Fetal Alcohol Spectrum Disorders

BACKGROUND

Maternal consumption of alcohol during pregnancy has been linked with a number of adverse fetal outcomes [4]. These include fetal alcohol spectrum disorders (FASD), which consist of several conditions: FAS, pFAS, ARBD, and ARND (see Terms and Concepts).

FASD is linked to heavy prenatal exposure to alcohol, which is a teratogen, and at high concentrations and can cause structural changes in the developing central nervous system, which manifest themselves as cognitive deficits and behavioral problems [5], the severity of which depends on the level and pattern of maternal consumption. The deficits associated with FASD persist throughout the lifetime of the affected individual.

Within the context of the total global burden of disease, FASD is among the conditions wholly attributable to alcohol consumption (WHO, 2014). Studies have indicated that FASD contributes considerably to the social cost of harmful drinking [6-8].

There is no conclusive evidence of a link between occasional, light, or even moderate drinking during pregnancy and an increased risk for FASD [9, 10]. However, as the threshold of maternal consumption at which risk increases has not been defined, government and other recommendations around drinking during pregnancy generally point to abstinence to avoid adverse effects on the developing fetus (see *IARD Policy Table Drinking Guidelines: Pregnancy and Breastfeeding* for more information).

While drinking during pregnancy has been linked to a number of outcomes, this *Health Review* focuses on the available evidence on the development of FASD.

SUMMARY OF THE EVIDENCE

Drinking patterns, maternal risk factors, and FASD

Maternal drinking during pregnancy and fetal exposure to alcohol have been linked with a number of adverse developmental and health outcomes that include FASD.

- The evidence conclusively shows that heavy maternal drinking during pregnancy is both a necessary precondition and the main risk factor for the development of FASD [11, 12].
- A “diagnosable condition within the FASD spectrum is not likely to occur” in the absence of regular heavy drinking [12], p. 17).
- Multiple studies have found that the highest rates of FASD incidence, particularly of the more severe FAS and pFAS, are linked to patterns of frequent binge drinking by pregnant women [11, 12].

Fetal development occurs in stages. Therefore, the particular timing of heavy maternal drinking during pregnancy is likely to be associated with different deficits.

- The typical facial abnormalities, which are diagnostic criteria for FAS and pFAS, develop between the sixth and ninth weeks of pregnancy, pointing to particular vulnerability to heavy maternal drinking during this time [12].
- The neurological deficits also point to the period of gestation during which neural crest development takes place as a period of particular fetal vulnerability [13-15].

Other maternal risk factors

Heavy drinking is a strong risk factor for FASD, but does not always result in the development of these disorders. Other individual level maternal factors have been shown to affect the association between heavy drinking during pregnancy and FASD [12].

- Among women with comparable drinking patterns during pregnancy, older mothers are more likely to give birth to a child with FASD [11, 16, 17], and the risk of having an FASD child is increased with more pregnancies and births [16].
- Body size, measured by body mass index (BMI), also appears to modify the risk for FASD. Some studies have shown that among pregnant women who drink heavily, smaller women are more likely to give birth to a child diagnosed with FASD [12, 16, 18, 19], although other studies report an association with higher BMI [20].
- Poor maternal nutrition and diet, in conjunction with patterns of heavy drinking, may also increase the risk for FASD [15].
- Alcohol metabolism has also been implicated in the relationship between maternal drinking and FASD. Slower alcohol metabolism in some women may result in higher sustained blood alcohol levels, exposing the developing fetus for longer periods of time [21, 22].

In addition to factors which modify the relationship between alcohol consumption and FASD outcomes, studies have also shown a number of variables that are associated with an increased risk of FASD.

It should be noted that there is not necessarily a causal relationship between all potential risk factors and FASD.

- For example, other maternal risk factors include drinking alone [20], family members who abuse alcohol [11, 20], having less stable domestic partnerships, and being at risk for domestic violence [18, 23].
- According to a systematic review, FASD births are more common in women with low socioeconomic status and educational level [11].

Although the focus of research on FASD has generally been on maternal risk factors, new evidence from animal research suggests that the paternal drinking prior to conception may also play a role, although the full mechanism remains to be elaborated [24].

Diagnosing FASD

Several characteristic features are used to diagnose FASD. These include

- particular facial features (dysmorphia), which are most pronounced in the conditions at the more severe end of the spectrum (e.g., FAS) [25];
- inattention, hyperactivity, and impulsivity [26-28], often diagnosed as ADHD, and difficulty with emotion recognition [29, 30];
- significant cognitive deficits, notably in executive functions, such as working memory, inhibition, and set shifting [30, 31]; and
- impairment of both gross and fine motor skills [32, 33].

