagnostic guidelines were developed and refined through the 70s and 80s,[7,12,13,14] culminating in 1996 with the publication of the Institute of Medicine (IOM) guidelines.[1] While the IOM guidelines reflected an important advancement, the IOM committee continued to feel: 1) “a medical diagnosis of FAS remained the purview of dysmorphologists and clinical geneticists,” and 2) the guidelines remained intentionally broad and conceptual (gestalt) rather than specific and operational (case-defined).[15,16] For example, the guidelines for CNS dysfunction did not address how many areas of deficit must be present or how severe the deficits must be. The guidelines for the facial phenotype did not address how many features must be present, how severe each feature must be, or what measurement scales should be used to judge their severity. And introduction of the term ARND ran counter to the retraction of the term Fetal Alcohol Effects (FAE) the year prior.[17] Overall,

guidelines through 1996 were not sufficiently specific to ensure diagnostic accuracy (the ability to derive the correct diagnosis) or diagnostic reproducibility (the ability for two different clinicians to derive the same diagnosis in a given patient).[18]

Problems

In the absence of an accurate/reproducible method of diagnosis, diagnoses continued to vary widely between clinics.[1,18,19] From a clinical perspective, diagnostic misclassification leads to inappropriate patient care, increased risk for secondary disabilities[20] and missed opportunities for prevention.[15,21,22] From a public health perspective, diagnostic misclassification leads to inaccurate prevalence estimates.[15] Inaccurate estimates thwart efforts to allocate sufficient social/educational/medical services to this high-risk population and preclude the accurate assessment of prevention efforts. From a research perspective, diagnostic misclassification prevents detection of clinically-meaningful contrasts between groups and valid comparisons of outcomes between studies.[23]

Research Context

To overcome the limitations of the physician-focused gestalt approach to FASD diagnosis, the FASDPN introduced an interdisciplinary team approach in 1993 (medical doctor, psychologist, speech-language pathologist and occupational therapist)[24,25] guided by a rigorous, case-defined set of guidelines (FASD 4-Digit Diagnostic Code) in 1997.[15,16] Briefly, the 4 digits of the 4-Digit Code reflect the magnitude of expression of the 4 key diagnostic features of FASD in the following order: 1) growth deficiency, 2) FAS facial phenotype, 3) CNS structural/functional abnormalities, and 4) prenatal alcohol exposure (Fig. 1).[15] The magnitude of expression of each feature is ranked on a 4-point scale, with 1 reflecting complete absence of the feature and 4 reflecting severe presence of the feature. Each rank is specifically case-defined. The 4-Digit codes range from 1111 to 4444. To date, every combination of Code has been observed in the FASDPN clinics, reflecting the true diversity of outcome associated with prenatal alcohol exposure. The subset of 4-Digit Codes that fall under the umbrella of FASD can be grouped into three clinically meaningful and distinct diagnostic subgroups:

1. FAS/PFAS (severe neuropsychological impairment with the FAS facial phenotype);
2. SE/AE (severe neuropsychological impairment without the facial phenotype); and
3. ND/AE (moderate neuropsychological impairment without the facial phenotype).[23,26,27]

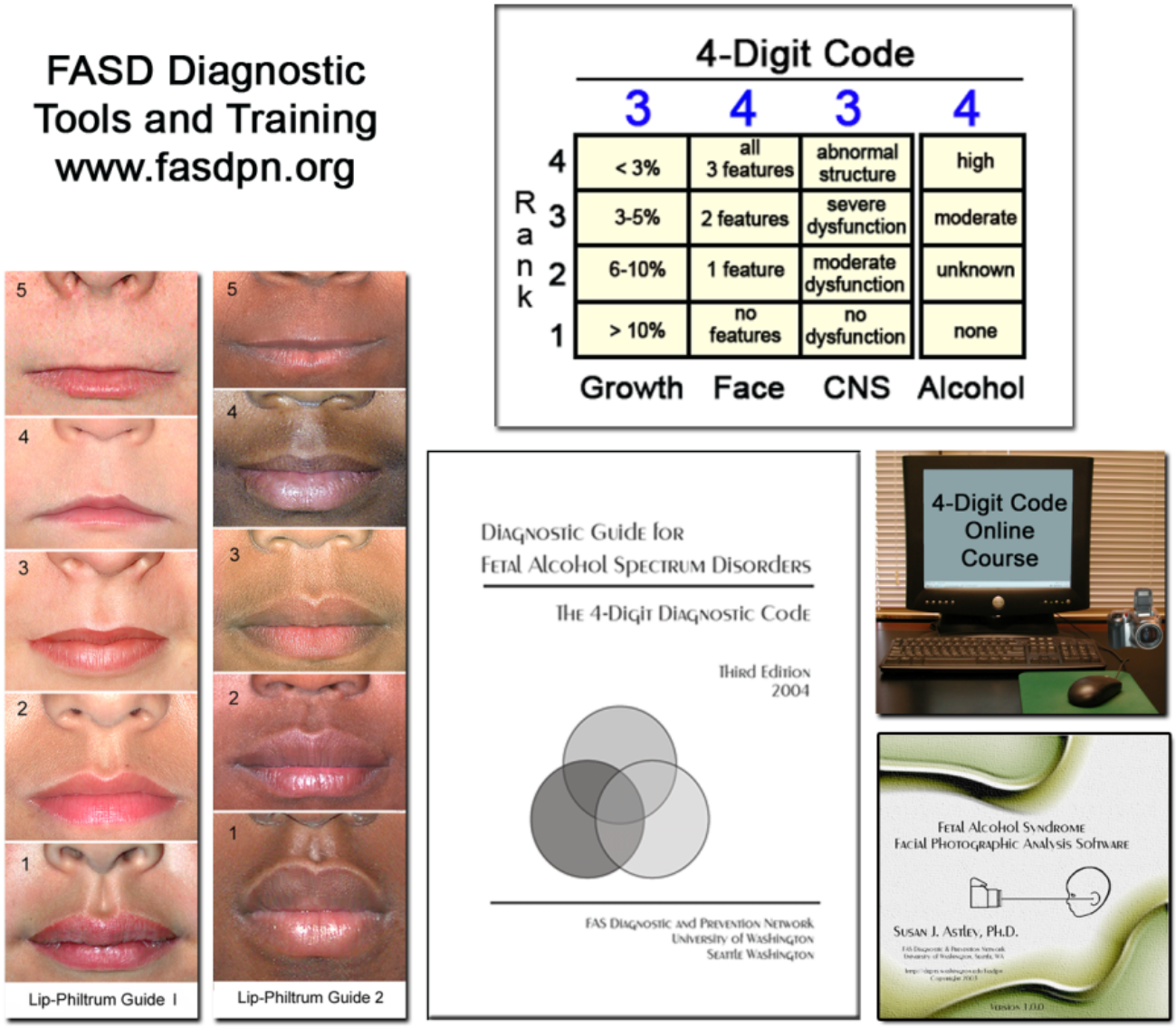


Figure 1. Fetal Alcohol Spectrum Disorders: 4-Digit Diagnostic Code: guide, tools and training.

Key Research Questions

Requisite to the development of diagnostic guidelines is validation of their performance, both before and after their release. Performance should be authenticated through published empirical studies. Measures of performance include accuracy, reproducibility, validity, and practicality.[28] Diagnostic teams should look for the following benchmarks in current FASD diagnostic guidelines:[1,3,28-32]

1. Are the guidelines evidence-based and developed from a broad, representative population-base? The evidence-base should include validation of performance prior to the guideline's release.
2. Do the guidelines endorse an interdisciplinary approach to diagnosis?
3. Are the diagnostic criteria specifically and comprehensively case-defined?
4. Do the diagnostic tools maximize measurement accuracy and precision?
5. The features that characterize FASD (growth, face, CNS, alcohol) are not simply present or absent. Each present along separate, clinically meaningful continua. Are these continua reflected in the guideline's measurement and classification scales?
6. The validity of an FAS diagnosis rests entirely on its unique facial phenotype. Therefore, the sensitivity and specificity of the FAS facial phenotype must be high (>90%) and empirically confirmed. Do the guideline's facial criteria meet these criteria?
7. Do the guidelines identify diagnostic subgroups that are: a) clinically and statistically distinct from one another, b) reflect a continuum of increasing neuropsychological and physical abnormality, and c) span the full continuum of FASD?
8. Does the diagnostic nomenclature assert clinical integrity?
9. The validity of the scales used to measure and classify exposures and outcomes is demonstrated by their ability to detect statistically-significant, physiologically meaningful correlations between physical outcomes, functional outcomes and alcohol exposure levels. With the scales: Does face predict brain? Does neurofunction correlate with neurostructure? Do diagnostic subgroups have unique alcohol-exposure patterns?
10. Are the guidelines readily adoptable into clinical practice? Their practicality should not be at the expense of their accuracy and precision. Training should be expedient, affordable, universally available and competency-based.

Recent Research Results

Below are examples of how the FASD 4-Digit Code meets all 10 benchmarks.

1. *Evidence-based*: The medical records of 1,014 patients (newborn-adult, all races) receiving FASD diagnostic evaluations in the statewide FASDPN were used to develop the 4-Digit Code. Its performance was validated prior to its release through both empirical analysis

and a two-year trial of use by an interdisciplinary team.[15]

2. *Interdisciplinary approach*: The guidelines necessitate the measurement and differential interpretation of physical (growth and dysmorphology) and functional (psychological, language, motor-sensory) outcomes, often in the context of complex social/environmental settings. This requires the expertise of an interdisciplinary team.[25,26]

3. *Case-definitions, measurement tools*: Continuum of exposure and outcome: Case-definitions, measurement tools: All criteria are specifically/operationally case-defined. For example, in contrast to the IOM definition of the FAS facial phenotype ("a characteristic pattern that includes features such as short *palpebral fissure length (PFL)*, flat upper lip, flattened *philtrum* and flat midface"),[1] the 4-Digit Code defines how short, how thin, and how smooth these first three features must be, and provides tools (Lip-Philtrum Guides and FAS Facial Photographic Analysis Software[33]) to accurately measure these features along their full continuum. The 4-Digit Code also recognizes the FAS facial phenotype is not simply present or absent. Its magnitude of expression is measured on a 4-point scale.[15]

4. *Continuum of exposure and outcome*: All FASD features are measured and classified on continuous or ordinal scales. Lips and philtrums are measured on 5-point *Likert scales*. Growth, face, CNS and alcohol are ranked on 4-point scales (Fig. 1). Even the diagnostic subgroups (ND/AE, SE/AE, and FAS/PFAS) reflect three distinct groups with increasing physical/functional impairment.[15,23,26,27,34,35]

5. *Specificity of FAS face*: The Rank 4 FAS facial phenotype is over 95% sensitive and specific to FAS and prenatal alcohol exposure.[2,36,37]

6. *Distinct diagnostic subgroups*: *MRI* /*MRS* /*fMRI* [23,26,27,34,35] have confirmed ND/AE, SE/AE and FAS/PFAS are three clinically distinct, increasingly more severe diagnostic subgroups with unique alcohol exposure patterns. For example, although FAS/PFAS and SE/AE both present with severe dysfunction and disproportionately smaller *caudates*, only FAS/PFAS has the full FAS facial phenotype, disproportionately smaller frontal lobes, significantly lower neurocholine levels, and a significantly higher frequency and duration of alcohol exposure. And although neither SE/AE nor ND/AE present with the full FAS facial phenotype, SE/AE presents with more severe dysfunction, disproportionately smaller caudates and a significantly higher quantity of alcohol exposure. And despite ND/AE's moderate dysfunction, MRI confirms a high prevalence of underlying neurostructural abnormality.

7. *Nomenclature integrity*: The terms SE/AE and ND/AE replace the terms ARND and FAE to accurately document an individual's outcomes and exposure without implying a causal association has been confirmed (or ruled-out) between the two.[15,17,28,29]
8. *Validity*: Published empirical studies[2,15,23,26,27,34-37] document a broad array of physiologically cogent relationships between exposures and outcomes. A few examples: Face predicts brain: IQ and regional brain volumes decrease incrementally and significantly with increasing expression (Ranks 1-4) of the FAS facial phenotype. Neurofunction correlates with neurostructure: The 3-point scale for CNS dysfunction (Rank 1=none, Rank 2=moderate, Rank 3=severe) is significantly associated with decreasing caudate volume.
9. *Readily adoptable into practice*: The guidelines and tools are distributed free or at cost via the web. Training is online, accredited, low-cost and can be completed in a weekend.[38]

Research Gaps

The problems (outlined above) that initially hindered FASD diagnosis have now been overcome with the adoption of rigorous diagnostic guidelines administered by interdisciplinary teams.[2,3,15,23,26-28,34,35,37,39] It is now time to focus research on FASD intervention.[40]

Conclusions

The FASD 4-Digit Diagnostic Code offers an intuitively logical, numeric approach to reporting outcomes and exposure that reflects the true diversity and continuum of disability associated with prenatal alcohol exposure. It also offers substantially greater precision, accuracy and validity than the gestalt method of diagnosis, through the use of quantitative measurement scales, specific case-definitions and an interdisciplinary team approach.

