Fetal Alcohol Spectrum Disorder

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ABSTRACT

Background: Maternal alcohol use during pregnancy leads to fetal alcohol spectrum disorder (FASD) in their children. FASD is characterized by typical facial features, growth retardation, intellectual dysfunction and behavioral problems. Justification: Alcohol is neurotoxic to the brain during the developmental stage. Behavioral problems in children with FASD start at an early age and progress to adulthood. It is an important preventable cause of intellectual dysfunction and behavioral problems. This article reviews current prevalence, clinical features, pathogenesis and differential diagnosis of FASD. It also highlights the need for physicians to be aware of this condition. Search strategy: Articles were searched on the internet using ‘fetal alcohol syndrome’, ‘fetal alcohol spectrum disorders’, ‘women and alcohol’. Following links were used to locate journals; EBSCO, OVID, Science Direct, PubMed and NIAAA. Main conclusions: Alcohol consumption during pregnancy can lead to a spectrum of deficits. Though physical features are essential to make the diagnosis of FAS, it is important to note that neurocognitive and behavioural deficits can be present in the absence of physical features (alcohol related neurodevelopmental disorder or ARND). Because there is no known safe amount of alcohol consumption during pregnancy, abstinence from alcohol for women who are pregnant or planning a pregnancy must be strongly advised.

Key words: Alcohol related neurodevelopmental disorder, Fetal alcohol syndrome.

INTRODUCTION

Alcoholic beverages and the problems they engender have been familiar fixtures in human societies since the beginning of recorded history. Alcohol related problems have been mainly male-focused(1). Recent research has however established that even though fewer women drink alcohol than men, the biomedial and other consequences of women’s alcohol use may be greater than that of men for the same amount of alcohol used(2). Alcohol is known to cause many ill effects. It can affect the developing fetus, resulting in a set of birth defects called fetal alcohol syndrome (FAS)(3,4). The adverse effects of alcohol on the developing fetus represent a spectrum of structural anomalies, behavioral defects and neurocognitive disabilities, most accurately termed fetal alcohol spectrum disorders (FASD). Currently it is known that FAS is not a single entity but a spectrum disorder (fetal alcohol spectrum disorder or FASD) and FAS represents one end of the spectrum, representing the most severe form of clinical presentation.

WOMEN AND ALCOHOL

In general population studies throughout the world, as compared to women, men are more often drinkers, consume more alcohol, and cause more problems by doing so(1). However, in the US, approximately 60 percent of adult women drink alcohol, at least occasionally(5). Rates of drinking and heavy drinking tend to be highest among young women and decline steadily with age. In the United States, England, and Canada, 20%-32% of pregnant women drink, and in some European countries the rate is
higher, exceeding 50%(6). In a study in the Western Cape Province of South Africa, 34% of urban women and 46%-51% of rural women drank during pregnancy. Their drinking pattern was characterized by heavy binge drinking on weekends, with no reduction of use during pregnancy(6). Maternal drinking during pregnancy varies among and within populations throughout the world(7). Both animal and human studies have reported that binge drinking is more harmful to the developing brain than the regular pattern(8). According to the “Gender, Alcohol and Culture: an International Study” (GENACIS) in India, 5.8% of all female respondents reported drinking alcohol at least once in the last 12 months(9). In India, alcohol use is more prevalent in tribal women, tea plantation workers, women of lower socioeconomic status, commercial sex workers (women who sell sex for livelihood) and to a limited upper crust of the rich and is not favored by women from the middle or upper socioeconomic classes. In these high risk groups, the prevalence is around 28-48%(10).

**DEFINITION OF FASD**

The National Organization on FAS (NOFAS 2004), US, defined fetal alcohol spectrum disorders as the range of effects that can occur in a person whose mother drank alcohol during pregnancy, including physical, mental, behavioral, and learning disabilities, with possible lifelong implications. As this definition implies, multiple diagnostic categories - e.g. fetal alcohol syndrome (FAS), alcohol-related neurodevelopment disorder (ARND), and alcohol-related birth defects (ARBD) are subsumed under the term FASD. When signs of brain damage appear following fetal alcohol exposure in the absence of other indications of FAS, the condition is termed “alcohol related neurodevelopmental disorder” (ARND)(11).

**EVOLUTION OF THE CONCEPT OF FAS**

Some of the earliest literature available on maternal alcohol consumption and adverse birth defects dates back to the period of Aristotle(12). It has also been mentioned in the Bible(13). Later, it was mentioned in England in the 1700s where several physician groups described children of alcoholics as “weak, feeble, and distempered”(14) and “born weak and silly . . . shriveled and old”. The first good description on adverse effects of alcohol on birth was by Sullivan in 1899 where he described the offspring of alcoholic women imprisoned in England(15). He concluded that these women produced children characterized by a pattern of birth defects of increasing severity and higher rates of miscarriage; there was a tendency for healthier infants to be born when gestation occurred in prison (thus indicating abstinence as prevention). These children were not productive members of society as they aged, and male alcoholism was not a factor in producing the abnormalities. It was 70 years later that Lemoine of France in 1968 reintroduced the apparently ignored, unrecognized, or misunderstood concept of adverse outcomes resulting from fetal alcohol exposure. He studied more than 100 children of women who drank heavily and documented many of the physical and behavioral patterns among those children but did not present any definitive diagnostic criteria for diagnosing FAS or FASD. Later, in 1973, Jones, Smith, and colleagues were the first to describe in detail the consistent pattern of malformations among children of mothers with significant prenatal alcohol intake and to provide diagnostic criteria for the condition they termed FAS.