The extent of these deficits varies, depending on which disorder is manifested and its severity.

FASD-related impairments persist into adulthood, carrying with them implications for care and treatment of affected individuals [25].

- Adults with FASD (notably those with FAS) are more likely to be unemployed, living on disability, and have higher rates of both alcohol abuse and psychiatric disorders than their non-FASD counterparts [34].

TABLE 1: PREVALENCE OF FASD AND ITS CONSTITUENT DISORDERS IN COUNTRIES AROUND THE WORLD

Country / Region	Prevalence
Australia	FASD: 0.26 per 1,000 live births [45] 1.06 per 1,000 births [36] FAS: 0.06 per 1,000 live births [46] 0.01-0.03 per 1,000 live births (Victoria only) [47] 1.33 per 1,000 births [36] Indigenous groups: FASD: 4.08 per 1,000 live births, compared with 0.03 in non-Aboriginal groups [45] FAS: 0.146 per 1, 000 total population for children < 5 years at diagnosis compared with 0.004 in non-Aboriginal groups [46] FAS and pFAS: 120 per 1,000 children (remote community in W. Australia) [48]
Canada	FASD: 9 per 1,000 live births [49] FAS: 1 in 1,000 live births [50] Indigenous groups: FAS: 7.2 per 1,000 live births (Incidence; Northeastern Manitoba) [51]
Croatia	FAS: 16.9 per 1,000 school children (observed prevalence in single rural region) [52] pFAS: 49.7 per 1,000 school children (observed prevalence) [52] FAS / pFAS: 12.1 per 1,000 school children (with confirmed pregnancy alcohol exposure) [52]
Norway	FAS/FASD: 0.3 per 1,000 [53] FAS: 0.2 per 1,000 [53]

Country / Region	Prevalence
Ireland	FAS: 0.05 per 1,000 total births (maternity hospital population in Dublin) [54]
Israel	FASD: 150 per 1,000 among pre-adoption and foster children [55]
Italy	FASD: 36 per 1,000 school children [43] 2.3 – 6.3 per 1,000 school children (Rome region, urban and rural) [56] FAS: 6.2 per 1,000 school children [43] 4 - 12 per 1,000 school children (Rome region, urban and rural) [56] pFAS: 28 per 1,000 school children [43] 18.1 – 46.3 per 1,000 school children (Rome region, urban and rural) [56]
New Zealand	FASD: 0.11 per 1,000 births [36]
South Africa	FASD: 72 per 1,000 school children [43] 135 per 1,000 first-grade students [57] 64 per 1,000 first-grade students (two suburbs of Kimberly in Northern Cape Province) [58] 113.22 per 1,000 births [36] FAS: 50 per 1,000 school children [43] 55 per 1,000 first-grade students (two suburbs of Kimberly in Northern Cape Province) [58] 100 per 1,000 children (rural Western Cape Province) [59] 59 per 1,000 first-grade students [57] 55.42 per 1,000 births [36] pFAS: 19 per 1,000 school children [43] 75 per 1,000 children (rural Western Cape Province) [59] 45 per 1,000 first-grade students [57] 28.29 per 1,000 births [36]

Country / Region	Prevalence
United States	FASD: 16.5 per 1,000 school children [42] 24 – 48 per 1,000 children (middle SES community in Midwest) [59] 169 per 1,000 children in federal child-care system [60] FAS: 4.9 per 1,000 school children [42] 2.8 - 4.6 per 1,000 live births [61] 0.3 – 0.8 per 1,000 children (communities in Arizona, Colorado, New York) [62] 6 – 9 per 1,000 children (middle SES community in Midwest) [59] 60 per 1,000 children in federal child-care system [60] pFAS: 11-17 per 1,000 children (middle SES community in Midwest) [59] 11 per 1,000 school children [42]

Estimating prevalence

Information on the prevalence of FASD, both globally and in individual countries, is scarce, and where it exists, is highly varied and of questionable reliability.

While it has been suggested that, globally, 5% of all pregnancies may result in children with FASD [35], individual studies cover few countries, where they often focus on small populations.