Implications for Parents, Services and Policy

Parents (830 over 13 years) have expressed high satisfaction with the FASDPN interdisciplinary approach to diagnosis using the 4-Digit Code.[26] They report the method was easy to understand and provided them with information they were unable to obtain elsewhere (99% would recommend the clinic to others). The FASDPN model has also earned the respect of service providers statewide. The diagnostic reports provide the detail and direction providers need to qualify children for services. Parents of children with FAS/PFAS, SE/AE and ND/AE confirm being able to access and benefit from recommended interventions.[26] The interdisciplinary model

and 4-Digit Code have been adopted worldwide, often initiated and supported through legislative policy.[26,41-44]

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Socioemotional Functioning of Individuals with Fetal Alcohol Spectrum Disorders

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Introduction

Since the identification of fetal alcohol syndrome (FAS) over 35 years ago, mounting evidence about the impact of maternal alcohol consumption during pregnancy has prompted increased attention to the link between prenatal alcohol exposure (PAE) and a constellation of developmental disabilities that are characterized by physical, cognitive and behavioural impairments.[1] These disabilities include a continuum of developmental disorders known as fetal alcohol spectrum disorders (FASD). The entire continuum of effects is estimated to represent at least 1% of all live births in the United States,[2] suggesting that FASD represents a significant public health concern. Longitudinal studies suggest that individuals with FASD are at a greatly increased risk for adverse long-term outcomes, including mental health problems and poor social adjustment.[3]

Subject

A substantial body of research has documented significant neurocognitive difficulties among individuals with FASD.[4,5,6,7,8,9] Given the neurocognitive problems associated with PAE, it is not surprising that psychosocial dysfunction has been consistently noted in the literature.[3] Furthermore, reports suggest that individuals with PAE are overrepresented in psychiatric samples[10] and in juvenile detention and correctional settings.[11,12] This review summarizes much of the existing literature on mental health outcomes of individuals with PAE across the lifespan, including findings in infancy and early childhood, middle childhood, and adolescence and early adulthood.

Problem

Reviews of studies examining the relationship between parental alcohol use and various indices of children's emotional adjustment have noted that some of these linkages may be attributable to

PAE and yet these linkages remain relatively unexplored in the literature. Furthermore, despite the evidence of a significant association between alcohol exposure in utero and psychiatric risk, experience suggests that exposure, and even FAS, is infrequently identified by mental health practitioners.[13] Failure to recognize the broad and unique needs of individuals with FASD and their families can lead to multiple treatment failures, consequent worsening of symptoms, and high personal and societal costs.

Research Context

There are a number of methodological problems with much of the available research on the etiological role of PAE on socioemotional outcomes[14] Key methodological concerns include biased sample representations, the reliance on self-report measures, and a failure to adequately consider other factors that might play a significant role in explaining a reported relation between alcohol consumption in pregnancy and later mental health.[15,3] These variables include (but are not limited to) the use of other substances and smoking during pregnancy, maternal nutrition, socioeconomic status, the individual's genetic loading for mental health problems, problems in parenting, and early deprivation or abuse. In spite of these potential limitations, well-designed studies do exist that shed light on the mental health outcomes of individuals with FASD.

Key Research Questions

What are the mental health outcomes of individuals with PAE across the lifespan?

Recent Research Results

Infancy and early childhood. Some studies examining the relationship between parental alcohol use and various indices of young children's emotional adjustment have noted that some of these linkages may be attributable to PAE and yet these linkages remain relatively unexplored. This is surprising considering that there is a substantial body of literature on the association between maternal alcohol consumption during pregnancy and poor neurobehavioural outcomes in their offspring. At birth, there are signs of central nervous system dysfunction in infants born to mothers who report consuming alcohol during pregnancy. These include reports of jitteriness, irritability, autonomic instability, slow habituation, low levels of arousal, increased levels of activity and disturbances in sleep patterns.[7] Behavioural difficulties continue into early childhood with deficits in sustained attention, heightened emotional reactivity, increased activity levels, and irritability.[16] The significance of these early neurobehavioural effects is apparent in the

impact they may have on early mother-child transactions. Thus, the effects of alterations in child behaviour on the mother-child relationship may be one of the most significant results of PAE.

A few studies have incorporated a transactional model to explain the relation between PAE and socioemotional functioning in infancy and early childhood.[17,18,19,20,21,22] For example, one study of middle-class women and their infants found that mothers who drank more heavily during pregnancy had infants who displayed higher levels of negative affect in mother-child transactions, as compared to infants with less prenatal exposure.[21] The mothers of these more negative infants interacted in ways that were less responsive and developmentally stimulating, and their infants displayed higher levels of insecure attachment behaviours. In a follow-up study through the end of early childhood, results indicated that young children exposed to more alcohol during gestation had higher self-reported depression scores.[19] Moreover, early irritability in the more heavily exposed infants at one year of age predicted higher levels of depression at six years of age.[18] These findings emerged even though the mothers in this sample had not been identified as high-risk drinkers, were not currently drinking, and the children in the sample were functioning within the high average range of intelligence.

Expanding this line of inquiry to children with greater levels of cumulative risk, investigators found that in a group of children living in poverty, there was an even greater association between PAE and attachment insecurity.[22] Strikingly, 80% of children in the moderate-heavy alcohol exposed group displayed attachment styles classified as insecure. The rate of insecure attachments found among the more heavily prenatally alcohol-exposed youngsters in the sample was significantly higher than rates reported in other samples of children of similar ages, socioeconomic status and ethnic backgrounds.[23,24]

Further analyses provided insight beyond documentation of the direct relationship between PAE and quality of attachment. Congruent with findings in the middle-class sample, prenatal exposure in the poverty sample also related to temperamental differences in the child, and these temperamental differences affected the mother's ability to relate to her child on an emotional level. Thus, PAE appeared to predispose the child toward exhibiting more negative affect in the mother's presence. Display of negative affect was related to the mother's inability to provide a "supportive presence" while interacting with her child, which was associated with higher levels of attachment insecurity and depressive symptoms during the preschool years.[20]

Although most studies showing an association between maternal alcohol misuse and psychiatric symptoms in children have generally been interpreted as reflecting the impact of the postnatal environment, and especially the effects of living with an alcoholic mother, these transactional studies show that PAE can also act as a significant risk factor in the emergence of early onset psychopathology. This risk is conveyed through the mother's response to the primary neurological and temperamental deficits resulting from the child's exposure to alcohol in utero.

Middle childhood. A few studies are notable for examining psychopathology in children with FASDs in middle childhood. In one clinic-referred sample of alcohol-exposed children between the ages of 5 and 13 years, 87% met criteria for a psychiatric disorder.[25] Another recent study examining the psychiatric conditions of a clinically-referred sample of children with heavy PAE and unexposed control children using structured clinical interviews of their parents, revealed that 97% of the alcohol-exposed children met criteria for at least one Axis I diagnosis on the DSM-IV compared to 40% of the unexposed children.[26,27] The association between PAE and psychiatric diagnoses was further explored in a relatively large non-clinic sample of children (n = 130) with or without PAE who also had social skills deficits using a well-validated standardized clinical interview.[27] After controlling for important covariates, results revealed statistically significant effects of PAE in predicting internalizing disorders of depression, separation anxiety disorder and generalized anxiety disorder and externalizing disorders, including attention deficit hyperactivity disorder, oppositional disorder and conduct disorder. Prenatal exposure to alcohol did not predict symptoms of schizophrenia but was predictive of symptoms of mania and hypomania. These results confirm that children with PAE exhibit significantly more symptoms of psychopathology, including mood, anxiety and disruptive disorders, when compared to children without exposure. Furthermore, child characteristics and environmental factors appear to add to the prediction of psychopathology. Specifically, having a lower IQ, poorer social skills, and living with a single/divorced or a non-biological caregiver was associated with greater risk.[27]

A final study emphasizes the potential dangers of even small levels of alcohol consumption during pregnancy on developmental outcomes. Sayel and associates[28] sampled the drinking patterns of 12,678 pregnant women during the first 18 weeks of gestation. They then measured the mental health outcomes of the children at four and eight years of age. After controlling for a range of prenatal and postnatal factors, the consumption of less than one drink per week during the first trimester was found to be associated with clinically significant mental health problems in girls at four and eight years of age.

Adolescents and young adults. Mental health problems are hallmark secondary disabilities in adolescents and young adults with FASD. In their seminal cross-sectional study of the developmental outcomes of adolescents and adults with PAE, Streissguth and associates found that 94% reported mental health problems.[29] Similarly, in the Seattle Longitudinal Prospective Study on Alcohol and Pregnancy, there were noted associations between greater PAE and elevated rates of behaviour problems and aspects of antisocial behaviour in 14-year-old adolescents.[30] A follow-up of this sample at age 25, using structured clinical interviews, revealed that the odds of the appearance of passive-aggressive and antisocial personality disorders was double in adults exposed to one or more binge episodes in utero compared to those who were exposed to low to moderate levels.[31]

In an investigation of 1,252, 17-year-old adolescents from the Minnesota Twin Family Study, both parents and adolescents completed structured diagnostic interviews to generate lifetime psychiatric diagnoses.[32] Mothers were also retrospectively interviewed about alcohol and nicotine use during pregnancy. Results were that PAE was associated with higher levels of conduct disorder symptoms in offspring, even after controlling for the effects of parental externalizing disorders (illicit substance use disorders, alcohol dependence and antisocial/behavioural disorders), prenatal nicotine exposure, monozygosity, gestational age, and birth weight.

Longitudinal research suggests that individuals with PAE also exhibit problems with the misuse of alcohol and other drugs as they mature. In addition to psychiatric symptoms, early work from the Seattle Longitudinal Prospective Study on Alcohol and Pregnancy revealed a relation between exposure and early experiences with alcohol among young adolescents[33] that developed into heavy drinking and alcohol-related problems in early adulthood.[34] In a similar prospective study, the association between maternal alcohol use during pregnancy and early drinking was examined in 4,363 adolescents taking part in the Mater University of Queensland Study of Pregnancy and its Outcomes conducted in Brisbane, Australia.[35] After controlling for other factors, adolescents whose mothers consumed three or more drinks per drinking occasion during pregnancy were at increased risk of drinking more alcohol in a binge pattern than those whose mothers consumed less alcohol. A follow-up study of this cohort at age 21 revealed a strong relationship between prenatal binge drinking and alcohol use disorders in the adult offspring.[36]

Research Gaps

While some research exists documenting the relation between PAE and later mental health outcomes, many questions remain. For example, what is the interaction between psychiatric disorders in this population and alcohol misuse or dependence? Are there indices of resiliency in individuals with PAE who do not appear to have psychiatric conditions? What are the most effective treatments for this population including psychosocial, family, and pharmacological interventions? Finally, there are gaps in the psychiatric literature on predictors of psychiatric risk that do not take into account the variance due to PAE and its potential significant effect on prediction and treatment outcomes.

Conclusions and Implications for Parents, Services, and Policy

Despite the evidence of a significant association between alcohol exposure in utero and psychiatric risk, experience suggests that exposure, and even FAS, is infrequently identified by mental health practitioners. This omission is unfortunate due to the observations of treatment resistance to medications and psychosocial therapies, as well as the frequent need for specialized educational services in this population.[37,38] Research on the psychiatric disabilities suffered by individuals with PAE throughout the lifespan highlights the need for training of mental health professionals in the identification of people with FASD and the provision of specific treatments to address the unique features of this developmental disability since early identification and treatment have been demonstrated to be protective against more serious psychiatric outcomes.[29] Failure to recognize the broad and unique needs of these individuals and their families can lead to multiple treatment failures, consequent worsening of symptoms, and high personal and societal costs.

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Children Prenatally Exposed to Alcohol: Comments on Astley, O'Brien and Mattson, and O'Connor

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Introduction

The three papers by Astley,[1] O'Brien and Mattson,[2] and O'Connor[3] reviewing the current knowledge base of Fetal Alcohol Spectrum Disorders (FASD) reveal the ongoing challenges that face researchers and clinicians, in particular the accurate diagnosis and meaningful differentiation of children who are prenatally-exposed to alcohol.

The diagnosis of Fetal Alcohol Syndrome (FAS) is based on three criteria: growth retardation, central nervous system (CNS) impairment, and characteristic facial dysmorphology.[4] However, as acknowledged in all of the papers,[1-3] most children with prenatal exposure to alcohol do not fully manifest these criteria but demonstrate a wide range of less specific physical changes and neurodevelopmental deficits. To address this issue, diagnostic terminology has been expanded to include a wide range of signs and symptoms that fall under FASD.[5] Although this terminology accomplishes what it was designed to do – encompass all children with prenatal alcohol exposure – its use has muddied the waters and led to even more confusion around the diagnosis of FAS. In addition, an inexact diagnostic approach complicates attempts to address the neurobehavioural profile and the clinical needs of children affected by prenatal alcohol exposure.

