Foetal Alcohol Spectrum Disorders and Imaging: A Brief Review

ROBERT PISANI

Foetal Alcohol Spectrum Disorders (FASD) refers to the collection of features seen as a result of prenatal alcohol exposure by the mother. FASD can be considered as an acquired brain injury, predominantly affecting neurocognitive development, amongst other organ systems (1). An effected individual may not necessarily possess all the characteristic features of the syndrome, with varying degrees of severity being displayed (2).

EPIDEMIOLOGY & AETIOLOGY

A recent study concluded that 1 in 13 women who consume alcohol during pregnancy had a child with FASD (3). There is no safe amount of alcohol to drink during pregnancy. However, a daily alcohol consumption of four or more drinks during pregnancy significantly increased the risk of developing FASD (4). FASD is considered to be one of the commonest avoidable causes of intellectual disability (1). In fact, approximately 1700 neonates are born each day with FASD globally, with a higher incidence amongst the high-risk populations, such as incarcerated cohorts; children in care; aboriginal populations and those under psychiatric care. Incidence is highest in South Africa (111.1 per 1000 population); however, an accurate quantification of FASD is challenging due to under-diagnosis and confusion with other syndromes, such as autism spectrum disorder or ADHD (3,5).

Alcohol is a teratogen which freely crosses the placenta from the mother to the foetus. This leads to a blood alcohol content of the foetus which is higher or the same as that of the mother for longer periods, since the developing liver cannot effectively eliminate it due to low levels of foetal alcohol dehydrogenase. Cytochrome P450 2E1 is one of the major enzymes which catalyses ethanol oxidation in the liver. Reactive oxygen species may be generated from this reaction when improperly coordinated in the foetus, leading to lipid peroxidation as well as protein and DNA oxidation, with detrimental effects (6). Moreover, the epigenetic effects of alcohol have also been studied, with DNA methylation and histone modification, further adding to the complex aetiology of alcohol-related damage (7).

The risk of damage from alcohol exposure is highest during the first trimester, especially during gastrulation and folding. However, alcohol exposure can impact foetal development at any point in the pregnancy (8).

DIAGNOSIS & CLASSIFICATION

Diagnosis of FASD can be challenging, given the variety of the phenotype. The basic diagnosis is made upon a positive history of prenatal alcohol exposure and the presence of severe impairment in at least three of the ten neurodevelopmental domains, listed below (9):

- Brain structure
- Motor skills
- Cognition
- Language skills
- Academic achievement
- Memory
- Attention
- Executive function, including impulse control and hyperactivity
- Affect regulation
- Adaptive behaviour, including social communication and skills

Moreover, there are four distinct sub-types of the spectrum (2):

- Foetal alcohol syndrome (FAS)
- Partial foetal alcohol syndrome
- Alcohol-related neurodevelopmental defects
- Alcohol-related birth defects

Foetal alcohol syndrome is the most severe form of FASD, with significant deficits in motor skills; cognition; memory and behaviour. Growth retardation is also a common feature. 'Partial foetal alcohol syndrome' is a diagnosis reserved for children with a confirmed history of alcohol exposure but do not display all the features of FAS and is typically milder. 'Alcohol-related neurodevelopmental defects' refers to children with behavioural and learning issues associated with prenatal alcohol exposure. Finally, 'alcohol-related birth defects' is when a neonate is born with organ damage related to alcohol (10). Figure 1 provides the diagnostic algorithm by which FASD can be accurately diagnosed.