**EPIDEMIOLOGY**

There are three kinds of epidemiological studies in FASD

- Passive surveillance systems
- Clinic-based studies; and
- Active case ascertainment approaches.

The passive system, which use existing record collections in a particular geographical catchment area (e.g., a town or state), yields much lower numbers than those from other methods. Active case ascertainment studies are unique in that they actively seek, find, and recruit children who may have FAS within the population under study, they generally yield the highest number of cases and rates of FAS for a particular population. Clinic based studies are generally conducted in prenatal clinics of large hospitals where researchers can collect data from mothers as they pass through the various months of
their pregnancies. The prevalence of FAS varies from region to region. Thus, the overall prevalence of FAS in the US from passive surveillance data is likely to be between 0.5 and 2.0 per 1,000 births. Active ascertainment methods suggest that FAS, ARBD, and ARND may affect 10 per 1,000 births (or 1 percent) or more, depending on the specific diagnostic methods and criteria used(16). The condition is better identified when children are examined at an early age. For example, a comprehensive study of 818 first-grade students in 12 of the 13 elementary schools in a South African community revealed the rate of 68.0-89.2 cases per 1000 births among children ages 5 to 9(17). Table I provides prevalence data of FASD in a few countries.

There is a trend towards an increase in the incidence and prevalence of FAS, according to the Birth Defects Monitoring Program of the Centers for Disease Control and Prevention, 1979-1992(21). No prevalence data is available from Asian population.

**CLINICAL FEATURES**

FAS denotes a specific pattern of malformations also called as triad of FAS, with a confirmed history of maternal alcohol abuse during pregnancy, they are prenatal onset of growth deficiency (length and/or weight) that persists postnatally, a specific pattern of minor anomalies of the face, and neurocognitive deficits(22).

**Facial features:** Three facial features (reduced palpebral fissure length/inner canthal distance ratio, smooth philtrum, and thin upper lip) are the cluster of features that differentiate individuals with and without FAS with 100% accuracy(23). Other facial features which can be present are short upturned nose, depressed nasal bridge, hypoplastic maxilla, ear anomalies (low set ears, malformed ears, “Railroad track” ear), palmar crease anomalies and micrognathia. Other organ systems may also demonstrate malformations in individuals exposed to alcohol prenatally(4,22).

**Cardiac:** Atrial septal defects, aberrant great vessels, ventricular septal defects, tetralogy of Fallot.

**Skeletal:** Radioulnar synostosis, Klippel–Feil Syndrome, hemivertebrae, camptodactyly, scoliosis, hypoplastic nails, clinodactyly, shortened fifth digits, pectus excavatum and carinatum.

**Renal:** Aplastic kidneys, dysplastic kidneys, ureteral duplications, hypoplastic kidneys, hydronephrosis, horseshoe kidneys.

**Ocular:** Strabismus, refractive problems secondary to small globes, retinal vascular anomalies.

**Auditory:** Conductive hearing loss, neurosensory hearing loss.

**Other:** Numerous malformations have been found in some patients with FASD. The etiologic specificity of most of these anomalies to alcohol teratogenesis remains uncertain.

**Neurocognitive deficits:** Neuropsychological impairments in FASD include lower IQ, achievement deficits, learning problems(24), deficits in memory, attention, visual-spatial abilities, declarative learning, processing speed(25) as well as language and motor delays(26). Children and adults with FASD also have deficits in executive functioning in the areas of cognitive flexibility, inhibition, planning, strategy use, verbal reasoning, set-shifting, working memory, and fluency(25). These children appear to be at increased risk for psychiatric disorders, trouble with the law, alcohol and other drug abuse, and other maladaptive behaviors. They are more likely than non-alcohol-exposed children to be rated as hyperactive, disruptive, impulsive, or delinquent. They also suffer from poor socialization and communication skills and are less likely to be living independently. Among FASD children, 48% of them have ADHD as comorbidity(27).

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence/1,000 births</th>
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<tbody>
<tr>
<td>US(16)*</td>
<td>10.0</td>
</tr>
<tr>
<td>South Africa(17)*</td>
<td>68.0-89.2</td>
</tr>
<tr>
<td>Russia(18)*</td>
<td>141.0</td>
</tr>
<tr>
<td>Canada(19)*</td>
<td>0.5</td>
</tr>
<tr>
<td>Italy(20)*</td>
<td>120.0</td>
</tr>
</tbody>
</table>

*Active case ascertainment; # Passive surveillance
PATHOGENESIS

Not every child whose mother drank alcohol during pregnancy develops FAS or ARND. Moreover, the degrees to which people with FAS or ARND are impaired differs from person to person. Factors contributing to this variation include maternal drinking pattern, difference in maternal metabolism of alcohol, difference in genetic susceptibility, timing of the alcohol consumption during pregnancy, and variations in the vulnerability of different brain regions.