Research and Conclusions

Diagnostic classification within FASD

Over the years, the relationship between functional impairment and the physical manifestations of prenatal alcohol exposure has remained unclear. In 2001, Astley and Clarren[6] found that alcohol-exposed children with more severe facial phenotypes demonstrated more impaired levels of cognitive, neurodevelopmental and visual motor functioning. Most recently, magnetic resonance studies of children with fetal alcohol spectrum disorders demonstrated increased brain damage that correlated with more severe facial dysmorphology and more severe

neurodevelopmental dysfunction.[7,8] On the other hand, Mattson, et al.[9] found that the degree of the severity of neurodevelopmental deficits evident in children with prenatal alcohol exposure is independent of the physical features associated with FAS. Further investigation of the connection between physical and imaging findings and the severity of dysfunction is necessary; however, accurate results depend upon a clear and consistent diagnostic schema across the fetal alcohol spectrum.

A recent study compared neurodevelopmental functioning among children with fetal alcohol syndrome (FAS), pFAS (partial fetal alcohol syndrome) and alcohol-related neurodevelopmental disorder (ARND).[10] Clinical criteria for placement in each of the diagnostic groups included confirmed prenatal exposure to alcohol, documentation of all three criteria for facial dysmorphology, and past or current growth impairment (height or weight) below the third percentile. In addition, in order to meet criteria for abnormal central nervous system functioning, children had to have a head circumference below the third percentile, evidence of global cognitive functioning below the third percentile, and/or three domains of neurodevelopmental functioning greater than two standard deviations below the normed mean, to ensure that children were not misclassified. It should be noted that this paper relied on third percentile rather than tenth percentile cut-off for definition of growth impairment and *microcephaly*, as opposed to the recommendations from the Centers for Disease Control and Prevention (CDC)[11] and the Institute of Medicine (IOM)[12] which rely on the tenth percentile as the defining cutoff.

The children who met tightly-defined physical criteria for a diagnosis of FAS were significantly different neurodevelopmentally from alcohol-exposed children who did not meet all criteria, while children with pFAS and ARND were similar in all neurodevelopmental domains that were tested. Children with FAS exhibited the most impaired level of general intelligence, significantly-worse language-based memory, and significantly-poorer functional communication skills. All three groups of alcohol-affected children demonstrated executive functioning deficits, but the FAS group of children performed significantly worse on sequencing and shift tasks than either the pFAS or ARND groups. Similar to previous studies of behaviour in children with FASD,[8-10,13-15] there was a high rate of diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) in each of the three groups: 60% of children with FAS, 88.9% of children with pFAS, and 76.9% of children with ARND met *DSM-IV* criteria for a diagnosis of ADHD.

In her paper, Dr. Astley[1] makes a strong case for clear and precise measurement and classification of children with prenatal alcohol exposure. However, although the 4-digit code[16] is well suited for use in specialty clinics and research programs, the reality is that most practitioners find it cumbersome when using it in the field. O'Brien and Mattson's paper[2] is a case in point. The authors use the term "FASD" to review the literature on neurobehavioural profiles, since most studies do not differentiate what specific diagnostic groups within the fetal alcohol spectrum the various studies are examining.

Secondary disabilities

Streissguth and her colleagues[17,18] defined the primary disabilities of FAS as those directly related to intrauterine alcohol toxicity. The notion of secondary disabilities was used to "encompass the measurable difficulties that people with FAS/FAE (fetal alcohol effects) face as they mature…."[13] In a four-year study of secondary disabilities, the researchers found that over 90% of the subjects had mental health problems.[18]

However, opinions regarding the etiology of mental health disorders in alcohol-exposed children vary widely. O'Connor et al[19,20] suggested that the high proportion of children with mood disorders was due to the damage sustained by the *basal ganglia* and *cerebellum*. On the other hand, O'Connor et al.[21,22] also posited that in addition to a genetic predisposition for depression and difficult temperaments that are a result of their prenatal exposure to alcohol, the development of optimal relationships between mother and child are impeded by the mothers' alcohol use and mood disorder. The role of out-of-home placement in increasing alcohol-exposed children's risk for mental health disorders[23] raises another confounding factor, since most research has documented an increased prevalence of psychopathology among children in the foster care system.[24-26]

A new study by our group[27] examines the prevalence of mental health disorders among children with FAS and ARND in out-of-home placement as compared to a similar group of children who had no prenatal exposure to alcohol. Not surprisingly, the rates of mental health disorders in both groups of children were markedly higher than rates found in the general population of children in the United States. The prevalence of mental health disorders among children in the alcohol-exposed cohort were similar to those rates found in previous studies of alcohol-exposed children.[18-23] ADHD was the most common mental health disorder, occurring in almost 75% of the alcohol-exposed group, significantly higher than the 58% rate found among the non-exposed

group. The study found only 19% of the alcohol-exposed children met criteria for a mood disorder, a rate similar to that of Fryer et al. (18%),[23] while the rate of mood disorders was significantly higher among the non-exposed children in our sample (37.5%).

In examining the relative contributions of factors related to prenatal alcohol exposure as opposed to child welfare factors related to being in out-of-home placement, logistic regressions revealed that children with a history of physical or sexual abuse, regardless of prenatal alcohol exposure history, had the highest rates of anxiety disorders, and environmental factors, such as number of placements and length of time in the current placement, were more predictive of mood disorder than the biological toxicity of alcohol exposure. Much further research is needed in this arena, especially work that includes appropriate comparison groups that can help differentiate biological and environmental factors that explain mental health disorders in children with prenatal alcohol exposure.

Policy Recommendations and Implications

There is a great deal of ongoing discussion and controversy regarding the diagnostic criteria for FAS, pFAS, ARND and other components across the fetal alcohol spectrum. The IOM[12] guidelines, as clarified by Hoyme,[28] utilize a cutoff for abnormal growth as the tenth percentile, require only two of three facial abnormalities, and are nonspecific as to central nervous system functioning. Current recommendations regarding facial criteria from the CDC[11] are more stringent than those of the IOM but set the threshold for abnormal CNS functioning only at greater than 1 standard deviation below the mean in three domains. In addition, thresholds for growth impairment (weight, height, head circumference) are set by the CDC at only the tenth percentile.

Based on current knowledge, I would recommend that the term pFAS be eliminated and alcohol-exposed children be diagnosed as having FAS or ARND. Confirmation of prenatal alcohol exposure should be required in all cases. Growth retardation should be defined as current or past weight and/or height less than the third percentile, rather than the tenth percentile. A finding of facial dysmorphology should require abnormal measurements of the upper lip (rank 4 or 5) and the *philtrum* (rank 4 or 5) and shortened *palpebral fissures* greater than two standard deviations below the mean.[6,29] This is consistent with the CDC's[11] and Astley's[6-8,30] recommendations, but more stringent than the guidelines issued by the IOM.[12] To qualify as having evidence of central nervous system abnormalities, the child's current head circumference

should be below the third percentile for age and gender rather than the tenth percentile as currently recommended, and/or the child should demonstrate functional deficits of global cognitive delays with performance below the third percentile on standardized testing or three or more domains of neurodevelopmental functioning more than two standard deviations below the normed mean on standardized measures of cognitive, executive, memory, adaptive, motor, attentional, social skills, or sensory functioning.

Children with documented prenatal alcohol exposure who meet all physical criteria for growth impairment and facial dysmorphology as well as neurodevelopmental deficits would be assigned a diagnosis of FAS. Children with documented prenatal alcohol exposure who do not meet all growth and/or facial criteria but who meet criteria for neurodevelopmental deficits would be classified as ARND. Utilizing two diagnoses – FAS and ARND – with strict criteria delineated for all to follow would create a common language and diagnostic schema that would be suitable in the clinical setting while establishing a consistency with ongoing research. This would be invaluable in further work to determine the neurobehavioural profile for the two groups.

Given the lack of clear evidence regarding the relationship between prenatal alcohol exposure and mental health problems, I would suggest we use more precise terminology and speak of mental health disorders that co-occur in children with FAS and ARND. Labeling mental health disabilities as “secondary” implies a more direct cause and effect association than can be documented through current research. Rather, the correlation is more likely the result of environmental factors that act on the biologically vulnerable brain of the child with FASD. From a policy perspective, eliminating the use of the term “secondary disabilities” would stress the importance of early identification and intervention for alcohol-exposed children at risk for abuse and neglect and the need to support and enhance the stability of the children’s placements whether they be in the biologic home or in out of home placement. This, in turn, would perhaps decrease the rates of mental health disorders in this population of high-risk children.

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Fetal Alcohol Syndrome Disorders: Comments on Astley, O'Brien and Mattson, and O'Connor

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Introduction

Jones and Smith[1] coined the term fetal alcohol syndrome (FAS) to label a pattern of altered growth and morphogenesis observed in a group of children born to alcoholic mothers. This pattern of dysmorphia included a cluster of facial anomalies (e.g., short *palpebral fissures*), growth retardation, and evidence of central nervous system (CNS) involvement (e.g., *microcephaly* and developmental delays). In the years following the publication of the Jones et al. paper, it became evident that the expression of this syndrome varied considerably as a function of differences in exposure (e.g., quantity, frequency, timing) and genetic factors. Since clinicians were reluctant to diagnose those individuals with partial expression of the syndrome, Clarren and Smith[2] introduced the term "suspected fetal alcohol effects (FAE)" to refer to such individuals. Although this term was meant to serve as a "bookmark" to facilitate further studies, service providers and teachers began to misuse it as a diagnostic term for labeling developmental issues in children with known or suspected histories of prenatal alcohol exposure. Since clinicians did not have a firm basis for linking developmental problems in these children to prenatal alcohol exposure, Aase et al.[3] recommended that the term FAE be abandoned. This presented the clinician with a challenging problem: Given that the majority of children with prenatal alcohol exposure do not exhibit clinically discernable dysmorphia, what labels should be used to denote their neurocognitive difficulties? The Institute of Medicine (IOM) report[4] sought to address the issues related to diagnosis by replacing the term FAE with two new diagnostic categories: alcohol related birth defects and alcohol related neurodevelopmental disorders. The replacement of the old term with two new ones did not, however, solve the primary diagnostic issue of linking prenatal alcohol exposure to cognitive-behavioural problems in a child. Astley and Clarren[5,6] developed the 4-Digit Code diagnostic system to tackle this issue.

Another approach to identifying alcohol-affected children without dysmorphia has involved a search for a syndrome-specific neurocognitive profile. It is now known that prenatal exposure to

alcohol produces a wide range of morphological and functional outcomes in the offspring, which are collectively called fetal alcohol spectrum disorders (FASDs). While alcohol-induced dysmorphia have been observed only in a minority of alcohol-exposed children,[7] cognitive behavioural problems have been found to be pervasive across the spectrum. However, the delineation of neurocognitive profile in alcohol-affected children has proven to be methodologically challenging because a wide range of factors interactively contribute to cognitive behavioural functioning. Therefore, the cognitive-behavioural phenotype in FASDs has been dubbed a moving target.[8] The focus of the paper by O'Brien and Mattson is to assess the progress that has been made in identifying a syndrome specific neurocognitive profile in children with FASDs.

An important question related to the functional outcomes of prenatal alcohol exposure concerns whether different levels of cognitive-behavioural problems in individuals with FASDs can be delineated. Streissguth et al.[9] reported a range of adverse life outcomes in adolescents and adults with FASDs, including mental health problems, disrupted school experience, trouble with the law, confinement, inappropriate sexual behaviour, alcohol/drug problems, dependent living and problem with employment. These adverse outcomes were labeled secondary disabilities since primary disabilities directly resulting from alcohol-induced brain damage, such as diminished IQ and memory problems, were considered to underlie them. Given that social-emotional problems cut across most of these secondary disabilities (e.g., trouble with the law, inappropriate sexual behaviour, problem with employment), some researchers have sought to understand the mechanisms underlying socio-emotional functioning of alcohol-affected individuals. O'Connor presents an overview of the findings from this line of research.

Research and Conclusions

The 4-Digit Code system[5,10] offers a non-medical, pragmatic approach to diagnosing the full spectrum children with FASDs. In this system, a diagnostic category is formed by combining the ratings of four variables relevant for diagnosing FASDs: growth, facial phenotype, CNS abnormalities, and prenatal alcohol exposure. Because this diagnostic system does not make biological assumptions, each variable is treated independent of others. Therefore, the question of whether CNS damage observed in a child resulted from prenatal alcohol exposure does not arise.