Sentinel facial features refer to the characteristic appearance that individuals suffering from FASD possess (1). These include:

- Short palpebral fissures
- Smooth philtrum
- Thin upper lip
- Epicanthal folds
- Flat nasal bridge
- Micrognathia

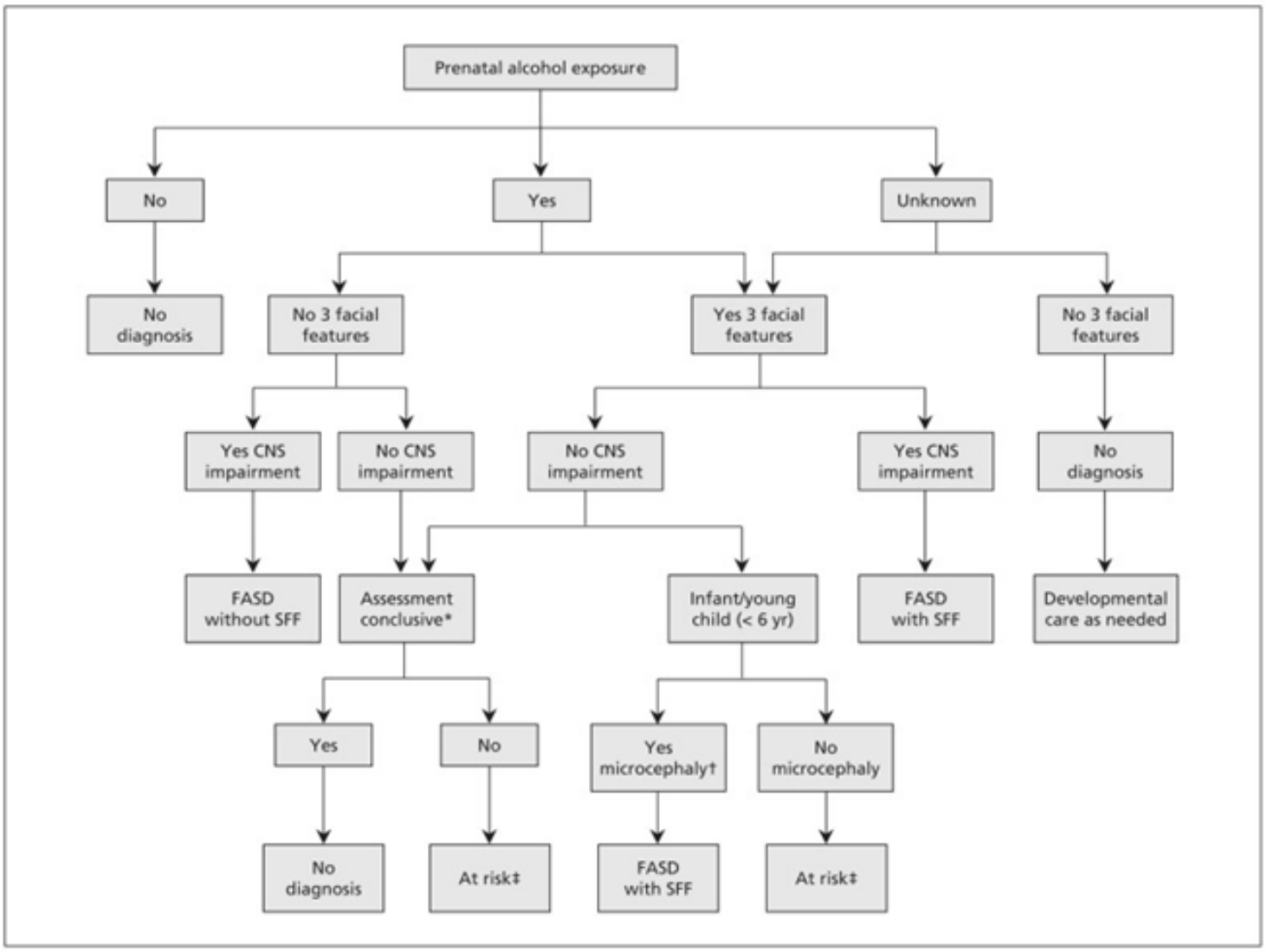

Figure 1: *FASD Diagnostic Algorithm. CNS involvement refers to impairment in 3 or more developmental domains. SFF – sentinel facial features. Obtained from: (23)*

PRENATAL DETECTION WITH ULTRASOUND

Ultrasound can lead to an early diagnosis of FASD in utero, allowing for more comprehensive interventions to be carried out. Detection may be subtle, especially in mild cases. However, since expectant mothers routinely undergo such ultrasound scans as part of antenatal care, it may be useful to implement FASD screening during such scans, especially in high-risk populations. Two questionnaires are routinely used to identify mothers at risk of drinking, namely the TWEAK tool (tolerance, worried, eye-opener, amnesia, cut-down) and the AUDIT tool (Alcohol Use Disorders Identification Test), (11,12).

