Fetal Alcohol Spectrum Disorders

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Abstract

FASD is a complex neurodevelopmental disorder related to prenatal alcohol exposure. A diagnosis of both inclusion and exclusion it is one that has been frequently missed due to the complexity of the overlap in symptoms with other conditions. It is only by careful evaluation of features, ruling out and ruling in symptoms that a confident diagnosis can be made.

Whilst FASD remains one of the most common causes of developmental delay, having been first recognized in 1973, many aspects remain unclear and under investigation. The rates of the disorder have been recognized to be as high as 3–8% of the population depending on the group studied. When considering poor understanding and recognition of the disorder alongside uncertain individual exposure risk prevention of the disorder remains a challenge.

The article will focus on the background, exposure risk, pathology and clinical evaluation and management of this disorder.

Keywords developmental delay; epigenetics; Fetal Alcohol Spectrum Disorder; Fetal Alcohol Syndrome; growth restriction

Background and history

Fetal Alcohol Spectrum Disorders (FASD) describes the range of disorders seen when a pregnant mother consumes alcohol at a level sufficient to cause harm. Fetal Alcohol Syndrome (FAS) represents the most commonly recognized part of the spectrum. Whilst reports of alcohol harm in pregnancy date back to biblical times, it was not until a short case series, published in the Lancet in 1973, that a name was attributed to this disorder. Later, it was established that a French paediatrician, working with midwifery colleagues, had identified 127 cases of a condition similar to that described by Smith and Jones in Seattle, 6 years prior to their naming of the syndrome.

Very early on, it became evident that the symptoms described did not represent the whole spectrum of presentation. It was noted that the effects of prenatal alcohol exposure seemed to be far greater than just the physical stigmata. This led to the introduction of the term Fetal Alcohol Effects (FAE). This label described the belief, that alcohol consumed by a pregnant mother, was having wider effects on behaviour beyond physical stigmata. Unfortunately the causal relationship and the evidence at that point in time were limited. To describe the relationship beyond an effect was not deemed appropriate.

In 1996, the Institute of medicine brought together experts working in this field, covering animal researchers, psychologists, paediatricians and wider advocates to discuss and formulate accepted diagnostic criterion for FAS but also the wider spectrum. Five specific diagnostic terms were established, namely FAS with and without confirmed maternal alcohol exposure; partial FAS (pFAS); alcohol-related neurodevelopment disorder (ARND); and alcohol-related birth defects (ARBD).

The Seattle-based Astley and Clarren refined the diagnostic techniques and criteria for diagnosis. This led to the four digit approach to diagnosis. However, when comparing the four digit approach to the Institute of medicine criteria, differences were found within the same population. This raised concern regarding the accuracy and validity of diagnoses made. Primarily, this related to the sensitivity and specificity attributed to the diagnostic labels. In 2005, Canadian diagnostic criterions were produced in order to try and bring together the best parts of both diagnostic formulations and help bring consensus to the field.

The term FASD has grown its usage from the turn of the millennium. An increasing recognition developed, underlying the primary and ongoing difficulties with function, related to how the brain was damaged and how behaviours subsequently presented. This was through direct presentations but also due to disabilities attributed to the disorder. Initially this term was used as an umbrella term for the diagnostic labels found underneath it, but increasingly has begun to be used in some circles as a more diagnostic label. The current 2015 revisions to the Canadian guidance have proposed that the terminology now reverts to Fetal Alcohol Spectrum Disorders with or without facial stigmata.

Levels of risk

What is a 'safe' intake of alcohol during pregnancy?

Since the first reports of alcohol exposure in pregnancy causing damage, there has been debate surrounding the level of alcohol exposure that is required to cause individual harm. This is a debate that has raged through both the academic and lay media.

All initial reports described very high levels of alcohol exposure leading to clear neurological and physical damage. It is widely accepted that high levels of alcohol exposure in utero are associated with high levels of risk to the developing fetus. However, this risk is not absolute. Some individuals appear to be significantly less vulnerable at any level of exposure, suggesting individual differences in susceptibility.

This variability in individual susceptibility has pervaded into the low to moderate alcohol exposure level debate. The evidence gathered from animal studies and over the last 10 years through large-scale cohort studies seem to suggest evidence of harm even at lower levels of exposure for some children which may present only in later childhood.

While studies conducted on younger children have identified limited, if any effects, at the lower alcohol exposure, all have confirmed higher exposure levels are associated with neurological deficits. In older children there is some evidence for differences in function even at low levels of exposure. For example, whilst evidence from the millennium cohort up to the age of seven as well as the Danish cohort study up to the age of five showed limited impact compared to non-exposed individuals, studies in older children and where genetic vulnerabilities to alcohol metabolism were identified, differences in cognitive abilities were seen even at low-level exposure.