- As Table 1 shows, the prevalence of FASD and its constituent disorders ranges significantly across countries and also across individual studies within countries.
- A recent systematic review and meta-analysis found FASD prevalence estimates among South Africa, the United States, Canada, Australia, and Italy to be heterogeneous and difficult to compare [36].
- The best studied cases are the Western Cape Province of South Africa, the United States, Canada, and Australia, where prevalence is often assessed among indigenous groups.

The collection of data on FASD prevalence is challenging for a number of reasons.

Methodological differences in screening, diagnosis, and reporting practices [37, 38] mean that there is limited comparability across studies and in what is being measured.

- Diagnosis of FASD relies, in part, on characteristic facial features, growth retardation, and neurological symptoms. However, these are usually present in the most definitive cases of FAS, the most severe among the disorders. As a result, the less severe disorders of the spectrum may be missed, particularly in the absence of evidence of maternal drinking during pregnancy [25, 39].
- The lack of consistency regarding diagnostic guidelines for identifying the various disorders that make up FASD has also been identified as an obstacle to reliable estimates of prevalence [40].
- Prevalence data are often derived from small sample sizes, making generalizations about prevalence at the population level difficult [40].
- There is evidence that different diagnostic criteria for the morphological characteristics associated with FASD may be needed for different racial groups [39].
- It has been suggested that pediatricians and other health workers often lack the skills needed to correctly diagnose FASD [41].
- Since FASD is often most prevalent among particular populations, such as indigenous groups, who are outside of the mainstream for health care, reaching them for diagnosis may be difficult [42].

The age at which children are screened and diagnosed with FASD influences whether critical symptoms are present and can be identified.

- Certain neurological and behavioral deficits of FASD do not clearly manifest themselves until the age of 3 years [43]. It has been suggested, therefore, that screening of school-aged children yields most reliable estimates.
- While biomarkers of prenatal alcohol exposure could serve to identify at-risk individuals at birth, such an approach may have legal and ethical implications regarding maternal drinking [44].

As a result, accurately estimating the prevalence of FASD is more challenging than for many other conditions [4], and the prevalence of the disorders is likely to be underestimated.

There is evidence that FASD, or at least some of its constituent disorders, is higher among certain populations, notably among the disadvantaged.
- For example, FASD is more common among indigenous populations, including Native Americans in the United States [63, 64], First Nations populations in Canada [51], and Aboriginal communities in Australia [45, 46, 48].
- In South Africa, the prevalence of FASD is reportedly significantly higher among Black African populations than among those of mixed ancestry [58].
- Higher prevalence among these groups [37, 40] has been linked with social exclusion and other factors.

PREVENTION APPROACHES

Effective prevention of FASD relies on awareness and understanding of the risks and the potential effects of alcohol consumption during pregnancy among the general population and, particularly, among pregnant women. It also includes the ability to provide current and relevant information about FASD to expectant mothers, to offer advice about risk factors and counseling about changing risky behaviors, and to recognize signs and symptoms of harmful drinking patterns.

Various measures to address harmful drinking by pregnant women have been applied effectively for the prevention of FASD. They include:
- Screening and brief intervention (SBI) to identify harmful drinking patterns during pregnancy and to offer counseling to change them [65];
- Peer-based interventions to change attitudes and social norms around drinking in pregnancy [66];
- Treatment for alcohol dependence in pregnant women [66].

There is evidence that messages about FASD and risk factors are not always being adequately conveyed to pregnant women and to those at increased risk, including by health professionals [67].
- Research has identified a lack of general knowledge about FASD in countries like South Africa [66, 68], where rates are among the highest in the world, and elsewhere (e.g., UK) [69, 70].
- Women may also receive contradictory messages about drinking during pregnancy, and are influenced by their own attitudes and those of their peer group, and by prevailing heavy drinking patterns [66, 68].

Adequate training of professionals is essential for the prevention of FASD, for diagnosis, and for treatment.
- There is a need for improved education of pediatricians [70] and other health workers, as well as midwives, who play an important role as primary health care providers in many cultures [65].
- It has also been suggested that community workers should also be trained to screen for FASD, particularly among hard to reach populations, and where access to health workers may be difficult [71].

Early identification of at-risk pregnancies is crucial for the prevention of FASD.
- Research shows that mothers of children diagnosed with the disorders are less likely to access prenatal care and at a later stage of pregnancy than women with children without an FASD diagnosis [11].
- A study of a heavy drinking population in South Africa found that cessation of drinking after the first trimester decreased the likelihood of FASD compared to pregnancies in which drinking continued throughout all three trimesters [72], pointing to the importance of early identification of at-risk pregnancies.