The 4-Digit method has made two important contributions to diagnosing fetal alcohol spectrum disorders. First, it has considerably improved the reliability of diagnosis through the

development of tools to measure facial features, standardization of measurements, and manualization of the diagnostic procedures. Second, since the 4-Digit Code System employs a standardized procedure of classification, it can be used by a clinical team without specialized training in dysmorphology. This has allowed identification of children with prenatal alcohol exposure in clinics where dysmorphology services are not available.

Despite these merits, the 4-Digit Code system has some shortcomings, which, in my view, result from using a non-biological approach to classifying and understanding a biological phenomenon. From a statistical point of view, improved reliability of measurements does not ensure greater validity. Classification of a diagnostic feature using conventions such as “two standard deviations below the mean” will result in arbitrary groups which may not correspond to real divisions (taxa) in the phenotype. As Meehl[11] reminds us, classification is an “enterprise that aims to carve nature at its joints (plato), identifying categories of entities that are in some sense (not metaphysical essentialist) non-arbitrary, not man-made” (pp 268).

O’Brien and Mattson summarize the key findings from the studies of neurocognitive functioning of children with FASDs and suggest that this clinical group exhibits a specific profile in comparison to IQ-matched controls and those with ADHD. For example, group comparisons between FASD and ADHD revealed that both groups showed impaired performance on a sorting task, but only the FASD group displayed deficits in letter fluency and letter-number switching. Compared to IQ-matched controls, the FASD group had more externalizing problems, impaired adaptive skills, and verbal learning difficulties. While these findings are interesting, a question can be raised about their generalizability. Particularly, parent-rated behaviours such as externalizing problems and adaptive skills are substantially influenced by socio-cultural experiences and the quality of parenting. A wide range of variables including language, cultural experiences, and genetic/epigenetic factors, are also known to moderate performances of complex tasks.[12] As the authors point out, contributions from different variables to the aforementioned group differences should be addressed in future research.

O’Connor underscores the importance of considering the interactive effects of multiple variables on socio-emotional functioning in individuals with FASDs. Particularly, psychiatric difficulties in this population develop within the matrix of a multitude of factors including maternal nutrition, socio-economic status, genetic loading for psychiatric illness, problems in parenting, and adverse life experiences. Therefore, O’Connor and others[13,14] have used a transactional model in the study of emotional difficulties in children with prenatal alcohol exposure. Research conducted within

the transactional model has demonstrated that neurobehavioural effects of prenatal alcohol exposure in infants such as jitteriness and irritability have a negative impact on early mother-child interactions, which, in turn, lead to long-term adverse emotional outcomes in the child. Consistent with these findings, research in social neuroscience has revealed that the quality of mother-child interactions influence the child's stress responses, which is mediated through the *hypothalamus-pituitary-adrenal (HPA) axis*.[15]

Implications for Services and Policy

I agree that the 4-Digit Code system has had a significant impact on diagnosis of fetal alcohol spectrum disorders, particularly in the U.S. and Canada. The Canadian Diagnostic guidelines[16] have incorporated the 4-Digit Code and the diagnostic categories proposed by the IOM report. The Canadian investigators found the 4-Digit method appealing mainly because its use of quantitative, objective measurement scales and specific case definitions. According to Astley et al.[17] parents and service providers have expressed satisfaction with the diagnostic reports which provide the information necessary for qualifying children for services.

Despite these advances, I believe that diagnosis of the full spectrum of fetal alcohol effects can be improved by incorporating the findings from cognitive and behavioural neurosciences. Meehl[11] compellingly argued that a solution to the question, "how shall we classify?" should be sought through applied mathematics. Taxometric analyses of morphological, neuroanatomical, cognitive and behavioural measures from children with FASDs may reveal whether the underlying (latent) patterns of data reflect non-arbitrary categories or dimensional distributions. Identification of natural categories or dimensions will lead to the development of appropriate interventions.

As O'Brien and Mattson point out, the identification of syndrome-specific profiles would allow diagnosing alcohol-exposed children without discernable dysmorphia. The delineation of a neurocognitive profile will also inform the development appropriate therapies. We have recently proposed that children with FASDs have a deficit in the integration of multiple elements or relations in working memory due to slow processing of information.[18] This proposal has specific implications for the development of interventions for alcohol exposed children. O'Connor has presented evidence that psychiatric problems are highly prevalent among individuals with prenatal alcohol exposure.[19] This finding highlights the importance of early screening for socio-emotional problems in this population. The finding that positive mother-child interactions and the stability of home environment support emotional development in children has implications for

the development of policies pertaining to placement of alcohol-affected children in foster care and parent training.

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Early Intervention for Children with Fetal Alcohol Spectrum Disorders

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Introduction

First identified in the United States nearly 50 years ago,[1,2] Fetal Alcohol Syndrome (FAS) is a major birth defect resulting from prenatal alcohol exposure (PAE) and is characterized by a distinct pattern of facial abnormalities, stunted growth, and central nervous system dysfunction. The term fetal alcohol spectrum disorders (FASD;[3] is an umbrella term used to reflect the full range of effects associated with PAE, and in addition to FAS, includes partial FAS, alcohol related neurodevelopmental disorder (ARND), and alcohol related birth defects (ARBD).[4] FASD places a significant burden on both affected families and society. FASD is estimated to affect 3.1 to 9.9% of first grade children in the United States.[5] The annual cost estimate for all individuals with FASD in the U.S. ranges from $1.29 to $10.1 billion.[6,7]

Subject

This paper reviews recent progress in the development of early interventions for young children with FASD, current challenges in providing services for young children in this high-risk population, and potential directions for future research.

Problems

The deleterious effects of PAE are evident as early as infancy for both animals[8] and humans[9]. In infants and toddlers PAE has been associated with global developmental impairment, including deficits in cognition, motor skills, language skills, emotion and relational skills, information processing, and memory.[9] Studies have also identified that PAE is related to infant and toddler sleep abnormalities, sensory system challenges[10–12], as well as alterations in pain regulation[13], reactivity to stress[14], and higher rates of insecure attachment[15].

PAE has lifelong implications for child functioning and adaptation. Significant behavioural, cognitive and emotional difficulties have been reported among individuals with FASD throughout the life span, including intellectual and learning disabilities, executive dysfunction, memory problems, speech and language delays, and internalizing and externalizing behaviour problems.[16] Children with PAE are also at increased risk for many secondary disabilities, including comorbid psychiatric conditions, school failure, alcohol and substance abuse problems, and delinquency.[17–20] These challenges can then affect the whole family system. Parents of children with FASD report increased parental stress, decreasing family functioning, and decreasing parental attention to unaffected siblings.[21] However, it is important to note that children affected by PAE have very heterogeneous profiles of functioning within and across children. Most notably, many providers and parents can be misled when children affected by PAE have an average IQ range but perform poorly in many other domains of life.[22] It is essential that assessment be comprehensive in order to fully understand both areas of weakness and strengths. This allows providers to appropriately identify intervention targets and bolster children's strengths to promote lifelong resilience.

Despite the early onset of cross-domain challenges, many children may not be referred for screening until relatively late (if ever), thus missing out on the potential benefit of early intervention.[23] FASD appears to be under-recognized and under-treated, particularly in certain high-risk contexts, including both in- and out-patient psychiatric populations, the child welfare system, and juvenile detention and correctional facilities.[20,24–27] The importance of early identification is highlighted by findings that an early diagnosis is one of the strongest predictors of more positive outcomes for these individuals.[28] Further, early identification and treatment may better serve the entire family system, and mitigate downstream effects of PAE on parent stress, sibling relationships, and whole family functioning.[21]

Research Context

In the last two decades, some progress has been made in the development of treatments for individuals with FASD, but those focusing on young children have been more limited. Early intervention studies present significant methodological challenges with this population. First, recruitment of study participants can be challenging when many children with FASD are not identified until school-age.[24] Additionally, many children impacted by PAE are involved in the child welfare system and thus may be even less likely to referred for and receive a diagnosis when indicated. Moreover, for those children in the child welfare system who have been

accurately diagnosed, obtaining proper consent to enroll them in early intervention programs can be difficult. Additionally, selecting an appropriate control group can also be challenging.[27,29] Given the abundance of developmental challenges for this population, utilizing no-treatment control groups raises ethical issues, whereas utilizing standard of care control groups may work against finding any significant effects for programs in their early stages of development.

Key Research Questions

Several key lines of inquiry are currently being addressed in research on early intervention for FASD. Such questions include:

1. How can animal models inform our development of interventions for young children with PAE?
2. To what extent can early intervention programs address some of the primary developmental challenges seen in infants and young children affected by PAE?
3. What developmental domains are appropriate targets of intervention?

Recent Research Results

1. Animal Studies

Several lines of animal research suggest the promise of various prenatal and neonatal interventions. For example, in mice lithium has demonstrated some protection against ethanol-induced excessive cell death during development, and have lasting positive effects on cognitive functioning into adulthood.[30–32] The benefits of prenatal and postnatal treatment with neuroprotective peptides in mitigating the effects of PAE on brain development have also been reported in studies of mice.[33–37] Additionally, studies with perinatal rodent models of FASD have also used antioxidant supplements at the same time they consumed alcohol and saw reductions in offspring oxidative stress and cell loss. Other rodent studies have used prenatal nutrients such as choline, docosahexaenoic acid, betaine, folic acid, methionine, resveratrol, and zinc and found promising results in their attenuation of the epigenomic effects of alcohol.[38] Animal models of post-natal supplementation of nutrients such as Vitamin C, Vitamin E, resveratrol, curcumin, melatonin, alpha-lipoic acid, selenium, omega-3, Choline, and EGCG have also demonstrated varying positive effects on cellular and neural development.[38]

Research on behavioural and environmental interventions with rat and mice models have demonstrated positive results. Research has supported the positive effects of neonatal handling, postnatal environment enrichment, and rehabilitative training on rats and mice with perinatal alcohol exposure.[39] For example, enriched environments in adolescent rats with PAE lead to decreased emotionality, increased attention, and fewer cognitive impairments in adulthood.40 Further, exercise has been found to improve learning and memory among alcohol-exposed rats[41], whereas introducing complex motor training during the postnatal period effectively remediated the motor deficits of alcohol-exposed rats[42].

2. Intervention for Mothers with Substance Abuse Challenges

One method studied in humans to mitigate the effects of PAE is to employ preventative intervention services for mothers with histories of substance abuse problems or who endorse alcohol use during physician screening. One program that attempts to prevent future alcohol exposed births is Parent Child Assistance Program (PCAP). PCAP is a comprehensive case management and recovery support program for women at risk for giving birth to a child with FASD. The intervention decreased alcohol and drug use among parents, increased the use of contraception, and increased medical and mental health care services.[43,44] However, there were no specific improvements in outcomes for children with FASD as a result of this intervention.[45] A similar program is New Choices, which provided addiction counseling, parent education and counseling, peer support and enrichment programs for children. A preliminary evaluation found that mothers demonstrated improvements in depressive symptoms and empathy for their children, and children exhibited improvements in social development.[46,47]

Several other wraparound service programs have been implemented in Canada and shown effectiveness in preventing PAE births.[48,49] Further, participation in programs such as Women-Infants-Child (WIC) program in the USA can increase use of prenatal care among women at risk for consuming alcohol when pregnant.[50] One intervention provided brief intervention services where parents were given nutritional counseling. Compared to an assessment only condition, parents who participated in the brief intervention were five times more likely to report abstinence, and their newborns had higher birth weight and decreased mortality.[51]

In general, population based screening and preventative strategies must be designed to reach populations at heightened risk for alcohol exposed pregnancies. This includes people with histories of substance use challenges, depression, anxiety, or histories of trauma including child

welfare or legal involvement.[52–54] Most importantly, screening and intervention programs need to be non-judgemental and specifically target reducing stigma and bias around substance use challenges.[55] Generally, programs aimed at preventing PAE or targeting mothers who did consume alcohol during previous pregnancies are effective at improving mother mental health and decreasing the likelihood of another PAE birth. However, findings suggest limited effects of this type of intervention on outcomes for children with FASD, particularly if direct early intervention is not provided to the child.