A number of sonographic biomarkers visible during the second and third trimesters can be affected with prenatal alcohol exposure. These involve measurements of the conceptus, which are then compared to the normal reference measurements, and include the following (11,12):

- Transverse cerebellar diameter (TCD);
- Outer orbital diameter (OOD);
- Occipital-frontal diameter;
- Fronto-thalamic distance (FTD) – the distance between the internal aspect of the frontal bone and the posterior aspect of the thalami;
- Interorbital distance (IOD);
- Caval-calvarial distance (CCD) – the distance between the internal aspect of the frontal bone and the posterior margin of the septum pellucidum;
- Orbital diameter (OD);
- Reduced biparietal diameter and femur length – reflecting intrauterine growth restriction.

Once detected on scanning, efforts should be made to stop any further alcohol intake by the mother. Prenatal nutritional changes may help mitigate some of the effects of alcohol. In rodent models, a diet rich in antioxidants (i.e., vitamin A, vitamin E and omega 3 fatty acids) has been shown to lead to offspring with less oxidative stress and behavioural issues (7). However, further research must first be performed in order to conclusively apply this to humans. The same study also found that exercise in the affected individual may improve learning, coordination and memory (7).

Upon birth and clinical confirmation of the diagnosis, initiation of early intervention services may occur. These typically include special education; frequent check-ups and behavioural therapies. If warranted, parent training and/or relocation of the child into a more stable household may be done for the child's best interest. No treatment or cure is currently available for FASD; however the symptomology may be treated, using a combination of neuroleptics, stimulants and anxiolytics (13).