A comprehensive approach to the prevention of FASD that includes combination of multiple elements is likely to yield the best results [73, 74].

METHODOLOGICAL CONSIDERATIONS

There are several methodological considerations regarding studies on FASD and the available evidence on its constituent disorders.

Confounding

Confounding variables can obscure the true nature of the relationship between drinking and outcomes. Confounders relating to FASD are no different and need to be identified and controlled. They include poverty and malnutrition, and health status of the mother, which play a potential role in both drinking patterns and outcomes. Since FASD prevalence is significantly higher among marginalized groups of society than among the general population, the role of these confounders cannot be ruled out.

Reliability of Data

Information about the exact nature of the relationship between maternal alcohol consumption, prenatal exposure, and FASD relies on data that may be incomplete.

- Studies on prevalence are often confined to particular sub-populations and rely on small sample sizes, making estimates about the general population difficult.
- Many studies rely on cohorts of children in orphanages or in foster care, offering little information about prenatal alcohol exposure or other potentially confounding factors.
- According to a recent study [60] only a small proportion of women whose children have been diagnosed with FAS provided information about their alcohol consumption.

Animal Models

Much of the evidence on FASD is derived from animal studies that have been used to establish the role of dose effect of alcohol exposure, nutritional status, maternal factors, and genetics, and also to assess the effects of prenatal alcohol exposure during different gestational periods [75]. Animal models are also useful tools for developing new treatments and interventions.

However, the direct transferability of animal model data to humans has been questioned, not only with regard to FASD but more generally.

At the same time, the reliability of human studies on FASD and the generalizability of results on FASD from special groups to the wider population also have limitations.

Misdiagnosing and Underreporting

Data on the prevalence of FASD are unreliable because of under-and misdiagnosis of the disorders and resulting underreporting.

- Currently, there is a lack of consistency in diagnostic guidelines for FASD screening and diagnosis.
- A lack of attention to FASD in many countries, including developed countries, has resulted in poor skills among pediatricians and health workers to diagnose cases of FASD.
- A higher prevalence of FASD among certain marginalized groups than in the general population also means that diagnosis is difficult, leading to underreporting.
- There have been attempts to extrapolate prevalence figures for some countries from existing international data from other countries. However, such an approach ignores the specific conditions, drinking patterns, social, economic, demographic, and other confounding factors that exist across countries.

TERMS AND CONCEPTS

Prenatal alcohol exposure refers to exposure of the developing fetus to any level of alcohol consumed by the mother.

Fetal alcohol spectrum disorders (FASD) is a group of conditions that affect unborn children, resulting from different levels and patterns of prenatal alcohol exposure. There are four categories of FASD diagnoses recognized by the U.S. Institute of Medicine [2, 3], all of varying levels of severity. Confirmation of maternal drinking is not necessarily a criterion for diagnosis, as information about prenatal alcohol exposure may be lacking. The effects of FASD for the child are irreversible.

- **Fetal alcohol syndrome (FAS)**, the most extreme form of FASD, is characterized by growth retardation, facial abnormalities, and structural or functional problems of the central nervous system (CNS), such as impaired motor skills, hearing loss, and hand-eye coordination deficits. Substantial regular or heavy episodic prenatal alcohol exposure may be either confirmed or unknown.
- **Partial fetal alcohol syndrome (pFAS)** are characterized by some but not all of the facial abnormalities observed in FAS in combination with either growth retardation or a neurobehavioral factor (such as age-inappropriate deficiencies in the areas of learning, impulse control, social perception, abstract thinking, and memory). Substantial regular or heavy episodic prenatal alcohol exposure may be either confirmed or unknown.
- **Alcohol-related birth defects (ARBD)** is characterized by congenital cardiac, skeletal, kidney, and eye malformations. Substantial regular or heavy episodic prenatal alcohol exposure must be confirmed.
- **Alcohol-related neurodevelopmental disorders (ARND)** are characterized by structural or functional problems of the CNS and / or a pattern of neurobehavioral factors (such as age-inappropriate deficiencies in the areas of learning, impulse control, social perception, abstract thinking, and memory). Substantial regular or heavy episodic prenatal alcohol exposure must be confirmed.

Teratogens are agents or factors that can disrupt the normal development of a fetus. These include maternal infections, household and industrial chemicals, drugs, and alcohol. The effects of teratogens depend on the level of exposure and the gestational period during which exposure occurs.

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