3. Cognitive and Educational Interventions

Some studies of cognitive and educational interventions for FASD have also included young children in their samples. Children aged 3 to 10 years with FASD who participated in a socio-cognitive habilitation program in mathematics in addition to receiving educational support, called Math Interactive Learning Experience (MILE). Children in the intervention showed greater gains in math skills compared to those who received educational support only[56], and these gains were maintained six months later.[57] Children also demonstrated overall improvements in achievement and in parent reported behavioural challenges.[58,59] Another intervention using applied behaviour analysis to increase verbal skills found improvements in functional communication and in emotional and behavioural functioning as well.[60] Finally, children aged 4 to 11 years with FASD participated in an intervention to promote the use of rehearsal strategies. Children in the experimental condition demonstrated significant improvement on a measure of working memory, whereas the control group showed no such improvement.[61]

4. Adaptive Social Skills

Individuals with FASD show deficits across multiple domains of adaptive functioning, including social skills and personal and community skills.[16] To address the lack of safety awareness often seen in children with FASD, a computer-based intervention was designed to increase fire and street safety skills in children aged 4 to 10 years old with FASD. Children receiving the intervention demonstrated significantly greater gains in safety-related knowledge and appropriate behavioural responses in comparison to the control group.[62] Targeting impairments in social functioning, an evidence-based, manualized, parent-assisted social skills intervention, Children’s Friendship Training (CFT),[63] was adapted for use with 6- to 12-year-old children with FASD. The intervention aimed to build social skills in a community mental health setting. CFT

targeted social network formation, how to talk with peers about activities, how to join play, as well as conflict avoidance and negotiation. Children in the intervention group experienced reductions in behavioural challenges, fewer hostile attributions and increased social skills.[26,64,65] Another intervention, Families on Track, also targeted children's social skills by combining parent behavioural consultation with weekly child skill groups for 4 to 8-year-olds. Families who participated had improvement in child emotion regulation, self-esteem, and anxiety, as well as decreases in disruptive behaviours. Additionally, parents showed increased FASD knowledge, better advocacy, increased social support, self-care, and parenting efficacy.[66]

5. Self-Regulation Skills

To address challenges with self-regulation skills, three studies evaluated the effectiveness of ALERT,[67] a program specifically adapted for children with FASD and designed to improve executive functioning. This intervention involves training teachers to provide one-hour manualized ALERT session across eight weeks. Children (six to twelve years old) showed improvements in executive functioning[68–71], selective attention, disruptive behaviours, math skills, and reading skills[70,72]. Another program, GoFAR, is a manualized computer intervention given to caregivers and children five to ten years old. GoFAR teaches metacognitive strategies to assist with problem solving around behavioural control, attention and adaptive functioning. Children who participated in GoFAR demonstrated improvements in self-regulation, attention, and adaptive living skills.[73,74] The SEEDS Family School Readiness Program was designed to promote self-regulation skills in young children with PAE and who have had involvement with the child welfare system. Children aged three to six years old who participated in the program showed greater improvements in self-regulation and early literacy skills compared to children in a waitlist control group. Additionally, compared to the control group, parents in the intervention group reported decreases in parent-child stress.[75]

Another approach is to target parent knowledge of the effects of PAE. While many parenting-focused and psychoeducation interventions are not exclusively focused on very young children with FASD, some interventions have included younger children in their samples. One study provided psychoeducation to parents about FASD and found improvements in knowledge, advocacy for care, parent behavioural regulation, and noted behavioural functioning improvement amongst children.[76] A recent app-based innovation of this program, Families Moving Forward Connect, was developed to provide care-giver self-delivery of psychoeducation and connection with other families who have children experiencing FASD.[77]

Another promising approach, has been to implement parent behavioural interventions that provide parents with skills to co-regulate with children, manage children's behavioural dysregulation, and ultimately assist their children in developing key self-regulation skills. Families Moving Forward (FMF), provides supportive behavioural consultation to promote parental self-efficacy and reduce child behaviour problems in families raising children aged 4 to 11 years with FASD. Caregivers in the FMF group reported greater improvements in parenting efficacy and greater reductions in child behaviour problems, compared to caregivers in the community standard of care group.[78] Another intervention, the Heart Start Model, used a relationship-based approach aimed at promoting children's healthy development, including their self-regulation skills, by enhancing early protective emotional relationships. Interventionists worked with parents starting when their children were 10 months old to form reciprocal relationships through the parent's own self-regulation processes and increased psychoeducation about infant development and cues. Children with heavy PAE and those with light/no exposure all improved in their social-emotional skills over the course of a year, with children with heavy exposure showing the greatest gains in skills.[79]

A number of existing early childhood evidence-based interventions have been adapted for children with PAE to support their social emotional development through attachment with caregivers. Interventions adapted from Parent Child Interaction Therapy (PCIT), Circle of Security, and Child Parent Psychotherapy (CPP), have shown efficacy in reducing caregiver stress, improving attachment and/or the parent-child relationships, and/or improving child self-regulation and behavioural challenges[80–82] among children and families impacted by FASD.

6. Nutritional Supplementation and Interventions

Recently, there has been increasing interest in the role of nutrition as a protective factor against the deleterious effects of PAE. Women who drink during pregnancy often have poor nutritional intake and demonstrating low levels of key vitamins and minerals.[83,84] Poor perinatal nutrition may play a part in magnifying the effects of PAE on child development. Prenatal supplementation of multivitamins/minerals including vitamin A, C, E, B1, folate, choline, iron, selenium, zinc, and DHA for women consuming alcohol has demonstrated better cognitive development, and improved infant growth among children with PAE.[25,58,85–87] Postnatally, a study of choline supplementation during early childhood found a dose-dependent improvement in memory.[88] At a four year follow up, the choline supplementation group had higher non-verbal intelligence, visual spatial skills, working memory, and verbal memory.[89] However, a study with 5-10-year-olds found

no effect of choline on cognitive performance[90], suggesting that there may be a sensitive period effect, where choline may only have effects when administered in specific developmental periods. Despite this promising emerging evidence, it is important to note that the majority of this work is in the preclinical phase and more work needs to be done in this area.

7. Pharmacological Interventions

Young children are increasingly likely to receive pharmacological interventions to address behaviour problems,[91] and children with FASD are likely to receive such interventions given their increased risk for behaviour problems. Community and clinic-based surveys, as well as large commercial claims databases indicate that about 57% of children with FASD received psychotropic medication, and stimulants were the most commonly used in children with FASD.[92,93] However, evidence to support stimulant medication for FASD is conflicting. For example, one RCT[94] found that there was no difference in attention or impulsivity but did show improvements in hyperactivity. Another RCT[95], showed no effects, with several adverse side effects. Preclinical data also suggest conflicting results of stimulant effectiveness[96]. Neuroleptics, most often Risperidone, is another commonly used medication to address behavioural challenges in children. In a study examining the efficacy of a social skills intervention, some children were assigned to also receive a neuroleptic. Those receiving neuroleptics exhibited greater improvements on all measures following completion of the intervention compared to children who were not receiving neuroleptics.[97] Another study looking at a combined Risperidone and stimulant found a decrease in aggressive behaviours and impulsivity in eight of the ten cases observed.[98]

Despite the common use of medication in this population, research on the efficacy of these medications for children with FASD has been limited by small pre-clinical studies or has entailed retrospective chart reviews rather than large-scale, double-blind, randomized controlled trials. Medication results often yield inconsistent and mixed results, with a higher likelihood of atypical responses to medication.[96,99] New work, given the complex heterogenous presentation of the effects of FASD, is exploring the use of algorithms and machine learning based on past chart reviews, to identify ideal medication prescription.[100] Until more systematic studies are done examining both the benefits and potential adverse effects of pharmacological regimens with this population, it is important to use caution in prescribing medications for children with FASD, particularly young children whose still-developing brains have already been impacted by PAE.

Emerging Areas of Research

Several lines of research are ripe for further investigation. The first is continued investigation on effective strategies to identify children affected by PAE and engage them with early intervention services. Improving diagnostic processes are one important step to enhancing access to services that may help mitigate the negative effects of PAE. For example, the term Neurobehavioural Disorder associated with PAE was proposed as a diagnosis in the Diagnostic Static Manual of Mental Disorders, 5th edition, to clarify the range of neurodevelopmental and mental health sequalae associated with PAE.[74] Diagnosing and treating children impacted by PAE implies the need for cross system collaboration and coordination of efforts to support families and young children affected by substance use challenges.

Further, there remains a need for long-term follow-up studies to examine whether early intervention programs are robust enough to reduce the emergence of secondary disabilities later in life. It may be also important for future studies to continue to investigate whether children with FASD do benefit from existing early intervention programs that support the parent-child relationship. Existing evidence suggest promising results for adapting these evidence-based interventions.[80–82] Further, using interventions like Attachment Biobehavioral Catch-Up[101] and Multidimensional Treatment Foster Care Program for Preschoolers[102] may better address the multifaceted environmental challenges many children with FASD in the foster care system also face. Early interventions involving the family system may also need to be adapted in different ways depending on the family context (i.e., birth families vs. adoptive/foster families). Further, there is a need to consider larger systems and understand cultural barriers to addressing FASD with current screening and intervention methods. For example, normative data for physical measurements often necessary to receive an FASD diagnosis are not available in many countries and/or subsets of races. There are also varying cultural attitudes towards drinking while pregnant or receiving mental health care that may decrease engagement in services. Researchers need to work with cultural liaisons and stakeholders to address these implementation and intervention development challenges.[66]

Additionally, there have been recent theoretical shifts in which researchers and practitioners are asked to move from a deficits-focused approach to a strength-based perspective that celebrates neural differences in functioning. Rather than focusing exclusively on areas of impairment, strength-based approaches aim to also identify and amplify skills and resources of children affected by PAE and their families in order to enhance their quality of life. Clinicians may identify

skill areas to target collaboratively with children and families, while encouraging self-advocacy, and continuing to grow areas of relative strength for children.[100,103] Although more work needs to be done in this area, one recent paper identified several strengths of individuals with FASD including, social motivation, persistence, positive mood, and several other person characteristics.[104]

Conclusions

PAE can significantly compromise young children's early development, particularly their capacity for self-regulation, which in turn may place them well on course for negative developmental trajectories. Deficits in self-regulation may confer further vulnerability by compromising early parent-child relationships (and potentially jeopardizing stable placements), impairing a child's ability to manage stressful situations, and interfering with their mastery of developmentally-appropriate tasks. Encouragingly, a growing number of studies have demonstrated that early intervention can at least partially remediate some of the primary deficits associated with PAE. In particular, over the last decade there has been growing support for family and child-based interventions focused on self-regulation in early childhood as mitigating self-regulation challenges and improving related outcomes.[73–75,80–82,85] Such approaches in early childhood are promising as they may also have the potential to mitigate some of the serious adverse outcomes often seen in individuals with FASD later in life. However, there is still a need to further expand services that target these skills. A recent study of families who received early childhood services noted that while many of their child's cognitive, motor, language, and sensory needs were being met, their self-regulatory and relational needs were not. Further, parents reported a need for assistance with basic survival needs such as respite care, and navigating many transitions in care.[105] Parents are essential agents of change and it is necessary to integrate them into interventions with young children. It is also essential to support the needs and functioning of parents so that they can effectively provide care and advocate for their children. There remains much work to be done in order to identify affected children as early as possible and to develop a comprehensive continuum of services for these children and their families.

Implications for Parents, Services and Policy

1. Continued efforts must be made to improve training of professionals who work with young children, such as pediatricians, pediatric nurses, child welfare workers, daycare providers, preschool teachers and early childhood mental health consultants. Such training should include a better understanding of the full range of effects that may be associated with PAE,

the importance of asking about and documenting a history of prenatal exposure to alcohol and illicit substances. This training can improve early diagnosis and increase the potential for early intervention to promote more positive outcomes for these children and their families.

2. Better collaboration across different systems of care (e.g., hospitals, child welfare, regional centers, Early Start and Head Start programs) is critical to identify, track, and coordinate services for children with FASD. Improved collaboration can help ensure that parents feel supported, and that these children do not slip through the cracks and are directed towards effective interventions.
3. It is critical that interventions for children with FASD start early and involves the entire family system. By bolstering the child's relationship and the family's social network we may be able to enhance the daily functioning and quality of life for these children.

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Supporting Parents of Children with Fetal Alcohol Spectrum Disorders, and Young Children with Significant Prenatal Alcohol Exposure

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Introduction

Fetal alcohol spectrum disorders (FASD) are lifelong, wide-ranging developmental disabilities caused by prenatal alcohol exposure (PAE). FASD is a global health problem[1] with high personal and societal costs.[2-3] Families across all ethnicities and socioeconomic levels are impacted. Some studies have estimated rates of the full range of conditions within FASD as high as 9 or 10 per 1,000 live births,[4-5] with greater prevalence in certain high-risk groups.[6-8] New prevalence data from systematic school screening further heightens concern.[9] Needs assessment data make clear that parents raising children with FASD require a range of support and family-focused services over the lifespan.[10]

Subject

Families bear the main responsibility for care of children with FASD. Young children at risk for FASD due to significant PAE often show developmental or behavioural difficulties.[11-12] Individuals with FASD typically show lasting learning problems, maladaptive behaviour, low adaptive function. They can show various "secondary disabilities," most commonly mental health problems, but sometimes also such lifestyle problems as disrupted school experiences, trouble with the law or employment difficulties.[3,13-14] Both groups often experience associated social problems and caregiving instability[3,12,15] that may increase risk of or help to explain negative outcomes.[16-18] Parents must often provide more intensive assistance to children with FASD than expected for age, in childhood[19] and into adulthood.[3] Whether in birth, adoptive, foster or kinship homes, caregivers raising children with FASD usually experience high caregiving stress and have many unmet family needs.[20-23] But a good quality caregiving environment, with a supportive parental presence and a stable, structured, consistent home,[24] is important to reduce risks of

secondary disabilities in FASD,[3] and improve outcomes for children born alcohol-exposed.[25] Early research and practical experience provide models for parent support and family-focused intervention.