In developing organisms, a readily observable condition that results from ethanol exposure is excessive cell death. It appears that ethanol triggers apoptotic neurodegeneration by a dual mechanism (blockade of NMDA glutamate receptors and excessive activation of GABA receptors). With respect to the typical facial features of FAS and the CNS abnormalities that develop concurrently, cellular loss at the rostral boundary of the preclosure forebrain and of the corresponding cell population that makes up the immediately postclosure telencephalic midline appears to be a key mechanism. This population of cells is now termed the anterior neural ridge (ANR) and is known to act during gastrulation and early postgastrulation stages as an organizer for the prosencephalon. Of particular note with respect to FAS is that the epithelium that lines the nasal cavities (i.e., that associated with the medial nasal prominences of the developing face), as well as the commissural plate of the telencephalon form from this progenitor population, a population that is particularly vulnerable to ethanol-induced cell death. In the presence of the typical FAS face, it is expected that this results from early loss of the commissural plate. In addition to the ANR, other cell populations of the embryonic face and brain are sensitive to ethanol-induced cell death. These populations include the neural crest, epibranchial placodes, and subpopulations of the otic placodes or vesicles. Depending on whether exposure occurs during the early, mid or late phase of synaptogenesis, ethanol triggers different patterns of neuronal deletion, each pattern having the potential to give rise to its own unique constellation of neurobehavioral disturbances. This mechanism has the potential to contribute to a wide spectrum of neuropsychiatric disorders. The CNS (neurobehavioral) effects are very likely triggered in the third trimester by a transmitter disruption mechanism, a mechanism that is only operative when synaptic connections are being established and which, therefore, could not possibly be operative in the first trimester.

IMAGING

Magnetic Resonance Imaging (MRI) of the affected children shows decrease in the over-all size of the brain of FAS children. The main areas affected in brain are the basal ganglia, corpus callosum, cerebellum, and hippocampus. Single Photon Emission Computed Tomography (SPECT) imaging in FAS children exhibited similar metabolic activity in both hemispheres of the brain which supports the findings of verbal or language deficits in FAS children. A functional MRI (fMRI) study revealed activation in an area called the dorsolateral prefrontal cortex in the FAS subjects but not in control subjects. This suggests working memory deficit.

COURSE AND OUTCOME

Many children with FASD show continued behavioral problems, psychiatric comorbidity and drug related problems. A study done by Streissguth assessed life outcomes of the Seattle cohort (all the FAS patients evaluated in FAS Diagnostic and Prevention Network, University of Washington, Seattle) during adolescence and adulthood using a Life History Interview with knowledgeable informants. These investigators found that prevalence rates of life-term adverse outcomes in this cohort were high, with 61% having had disrupted school experiences, 60% trouble with the law, 50% confinement, 49% inappropriate sexual behaviors, and 35% alcohol and drug problems. Those children receiving the diagnosis of FAS or FAE (fetal alcohol effects) at an earlier age and living in a stable and good home environment were associated with better life outcomes. Thus, these results suggest that postnatal environment directly and indirectly (through deficient cognitive functioning) influences behavioral outcomes.

ASSESSMENTS

- Assessments of physical deficits
IQ measures, achievement testing, and specific screening for learning disabilities

Attention, verbal learning and recall, verbal memory, auditory memory, spatial memory, auditory processing and verbal processing

Executive functioning abilities

Functional issues (cognition-based difficulties and emotion-related difficulties) related to deficits in executive functioning.

INTERVENTIONS

Emphasis should be on primary prevention strategies. For the children who are already exposed to alcohol during pregnancy, treatment will be identifying the above mentioned problem areas and handling them appropriately. Some of the interventions include the following(36) (i) environmental structuring (functional routines and structured teaching); (ii) visual structuring; (iii) specific task structuring; (iv) cognitive control therapy (progressive skill-building intervention process); and (v) recognize and regard the hopes, wishes, and desires of families to hold for their children with FAS.

If any medical, neurological or psychiatric problems are identified during the course of assessment, than handling those according to whatever current guidelines are available for that particular disorder. Care should be taken that as already there is damage to brain, medications have to be started at low doses and built up slowly. Animal studies have shown that choline supplementation can alter brain development following a developmental insult(37), like wise studies on medical management specific to FASD are coming up but are still at infantile stage.

WHY IS THIS CONDITION IMPORTANT?

FASD is the one of the preventable causes of intellectual dysfunction and behavioral problems. Alcohol prevalence is on the increasing trend among women. Most women who come to either obstetrics and gynecology department, pediatric and medicine department will not spontaneously reveal the history of alcohol consumption because of stigma associated with women and alcohol(38). So efforts should be made to elicit substance use history in women, especially in those who are in the reproductive age and mothers of children who have intellectual and behavioral problems. As there is no known safe amount of alcohol consumption during pregnancy, the American Academy of Pediatrics recommends abstinence from alcohol for women who are pregnant or who are planning a pregnancy.

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REFERENCES