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This causes ongoing uncertainty as to the level of alcohol which can be considered safe during pregnancy. Whilst for the majority, low-level exposure is not considered harmful; this does not appear to be the case for all children. The science is not currently able to define what a specific safe level is for any individual person.

This picture is complicated further by the fact that individuals are poor at estimating safe levels or alcohol intake. In one recent study people poured five times the expected level when trying to pour one unit. Society has yet to 'catch up' with the scientific consensus that alcohol can harm the unborn child. In the UK in 2014, 27% of women reported drinking throughout their pregnancy. The messages being delivered by research are perhaps unnecessarily complex and simplification of the issues may be more impactful. High-level exposure results in high risk of harm with low-level exposure low risk. However, there is no clear 'safe' level, particularly when detailed phenotyping occurs later in childhood. Therefore only abstinence can wholly avoid risk for alcohol impacting on the unborn child.

Pathology

Prenatal alcohol is harmful to the developing body and brain. Various mechanisms for this have been identified. Early work, using animal models, where other risk factors can be controlled for, showed that alcohol was doing direct damage to the developing animal fetus. Much of the early work focused on mouse models. Whilst the level of exposure that caused harm cannot be easily extrapolated to human models, the evidence of alcohol having a direct impact on the developing fetus was clear.

What also became evident early on, is that there were timing effects regarding exposure and outcome seen. For example, two of the three facial characteristics, namely the flattened philtrum and thin upper lip, have been shown to occur in a specific narrow window of vulnerability. If high levels alcohol exposure is not seen during these times, these features are often absent. As neurological development continues throughout all three trimesters the window for potential harm is largest for neurological outcomes. For example neural folding, neural migration and inter-neuronal connectivity all occur during the third trimester. These have been found to be affected by alcohol in vitro, correlating with post-mortem studies of individuals with FAS.

Mechanisms involving direct apoptotic damage to the developing neurones and cells through to increasing evidence for epigenetic modification of both DNA methylation and histone modification have been identified. There is no one single mechanism that has been found that explains all of the observed deleterious effects of alcohol. The complexity of alcohol's impact on the developing fetus, from pathological point of view, has led to a debate as to the specific aetiological relationship between alcohol exposure and FASD. What is clear is that prenatal alcohol exposure causes clear direct neurological deficits through a mixture of mechanisms.

Epidemiology

Initial estimates, regarding the prevalence of FAS were in keeping with it being a rare disorder. The belief existed, that the condition primarily existed in selective populations. It was not until later epidemiological studies took place, in wider populations, that better estimates developed. Unfortunately, many of these were extrapolated from clinic-based estimates. More direct active ascertainment studies, involving a two-stage approach with initial screening followed by more direct observation in school-age populations began to take place in various parts of the world. Studies in South Africa, Italy, Croatia and America have all identified rates of FAS at around 1 per 1000, with some studies reporting far higher rates.

For FASD an even wider prevalence has been identified. In specific townships in South Africa, rates as high as 8.1 per 1000 were found with other studies for example in Italy and Croatia between 3.2 per 1000 and 4.0 per 1000 respectively. These rates were far higher than expected and may reflect the difficult socioeconomic environments faced by mothers in these regions.

The criterion and methodology used in the existing studies have been criticized, due to some of the interpretive methods used in allocating cases. As such in 2011 World Health Organization initiated a series of studies to identify the prevalence rate of FAS and the wider FASD spectrum which are currently ongoing.

Knowledge of FASD

In order to both prevent cases and direct appropriate management of FASD when harm has already occurred, there needs to be a reasonable understanding of the disorder in professionals as well as recognition of harms in the public. International literature and recent publications in the UK have highlighted that the level of knowledge is poor. In professional groups, in one recent UK based study some had heard about the clinical syndrome, the majority knew little else. Diagnostic features, prevalence, management strategies and relationship to other disorders were all found to be poorly understood. Much of the information came from either the lay media rather than through specific scientific journal articles and therefore inconsistent messages were being presented. This meant for some, information ended up ignored. Worse, a degree of cynicism and reluctance to diagnose was also seen.

This was similar to the presentation in the general public. A lack of knowledge about the impact and relevance to individuals was found to lead many to ignore public health messages about safety and harm. Inconsistent messages again led to people ignoring advice. Targeted approaches were considered more appropriate; however constantly changing messages in the media led to uncertainty. Evidence suggested that carers and those looking after individuals with FAS struggle to get support and help, due to a combination of their own lack of knowledge and the professionals' inability to support them.

Clinical presentation

Developmental delay and presentation at different ages

When considering the clinical implications for individual, Table 1 highlights the changing presentation at different ages. It also presents the types of actions that are recommended for professionals at each stage, both when diagnostic criterion appeared to be met but also when a risk factor remains but a diagnosis is not possible.

The importance of understanding normal developmental trajectories in this group is clear. Broadly, alcohol causes a shift in