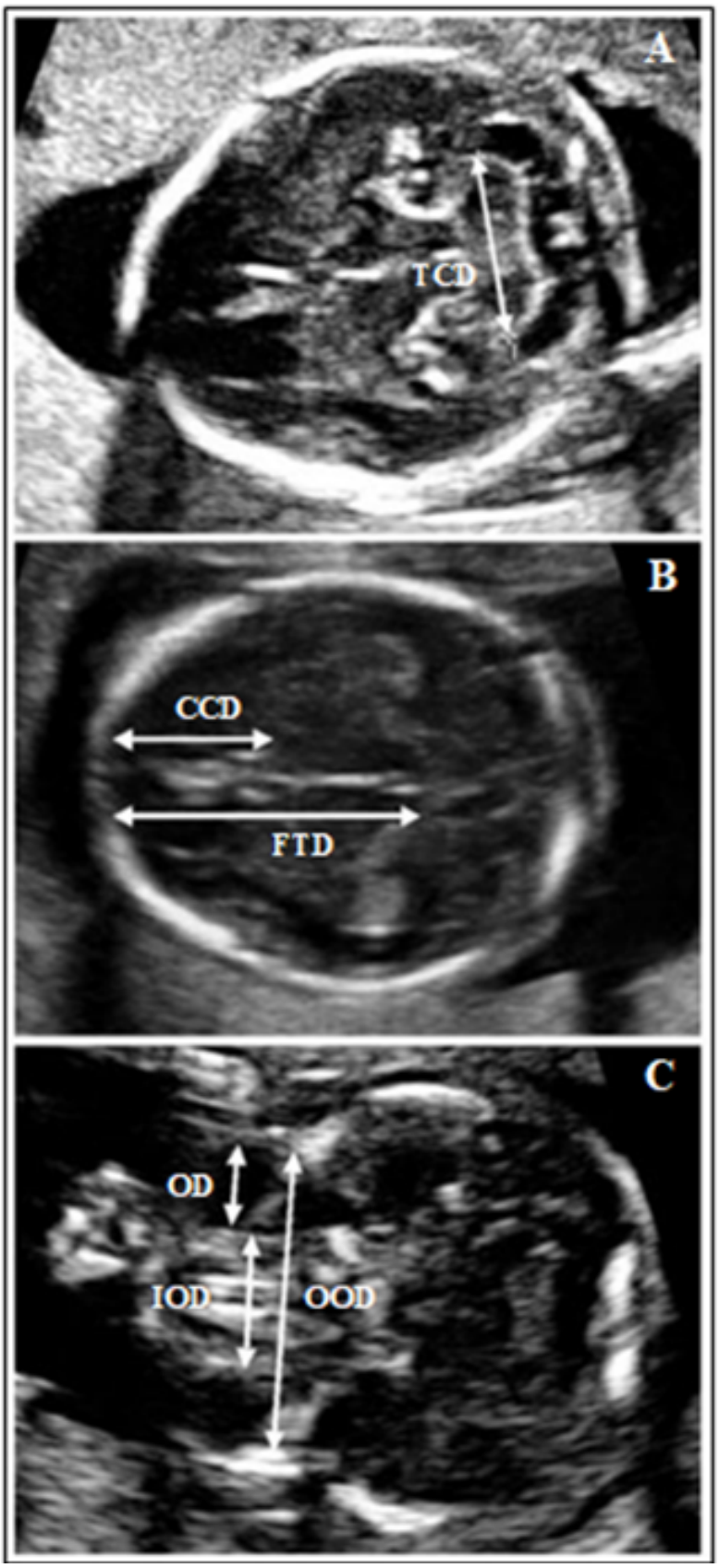

***Figure 2**: Prenatal ultrasound showing axial view of the calvaria with markers annotated. Obtained from: (11)*

NEUROIMAGING IN FASD

Although the diagnosis of FASD is mainly clinical, using the history and phenotype, radiological imaging in the context of FASD may aid in confirming the diagnosis (since some cases may be non-dysmorphic); assessing severity; evaluating associated comorbidities and deciding on appropriate management (14).

Imaging of the affected individual's brain is primarily done using Magnetic Resonance Imaging (MRI), allowing for excellent soft tissue definition without any exposure of infants and children to ionising radiation, as opposed to Computed Tomography (CT).

MRI studies typically reveal a generalised reduction of cerebral volume (i.e., microcephaly). Several studies have also noted that specific sites are especially affected by prenatal alcohol exposure, namely the corpus callosum; the frontal and parietal lobes; hippocampus; caudate nucleus and the cerebellar vermis (15). This may indicate that certain regions of the brain are more susceptible to alcohol-related damage (14). These changes are what lead to the neurocognitive impairments, and their extent depends on which brain regions are most affected. For example, anomalies in the frontoparietal lobes are consistent with the difficulties in planning and spatial memory commonly seen in FASD cases.

In severe cases, white matter hypoplasia may be observed on MRI, especially in the perisylvian and parietal regions on the brain. Such defects are best demonstrated with diffusion tensor imaging, a novel MRI technique which shows the white matter axonal pathways. Conversely, an increase in the grey matter density may be seen in the inferior parietal and superior temporal lobes (14).

In fact, through animal models and post-mortems done on confirmed FASD cases, it has been observed that dendritic arborisation is disrupted, with the resulting neurons having dendrites which are short and lack branches. Furthermore, while alcohol seems to inhibit all stages of brain development, the exception is neuronal apoptosis, which is increased due to the reduced stimulation by neurotrophins (16). Finally, alcohol suppresses the excitatory neurotransmitter glutamate and enhances the release of GABA, which exerts an inhibitory effect (17).

Other imaging modalities used to study the living brain include functional MRI (fMRI), which provides a better idea of how the individuals' brain processes information. This is done by measuring blood flow to the different parts of the brain following control questions. A recent study managed to demonstrate the working memory deficits in FASD patients on fMRI (18). Positron emission tomography (PET-CT) scanning provides insights into the metabolism of the brain; however, both fMRI and PET-CT scanning are typically reserved for research into FASD. Interestingly, multiple anomalies are found more frequently in older individuals (19).