Problems

Improved education, identification and service eligibility requirements needed. Community education about PAE and FASD remains incomplete, with misinformation still prevalent. Identification of affected individuals is still limited. Parents must often engage in advocacy just to receive help from multiple service systems.[10,12] Qualification for services is often based on criteria other than FASD, so services received may not be appropriate. There can also be social stigma about FASD, and societal resistance toward allocating resources to treat a preventable condition. All this means inadequate parent support.

A wide range of services needed. Support to birth parents must sometimes involve FASD prevention. FASD can be a "transgenerational" problem, as some affected individuals may have a child with FASD and need intensive parenting support.[26-27] FASD and PAE are often associated with psychosocial disruption, and these issues complicate or pose barriers to support and services. Services adapted to or specialized for FASD, or children at high risk because of PAE, are often needed but rarely available. Because FASD occurs so widely, services must be adjusted to work in different communities and cultures.

Intervention research needed. Although guidelines exist for a standard of care, evidence-based best practices for parent support and family-focused services for FASD have not been established. This is because there has been little descriptive or systematic intervention research, and only limited program evaluation of community intervention efforts so far.

Research Context

Systematic research attention to the characteristics, needs and strengths of families and individuals with FASD,[23] and to the development and testing of FASD interventions, has recently emerged. Guiding this research are the families' own first-person accounts, results of large-scale community needs assessments,[10] information derived from the experience within parent support networks,[28] and accrued clinical wisdom.[1, 29-34] But little is known about families raising individuals with FASD, and about what are risk and protective factors for this population.

Importantly, there is marked concern about the small amount of existing intervention research, and in particular studies with robust research design.[35-38]

Limited descriptive research about this population exists at this time. There is pioneering developmental research tracing early life paths for young children with significant PAE, and natural history research on risk and protective factors for individuals with FASD ranging in age from preschool to adulthood.[3,39-40] To move forward, researchers interested in parent and family support for FASD are turning to related literatures for guidance.[23,41] Data from study of developmental disabilities, and traumatic brain injury, for example, reveal that formal support to parents, case management, parent training in behavioural principles, strong "informal" parent-to-parent contact, and group interventions especially using cognitive-behavioural therapy all reduce caregiving stress,[42] and can lead to other aspects of positive individual and family function[43] (especially with multi-component interventions).[44] When disabilities and challenging behaviour co-occur, positive behaviour support interventions are useful,[45] and specific caregiving attitudes are central to positive outcome.[46-47] Developmental research supports use of early parent-child relationship-building intervention methods.[41,48] The coping literature indicates that caregiver sense of "perceived support" (vs. "received support") predicts positive outcome, and highlights the importance of a wide range of caregiver coping skills.[49-50]

Key Research Questions

Descriptive data

1. What are the "lived experiences," needs and strengths of parents raising a child with FASD, or young child at risk because of significant PAE?
2. What are pivotal risk and protective factors in caregiving attitudes, motives, coping styles and parenting practices?
3. How do patterns of lived experiences, and risk and protective factors, in FASD compare to those in other disabilities? And how do they differ by: Family type? Developmental stage? Severity of child's impairment? Cultural groups?
4. What are the gaps in existing parent support and family-focused services?

Effects of training and intervention

5. What types of provider training improve services within different service systems?

6. What are the effects of informal/natural parent support mechanisms (on-line, support groups, parent-to-parent support, etc.)? How must parent support be adjusted across the lifespan?

7. What types of respite are most beneficial to family adaptation?

8. What specialized parent education and parenting interventions are efficacious in improving individual and family outcome in FASD, at different ages and for different family types?

9. How do existing evidence-based parenting interventions (developed for other populations with similar symptoms) work for FASD, and how should they be adapted?

Translational Research

10. How can efficacious interventions be rapidly disseminated to community settings? What delivery systems increase efficiency, availability and cost-effectiveness of useful interventions (e.g., on-line, group formats, telemedicine)?

Recent Research Results

Current research describes "lived experiences" in a few small samples of caregivers raising children with FASD in several countries. Experiences differ between family types. Research reveals specific family needs and difficulties to be remediated, and effective parenting practices and positive child characteristics to be promoted in intervention.[21-23,51] Reviewers are mining other literatures to find useful treatment methods,[23,41] and critically examining the small database of existing FASD intervention research.[35-38,48] Reviews show little research focus so far on how to help families raising an individual with FASD,[38] though limited data do show that parenting interventions can lead to measurable improvement in caregiver and child outcomes. Enhancing quality of the parent–child relationship, decreasing parenting stress, fostering effective parenting skills, and increasing parents' sense of self-efficacy are all deemed critical components of any parenting intervention.[48]

Services to support families are often recommended in FASD diagnostic clinics, with treatment needs showing developmental trends.[52] Researchers are slowly identifying a range of efficacious parent support and family-focused interventions. There has been some evaluation of community programs. Qualitative evaluation of province-wide "key worker and parent support" programs in Canada, for example, suggests gains in caregiver, child and community outcomes.[53] In the U.S.,

systematic intervention research funded by the Centers for Disease Control and Prevention (CDC) has focused on caregivers of preschool and school-aged children with PAE or FASD. Among other findings, data reveal that specialized parent education groups do increase caregiver knowledge, and specialized behavioural consultation for caregivers of children with FASD and problem behaviour do improve caregiving and child outcomes.[54-57] These interventions are being translated into community settings. This research also shows how existing interventions should generally be adapted for FASD, with specific adaptations noted by some researchers[58] and experts.[34] CDC is now funding pilot study of a multi-component, intensive family-focused FASD intervention for the adolescent and young adulthood years.[59] In the U.S., research funded by the National Institutes of Health is examining the feasibility of multi-component early intervention services for families of young children at high risk because of PAE and electronic resources to more efficiently assist caregivers.[a]

Research Gaps

There are many research gaps. Population-specific descriptive data remain remarkably limited. Multiple samples must be assessed because of diversity in this clinical population, and variation in how services are provided across locations. Secondary data analysis should examine how typical interventions work for those with PAE or FASD. Key treatment ingredients must be identified. Evaluation of the impact of provider training, informal/natural parent support mechanisms, respite care, parent education, and specialized parenting interventions on caregiving, family quality of life and individual outcomes is needed using strong research design. Specialized parenting intervention models already shown to be efficacious should be replicated. Special focus is needed on developing treatments for underserved groups (families raising very young children with PAE or adolescents/young adults with FASD), and on comprehensive interventions that address FASD and co-occurring psychosocial disruption.[49] Translational research is important, to find how efficacious interventions can be disseminated and made most accessible and cost-effective.

Conclusions

It is surprising that a disability as common and burdensome to families as FASD still so often goes unrecognized or not appropriately served. Social and economic factors play a role. These include the pervasiveness of alcohol use in almost all societies, stigma and misconceptions about those affected, complexity of needed services, and resource limitations. A good quality, stable

caregiving environment is important to improve outcomes for FASD and young children at high risk due to PAE, and to reduce the risks for secondary disabilities. This, in turn, means lower societal costs. A wide range of parent support and family-focused services are needed but not yet available. Systematic FASD intervention research has begun, with promising results showing improved outcomes for parents and affected individuals, and successful efforts to disseminate interventions to community settings. “Practice-based evidence” on interventions has been compiled, and program evaluation is starting. But funding for increased intervention and translational research is essential.

Implications for Parents, Services and Policy

Parent support and family-focused services are an essential response to the global public health problems of FASD and PAE. Across cultures, parents and families shoulder the care of those with the lifelong disability of FASD. They must often provide intensive caregiving as their child grows into young adulthood and beyond, when societal supports are especially scarce. Data clearly show that a good home environment provides a set of protective factors related to higher odds of more positive life outcomes for individuals affected by FASD. The spontaneous, rapid growth of parent support networks since the 1990s anecdotally confirms that parent support is helpful to families.[28] But building a good home environment, and acting as an effective advocate for service access, generally requires more than self-help through networking with other parents. Customized, family-focused services are often necessary. Research has started to create and test appropriate intervention models for such services. Parents can play a key and compelling role in educating policy makers about the pressing, growing need for accessible, appropriate, effective family-focused services. Parents can be instrumental in bringing about the action steps listed below.

Below are proposed as action steps to build parent support and family-focused services and policy in the field of FASD:

1. Carry out multifaceted, culturally-sensitive educational campaigns and provider training to raise awareness, reduce stigma, increase identification and improve service provision.
2. Promote and evaluate caregiver self-help through natural/informal parent support mechanisms as a low-cost response in a time of resource constraints.

3. Conduct a comprehensive review of existing community-based intervention efforts in order to identify gaps and compile program evaluation data.
4. Evaluate all ongoing and future community-based programs that provide parent support and family-focused services.
5. Disseminate specialized FASD interventions already found to be efficacious, including parent education and behavioral consultation, adapting these to suit different communities and cultures.
6. Develop and test additional parent support and family-focused intervention approaches to fill service gaps. (These should be based on population-specific descriptive data and draw from related literatures, including testing whether existing evidence-based parenting interventions are useful for families raising individuals with FASD or PAE.)
7. Establish a standard of care and best practices for parent support and family-focused services. Once established, establish policy to promote adherence to the standard of care.

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Prevention of Fetal Alcohol Spectrum Disorders

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Introduction

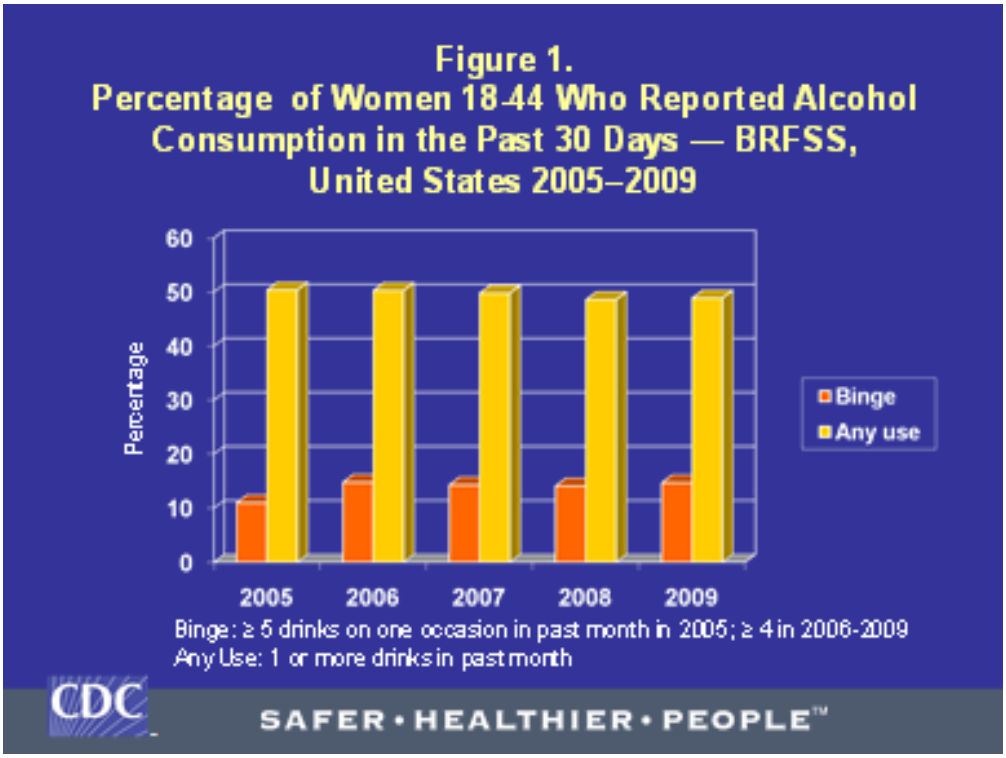
The scientific literature addressing alcohol use during pregnancy and the wide range of associated consequences has grown immensely over time in breadth, scope and understanding since the first article on Fetal Alcohol Syndrome (FAS) in the U.S. appeared in a 1973 edition of The Lancet.[1] In 1996, the Institute of Medicine (IOM) released a congressionally-mandated report by the Committee to Study Fetal Alcohol Syndrome that reviewed and summarized the knowledge amassed up to the mid-1990s. This seminal report provided recommendations concerning the diagnosis, epidemiology, prevention and treatment of FAS.[2] The committee recommended that the birth defects and developmental disabilities attributed to prenatal alcohol exposure be grouped into the four categories: Fetal Alcohol Syndrome (FAS), Partial Fetal Alcohol Syndrome (P-FAS), Alcohol-Related Neurodevelopment Disorder (ARND); and Alcohol-Related Birth Defects and Developmental Disorders (ARBD). In 2004, the term Fetal Alcohol Spectrum Disorders (FASD) was adopted as an umbrella term describing the wide range of physical, mental, behavioural and learning disabilities that can result from alcohol use during pregnancy, encompassing the four conditions listed above.[3] The most studied condition of the spectrum is Fetal Alcohol Syndrome. Current estimates of the prevalence of FAS in the U.S. range from 0.2 to 1.5 per 1,000 live births to 2 per 1,000 live births.[4,5,6] Prevalence rates of the full spectrum are generally thought to be three times the rate of FAS alone.[7] Estimates of the lifetime cost of FAS have been reported at $2 million per case.[8] Current efforts are underway among federal agencies, universities and professional societies to find a successful roadmap for combating this preventable, public health problem that affects America's children, families and society. This chapter will provide a brief overview of the problem, its challenges, and potential prevention solutions.

Subject

Survey results from the Centers for Disease Control and Prevention (CDC) using the Behavioral Risk Factor Surveillance System (BRFSS) report long-term trends in high rates of alcohol use among women of childbearing age (18-44) in the U.S. Between 1991 and 2005, approximately 55% of non-pregnant, and 11% of pregnant women, reported alcohol use in the past month.[9] Of special concern is that among those reporting alcohol use, 13% of non-pregnant and 2% of pregnant women reported binge drinking (defined as five or more drinks on one occasion in the referenced data set). Another study reported that binge drinking episodes increased from 1993-2001 with an estimated average of 37 episodes for each woman of childbearing age who reported binge drinking in 2001.[10] Binge drinking rates continued to rise from 11.9% in 2001 to 12.4% in 2002, and 13.0% in 2003. Women who reported binges, reported an average of three episodes per month. The highest binge rates were among women 18-24 years of age.[11]

In 2004, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) recommended a new definition of “binge drinking” for women – an episode of four or more alcoholic drinks consumed in a two-hour period.[12]

Figure 1 shows the prevalence of any alcohol consumption and binge drinking in the past 30 days between 2005 and 2009 in women aged 18-44 in the U.S. The graph includes data prior to and after the BRFSS adopted the new NIAAA definition of binge drinking for women. As shown, the prevalence of any reported drinking varied little and stayed around 50 percent for all five years. As would be expected, the prevalence of binge drinking increased from 11.0% in 2005 to 14.8% in 2006 when the definition of binge drinking changed from ≥ 5 drinks on an occasion to ≥ 4 drinks on an occasion. This suggests that surveys still using the 5-drink definition of a binge for both males and females may potentially underestimate the scope of risky drinking in women. From 2006 to 2009, the prevalence of binge drinking varied slightly between 14 and 15%. The data for the table are from respondents to the BRFSS who lived in the 50 states and the District of Columbia. These levels of any alcohol use in the past month, especially binge drinking, represent a significant risk because approximately half of all pregnancies in the U.S. are unplanned.[13] Further, many women do not realize that they are pregnant in the beginning of their pregnancies and may continue drinking during the early weeks of gestation.



Studies find marked differences in rates of alcohol consumption among non-pregnant women of childbearing age and pregnant women because most women reduce alcohol use when they find they are pregnant.[14,15] One Danish study found that the rate of reported binge drinking during pregnancy peaked at week three and thereafter continued to decline until week seven, after which binge drinking was rarely reported.[16] A Canadian study found that women in the preconception period did not change their drinking amounts and patterns while they were trying to become pregnant but after pregnancy confirmation, quantity, frequency and binge drinking declined significantly. The authors concluded that more preconception counseling should focus on risks of alcohol use during periods when pregnancy can occur (sexual activity and no use of contraception).[17]

Problems

While progress has been made in the prevention arena, it appears that women are not always hearing consistent messages about alcohol use during pregnancy. For example, in one study, women reported that they receive conflicting messages about alcohol use during pregnancy from family, friends, and providers, especially about what type of alcohol to drink and how much is dangerous.[18] As stated earlier, prenatal alcohol exposure is a common occurrence in the U.S. with 1 in 8 pregnant women self-reporting alcohol use during pregnancy.[9] This behaviour, while

modifiable, continues to persist despite the advisories and recommendations of experts calling for women who are pregnant, planning a pregnancy or could become pregnant to abstain from alcohol use. These include the 2005 reissue of the Surgeon General's Advisory on Alcohol Use in Pregnancy,[19] the Department of Health and Human Services' Dietary Guidelines for Americans,[20] the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics[21] and the National Institute on Alcohol Abuse and Alcoholism (A Clinician's Guide).[22] While there is a significant reduction in alcohol use after pregnancy recognition occurs overall, there is evidence that many women continue to drink while trying to get pregnant and after pregnancy recognition. In one study, based on a national sample of women of childbearing age, 45% of women reported drinking in the three months prior to pregnancy recognition, and 60% of women who reported drinking also reported not learning they were pregnant until four to six weeks gestation.[23] In another study, 50% of women who were trying to conceive reported continuing to drink alcohol.[17]

Research Context

The 1996 IOM report proposed an IOM Model for FAS Prevention that recommended three levels of prevention to reduce Fetal Alcohol Syndrome: Universal Prevention of Maternal Alcohol Abuse; Selective Prevention of Maternal Alcohol Abuse; and Indicated Prevention of FAS.

- Universal Prevention focuses on creating high levels of awareness of the consequences of alcohol use during pregnancy among the general population and women in particular. Examples include media campaigns, alcohol bottle labeling and national advisories.
- Selective Prevention strategies are directed toward sub-groups of the population known to be at increased risk for having an alcohol-exposed pregnancy (AEP). Examples include targeted screening and brief interventions tailored to the specific sub-group.
- Indicated Prevention includes multiple strategies of case identification of maternal alcohol abuse, brief intervention, formal treatment, long-term treatment and aftercare. Research has addressed many of the strategies used in the proposed three levels of prevention and found that alcohol screening and brief interventions (SBI) or extended brief interventions provide the most consistent evidence for success in bringing about alcohol use reductions. Systematic reviews by the United States Preventive Services Task Force (USPSTF) on alcohol screening and brief interventions concluded that they should be used in adults with alcohol use problems in primary care settings including non-pregnant and pregnant

childbearing aged women. While acknowledging the limited number of studies on SBI for non-pregnant and pregnant women, they concluded that the benefits of SBI to reduce alcohol misuse outweighed any potential harms.[24] Recent studies of effective alcohol screening and brief interventions among pregnant and preconceptional women have been reported since the USPSTF recommendations were issued.[25,26,27] Many employ previously developed brief screening instruments such as the T-ACE, TWEAK, AUDIT, and more recently, the AUDIT-C. A fuller description of studies related to the three levels of prevention is provided in Reducing Alcohol-Exposed Pregnancies: A Report of the National Task Force on Fetal Alcohol Syndrome and Fetal Alcohol Effect.[28] However, a 2009 systematic review by the Cochrane Collaboration on interventions aimed at reducing alcohol consumption in pregnant women and women planning pregnancy found only four studies that met their standards for inclusion within the years targeted in the search (1966-2007). They concluded that small sample sizes, methodological differences, inconsistency in findings, and other issues made it difficult to determine the basis for evidence-based recommendations. The review further called for additional well designed studies in this population.[29]

Key Research Questions and Research Gaps

Addressing important health problems, such as FAS, that can impair the health of individuals across their lifespan requires a substantive understanding of the problem and why we should be concerned about it, its associated risk factors, the health and economic impact, and importantly, what can be done about it. While there is consensus on the salient manifestations of FAS, estimates for how many children are affected with this syndrome varies widely as mentioned earlier.[6] Efficient population-based surveillance systems need to be developed to provide information on the full impact of prenatal alcohol exposure providing information for action and to build the public will and support necessary to prevent FASDs. Recent formative work in this area suggests that misconceptions about drinking during pregnancy continue to exist and women are not receiving clear and consistent messages about alcohol use before and during pregnancy. Efforts are needed to better frame messaging around drinking during pregnancy within the current climate of mixed messages that women sometimes receive from health providers, friends and family, and through the media.[30] Further research is also needed to better increase our understanding of women’s knowledge, attitudes and opinions about alcohol use and pregnancy and the role alcohol plays in the lives of women of reproductive age. This information can help

inform development of risk communication messages about the consequences of alcohol use during pregnancy, with appropriate content and tone for diverse populations of women. Also, despite the concerning rates of alcohol use among women of childbearing age, screening for alcohol use among female patients is not universally part of the standard of care among health providers. Ongoing provider education and training about FASDs and the risks associated with alcohol use and pregnancy are an important component of FASD prevention activities. In order to build a stronger evidence base for what works best in preventing alcohol-exposed pregnancy, more intervention research is needed to address the effectiveness of screening and brief interventions and other prevention strategies in women who could become pregnant, planning a pregnancy, or are currently pregnant.

The 2005 Message to Women from the U.S. Surgeon General Advisory advised women who are pregnant or considering pregnancy to abstain from alcohol use. Concern has arisen about this advisory among providers and women who only drink occasionally and chose to continue light to moderate alcohol use during pregnancy. Unfortunately, the evidence base for answering the question of the impact of light to moderate alcohol use on the exposed fetus includes studies with mixed results and contradictory findings. Clearly more in-depth research is needed to more definitively address the question of safety of light to moderate alcohol use during pregnancy.

Trends in alcohol use among women of childbearing age have remained steady suggesting that current prevention messages may not be reaching those to whom they are most relevant, may not be deemed credible, or are competing with conflicting or inaccurate messages from other sources (e.g., the media, health providers, and some internet sources). A consensus based on a thorough review of the scientific evidence could do much to establish consistency in advice and practice strategies to help women avoid alcohol-exposed pregnancies that could lead to FASDs.

Conclusions

Our understanding of the biomedical, epidemiological, and public health prevention strategies for FASD has grown exponentially over the past 38 years.[31] Despite progress made in knowledge, women of reproductive age (pregnant and non-pregnant) continue to report current alcohol consumption levels similar to those of 1991. The primary challenges at this point in time are to fill in the gaps preventing us from taking knowledge gained to the front line health providers and convince the public of the threat posed by risky drinking for women of reproductive age in general, and risks posed to the fetus if they are pregnant or could become pregnant. Of key

importance is teaching health providers in primary care settings how to screen and provide brief interventions and referral to women who are at risk for alcohol-exposed pregnancies.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Fetal Alcohol Spectrum Disorders and Nutrition

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Introduction

The consequences of prenatal alcohol exposure vary widely, and a number of factors, including prenatal nutrition, contribute to variation in the expression of fetal alcohol spectrum disorders (FASD). While nutrient deficiencies may exacerbate FASD, nutrient supplementation may decrease risk by ameliorating inadequate nutritional state or by acting via pathways that positively influence development. Thus, manipulations of nutritional status either during or after pregnancy may serve as potential interventions for FASD.

Subject

Elucidation of risk and protective factors for FASD is critical for the development of effective prevention and intervention strategies. Nutritional factors interact with alcohol, potentially exacerbating or protecting against FASD. Poor maternal nutrition is a significant problem in FASD, as the nutrients essential to support fetal development and preserve maternal health are often deficient with heavy alcohol use.[1,2] Heavy alcohol consumption is one of the leading causes of both primary and secondary malnutrition,[2,3] and undernutrition is a common characteristic of mothers in a majority of cases of FASD.[4] Not only may a woman who drinks during pregnancy consume inadequate nutrition, but alcohol itself can compromise nutrient absorption and utilization,[5] including thiamin, folate, pyridoxine, vitamin A, vitamin D, magnesium and zinc.[6-9] These insufficiencies are only compounded as alcohol is placentotoxic, impairing the ability of the placenta to deliver essential nutrients to the fetus.[10]

Research using animal models has shown that nutritional factors influence the *teratogenic* effects of prenatal alcohol exposure.[4] Studies report that diets low in important nutrients exacerbate alcohol's teratogenic effects in the offspring,[11-14] such as low birth weight,[12] physical anomalies,[14] brain damage,[15] and reductions in growth factors.[16] Some of these effects are due to slower rates of alcohol metabolism and resultant increases in blood alcohol level (BAL),[17-19] but some are independent of BAL. The effects of nutrient deficiencies not only cause short-term

effects but long-lasting problems due to *epigenetic* changes in fetal gene expression, which are enduring and pervasive.[20]

On the other hand, some nutritional factors may be protective.[21-24] The possibility that certain nutrients may reduce alcohol's teratogenicity provides an exciting opportunity to intervene in this clinical population. As such, the identification of effective nutritional supplements that reduce the severity of FASD is essential as micronutrients are relatively easy to implement, inexpensive, and safer to administer than other pharmacologic agents.