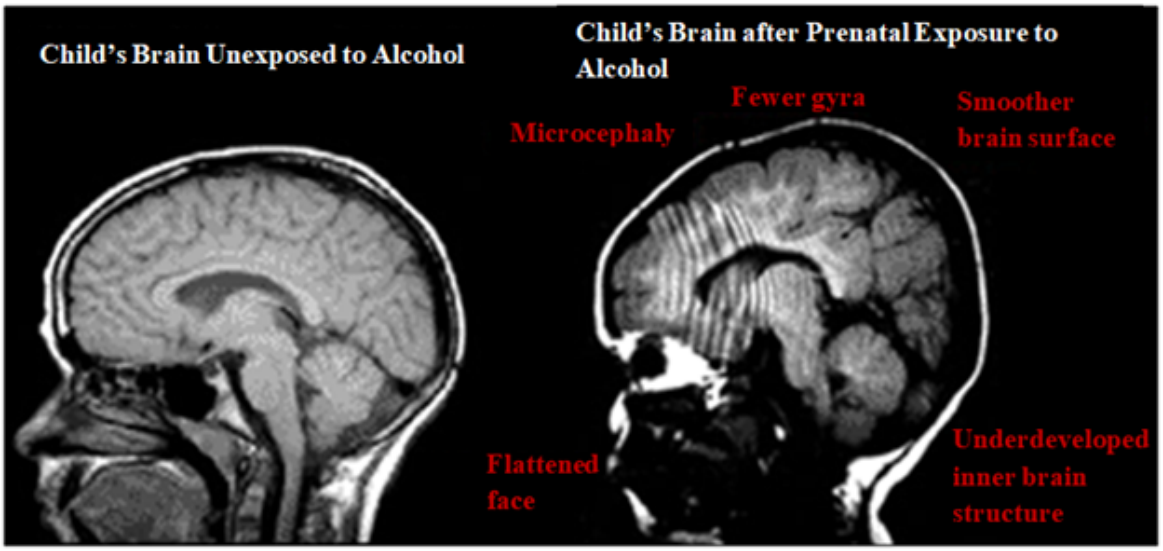

Figure 3: *Sagittal T1-weighted MRI of a healthy child and that of a child diagnosed with FASD. Obtained from: (22)*

OTHER ORGAN SYSTEMS AND IMAGING

Whilst the brain is the main affected organ, a number of associated features may be present in this disorder. These may be examined using several imaging modalities, depending on the site.

Acetaldehyde is a product of ethanol metabolism, which when in excess inhibits the formation of retinoic acid from retinol. Retinoic acid plays a key role in the proliferation and differentiation of cardiac progenitor cells, resulting in cardiac abnormalities in patients with FASD. Mainly, these include atrial or ventricular septal defects and atrioventricular valve defects (20). Such defects can be adequately visualised using echocardiography or cardiac CT when suspected.

Musculoskeletal defects are also common in FASD, and severe prenatal alcohol exposure may give rise to foetal alcohol myopathy; growth restriction and abnormalities in the neuromuscular junctions, which may possibly impair locomotion and cause hypotonia. Furthermore, the metabolism of glucose by skeletal muscle may be altered, causing glucose intolerance and insulin resistance. This in part contributes to the increased risk for individuals with FASD to develop type 2 diabetes (21). Other skeletal problems which may be encountered include radio-ulnar synostoses, pectus excavatum and congenital scoliosis (1). Ultrasound and MRI may be used to examine and skeletal muscle defects, while CT and planar x-rays may be used to evaluate any bony anomalies.

CONCLUSION

FASD is a complex and multifaceted disorder involving multiple organs. Radiological imaging, both antenatally and postnatally may assist in the diagnosis and management of the disorder, with the aim of ameliorating the individual's quality-of-life.

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Robert Pisani
2nd Year Medical Student