Problems

Although the damaging effects of alcohol on the fetus have been recognized for almost 40 years, there is still a need to identify effective interventions to reduce these effects. However, the interactions of nutritional factors and ethanol in pathophysiology of FASD are still not well understood. The complexity of nutrient assessment is a challenge to understanding nutrient deficiencies in FASD. Dietary recall studies often underestimate the incidence of deficiency. Furthermore, clear biomarkers of nutrient status are not always present, and they may be unreliable. For instance, a variety of biomarkers may be potentially useful in determining zinc status, such as urinary excretion and hair concentration; however, interpretation of these markers as indices of zinc *nutriture* are often inconsistent.[25,26] Moreover, assessment of maternal nutritional status is hampered by the potential for diverse responses in nutrient metabolism in pregnant women.[27,28] In fact, nutritional requirements during pregnancy are considerably different than those for non-pregnant women, and these levels can vary greatly depending on many factors. For example, plasma zinc concentrations may vary with infection, vigorous exercise, food intake, and proportion of plasma volume increase during pregnancy. Thus, inattention to these variables at the time of measurement may lead to inaccurate conclusions about maternal nutritional status. As such, assessing nutrient status in these women and understanding the effect of specific nutrient deficiencies in children prenatally exposed to alcohol is particularly challenging.

In addition, simple nutrient supplementation and fortification may not be the straightforward solution to prenatal nutrient deficiency in FASD. Complex interactions among micronutrients can facilitate or hinder absorption and bioavailability through a variety of different mechanisms, competing for transport proteins,[29,30] *chelating* organic substances, or other uptake mechanisms. Iron, copper and zinc competitively interact with each other under certain conditions, and

supplements with one may lead to deficits in another.[31,32] Clinical groups with higher zinc requirements, such as pregnant and lactating women, may even be more sensitive to iron-zinc interactions.[33] Thus, potential risks associated with interactions need to be thoroughly considered and care must be taken to ensure proper levels and ratio of each mineral to facilitate the most beneficial effects.

Research Context

Many of the studies examining the effects of nutritional supplements on outcome following prenatal alcohol exposure rely on animal model systems, which allow nutritional variables as well as other potentially confounding factors such as genetics and environment to be controlled. Epidemiological and clinical studies have assessed nutritional state of pregnant women who drink alcohol, but data are limited, as are data on the nutritional status of individuals with FASD. Moreover, studies on nutritional interventions, both during pregnancy and in individuals with FASD, have only recently been initiated.

Key Research Questions

While research has shown that suboptimal maternal nutritional status interacts with alcohol to interfere with healthy fetal development, the contribution of select nutritional factors in moderating FASD risk in humans is still not well understood. To what extent and by what mechanism do nutritional deficiencies during pregnancy influence alcohol's teratogenicity? How persistent, specific and important are the effects? What is known of the nutritional status of individuals with FASD? And finally, how can nutritional manipulations during the lifespan influence outcome, whether by compensating for a deficiency or by influencing developmental processes independent of baseline nutrient status? Understanding the mechanism through which nutrients may moderate or mediate the degree of alcohol damage will help inform the development of nutritional interventions for children affected by prenatal exposure to alcohol.

Recent Research Results

Early in FASD research, alcohol-nutritional interactions were investigated using animal models to determine how dietary factors might influence alcohol's teratogenic effects. Interest in this interaction has re-emerged given the increased risk of FASD in countries with poor nutrition.[34] Animal studies have clearly demonstrated that undernutrition increases ethanol-related fetal toxicity and changes in gene expression.[35] Several groups have examined the interactive effects

of specific nutritional deficiencies and developmental alcohol exposure. For example, in combination with prenatal alcohol exposure, the teratogenic effects of alcohol and low dietary zinc are synergistic, much greater than the effects of either alone.[36] The data also suggest that the relationship between alcohol exposure and zinc deficiency cannot be simply explained by an alcohol-induced zinc deficiency, but rather to independent but overlapping effects of each condition.[1,37,38] These findings are of great concern, given that insufficiencies of these same nutrients have been well documented in alcoholics.[39-43] Similarly, even moderate inadequacies of iron[4] or *choline*[45] during prenatal development exacerbate ethanol's adverse effects on physical and behavioural development.

In contrast, nutritional supplementation during prenatal alcohol exposure may reduce the severity of FASD. For example, antioxidants, including vitamin C, vitamin E and B-carotene, have also shown to provide significant protection against alcohol-induced neurotoxicity in animal models of FASD,[46,47] although one clinical study[48] using megadoses of vitamins C and E was terminated because of safety concerns. Animal studies also show that zinc supplementation during prenatal alcohol exposure reduces the severity of alcohol's damaging effects on physical development[22] and on learning deficits,[21,23] but not *cerebellar* cell loss.[49] Not only is zinc supplementation of value in modulating FASD risk in the offspring, it also confers beneficial effects for the mother.[50] Similarly, folate supplementation reduces the incidence of cardiac abnormalities.[51] Choline supplementation can also reduce the severity of physical, neuropathological and behavioural alterations associated with developmental alcohol exposure.[52,53]

What is particularly exciting is that nutritional supplements may effectively reduce the severity of FASD, even when administered during the postnatal period and after alcohol exposure has ceased. Postnatal choline supplementation in rodents reduces the severity of hyperactivity,[54] deficits in trace conditioning of fear responses[55] and eyeblink conditioning,[56] spatial memory,[57,58] working memory,[59] and reversal learning.[54] Importantly, in all of these studies, the beneficial effects of choline on behavioural performance was evident even after choline treatment had ceased, indicating that choline leads to long-lasting changes in brain function. Choline acts as a precursor to the neurotransmitter acetylcholine and to cell membrane components, but, like folate, it also affects the *homocysteine/methionine cycle* and *DNA methylation*; thus, its actions may influence multiple pathways important for brain development and function. Although it is not yet known if prenatal alcohol influences long-lasting choline status, these data suggest that

nutritional supplements may be effective even if they are not compensating for a nutritional deficiency.

Research Gaps

Despite the existence of animal data suggesting the feasibility of nutrient supplementation as a potential intervention for individuals with FASD, these studies are only now being implemented in human clinical populations. Clinical trials are needed to translate experimental findings in children with FASD. Furthermore, a formidable limiting factor in understanding the role of maternal nutritional status in FASD is the availability of the nutritional status of women who have been drinking and their children. Longitudinal prospective studies are needed to examine maternal nutritional status and its modulation of FASD risk, as well as the long-lasting effects of prenatal alcohol exposure on the nutritional status of the individual with FASD.

Conclusions

Although it is clear that nutritional state influences alcohol's damaging effects on the fetus, the specific interactions are not well understood. Elucidation of how nutritional factors moderate and mediate alcohol's teratogenic effects not only can help target prevention efforts to high-risk populations, but nutritional supplements may serve as effective interventions. In addition, given the role of nutrients on brain and behavioural development, nutritional supplements may effectively reduce the severity of symptoms in children with FASD, whether compensating for nutritional deficiencies or by acting on pathways that enhance behavioural and cognitive functioning.

Implications

The potential of nutritional interventions, either during pregnancy or in the individual with FASD, to reduce the severity of FASD and improve the quality of life of individuals who have been exposed to alcohol prenatally is promising.

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FASD: Prevention and Nutrition: Commentary on Floyd, Denny and Weber, and Nguyen and Thomas

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Introduction

Fetal alcohol spectrum disorders are preventable, but continue to be manifest nearly four decades after the first article on fetal alcohol syndrome was published in the US.[1] The review article by Floyd et al. summarizes the current status of prevention efforts, setting them in the context of the epidemiology of alcohol use by women of child-bearing age in the US. With regards to research on prevention, Floyd et al. summarize three levels of prevention approaches, provide the results of a 2009 Cochrane systematic review of research between 1966 and 2007 (which could only include four studies of sufficient merit) and then make reference to some recent studies published subsequent to 2007. The review article by Nguyen and Thomas highlights the potential importance of nutritional factors that could influence the expression of fetal alcohol spectrum disorders. Just as nutritional deficiencies may exacerbate FASD, their appropriate nutritional supplementation may mitigate against the harmful effects of prenatal alcohol exposure. Here, the preponderance of evidence relies on animal models, with studies involving humans in their nascent stages. Both articles highlight the promise and the challenges of research about this critical problem.

Research and Conclusions

Prevention

Drinking during pregnancy is fairly common, and perhaps even more frequent than the data summarized in the Floyd et al. review. Whereas many of the cited studies rely on queries about alcohol consumption in the month before surveys, Ethen et al. asked 4,088 randomly selected control women (who delivered live born infants without birth defects) from the National Birth Defects Prevention Study about drinking during their entire pregnancy.[2] The work of this group, which was not included in Floyd's review, found that 30.3% of all women had alcohol some time during pregnancy, and 8.3% had binge drinking (defined as 4 or more drinks on one occasion).

Indeed, since the Ethen et al. study included only women with live births without birth defects, the prevalence reported by this group may be an underestimate of the true prevalence of prenatal alcohol use since it also increases the risk of spontaneous abortion (miscarriage), fetal death and birth defects. Rigorous research on the prevention of fetal alcohol spectrum disorders is relatively sparse and appears to be concentrated on targeted screening and brief intervention efforts. Floyd et al. identified several areas for future investigation, including the influence of others' beliefs on pregnant women's alcohol consumption, the effect of the pregnant women's own knowledge about the consequences of prenatal alcohol use and the lack of clarity about the impact of light to moderate alcohol use on the exposed fetus.

Nutrition

The research on nutrient supplementation in human clinical populations is limited and has heretofore been largely confined to animal models. Diets low in important nutrients have exacerbated alcohol's *teratogenic* effects in animal offspring, including low birth weight, physical anomalies, and brain damage. Nutrient deficiencies may have both short-term effects, by impacting the rate of alcohol metabolism, as well as longer-term consequences by *epigenetic* changes in fetal gene expression. Nutrient supplementation to reduce alcohol's teratogenicity is a hopeful area for further development. However, conclusions about the impact of nutrient supplementation in humans are premature; the need for translational research cannot be disputed.

Implications for the development of policy

Both reviews emphasize the "positive" – that knowledge about prevention strategies for FASD has "grown exponentially" and that the potential of nutritional interventions, either during pregnancy or in the individual with FASD, is "promising." However, the real question to be raised is whether our collective efforts are truly commensurate to address the consequences of a known, preventable cause of birth defects and developmental disabilities. After all, pregnant women continue to consume alcohol at rates similar to those published in 1991.

In general, physicians have been slow to incorporate screening and brief intervention into their practices.[3] Explanations include lack of time, comfort or expertise.[4,5] Such barriers may be exacerbated with regards to women who drink alcohol, because women who are risky drinkers are less likely to be recognized, and therefore treated, despite their greater vulnerability to

alcohol's negative medical consequences.[6,7,8] Although women have had lower rates of alcohol use disorders than men in the past, the gender gap for drinking problems is narrowing.[9,10,11] Moreover, binge drinking is increasingly common among all groups, but its consequences are less well appreciated by patients and providers alike, so that information about this pattern of use is neither disclosed nor obtained.[12,13]

Such potential obstacles may become impassable when prenatal alcohol consumption is being considered. The stigmatization of prenatal alcohol use, especially heavy use, may lead to denial or minimization of actual consumption that may hamper our ability to truly understand its extent and consequences.[14] In addition, the debate on "safe drinking limits" during pregnancy continues.[15] As such, some have chosen to dispute or misunderstand the good intentions that come with the most prudent advice of abstinence from alcohol during pregnancy.[16]

On the other hand, there are instances of innovation that merit mention. Several major findings have come from studies involving screening and brief intervention for prenatal alcohol use. The results show that 1) pregnant women with the highest levels of alcohol use reduce their drinking most after a brief intervention that includes their partners, 2) brief interventions delivered by non-medical professionals in a community setting can lead to increased abstinence and improved outcomes, and 3) dramatic decreases in newborn morbidity and mortality can be realized by consistent maternal screening and brief intervention in an health maintenance organization using practices that exceeded the ordinary standard of care.[17,18,19]

What else do we need to know so that we can act to eliminate the fetal alcohol spectrum disorders? If we demand perfect, unassailable knowledge, then the resources necessary to obtain the data from well-designed studies are similarly required. Areas of much-needed investigation would then include: 1) establishing the safety (or not) of light to moderate prenatal alcohol use, 2) ascertaining the efficacy of screening and brief intervention for risk drinking women, pregnant or not, 3) identifying and then modifying the sources of personal, professional, and societal ambivalence about prenatal alcohol and other substance use, 4) translating the animal research on nutrient supplements and prenatal alcohol use to human clinical populations, 5) codifying the diagnostic criteria for the consequences of prenatal alcohol exposure in infants, children and adults, and 6) assessing the impact when data-driven, evidence-based changes in individual, professional, and societal behaviour are achieved.

These recommendations do not imply, however, that it is desirable to be complacent until all critics of our current knowledge base are satisfied. Indeed, perfection may be the enemy of the good enough when the well-being of our next generation is at stake.

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