Fetal alcohol spectrum disorder (FASD) is a term used to describe the spectrum of conditions associated with prenatal alcohol exposure. These are characterized by facial dysmorphia, growth deficits and central nervous system abnormalities. FASDs are the most common preventable cause of intellectual disability in the United States and have high financial costs. Therefore, efforts at prevention are paramount. When an individual with an FASD goes undiagnosed and when appropriate interventions are not instituted, secondary disabilities such as substance abuse, school dropout, and criminal involvement are common with corresponding suffering endured by both the affected individual and the family.

The diagnostic process opens up access to existing tools and resources, including the new American Academy of Pediatrics (AAP) FASD algorithm for the evaluation of FASDs, the new AAP FASD toolkit and evidence-based interventions specific to FASDs. Pediatric and adolescent clinicians are challenged to participate in the continuum of care from FASD prevention to identification, diagnosis, and management, including provision of supportive services for families in order for clinicians to make a difference in this 100% preventable disorder.

Definition of Terms

The term Fetal alcohol spectrum disorder (FASD) describes the spectrum of effects that can be observed in individuals who were exposed to alcohol in utero. As demonstrated in human and animal studies, effects of prenatal alcohol exposure include facial abnormalities, growth deficits, and central nervous system abnormalities. The exposure to alcohol affects the individual's development, learning, and cognition, producing characteristic ways of thinking and behaving. Developmental and behavioral problems in individuals with an FASD reflect alcohol's effect on the brain, and deficits can range from mild cognitive deficits to profound intellectual disability, from subtle effects on memory, executive function, and adaptive behavior to severe behavioral problems that result from poor self-regulation. At one extreme end of the spectrum of disorders arising from prenatal alcohol exposure is fetal alcohol syndrome (FAS). FAS is characterized by facial, growth, and CNS abnormalities in the background of alcohol exposure (Table 1). FAS is diagnosed by the triad of (1) characteristic facial features: short palpebral fissures or lateral eye openings (normograms for palpebral fissures are available from various sources), smooth philtrum, and thin vermilion border of upper lip (rank 4–5 on the University of Washington Lip–Philtrum Guide) (Fig. 1), (2) growth deficiency with a height or weight at or below the tenth percentile at any point of the child's life, and (3) evidence of central nervous system abnormality, which is structural, neurological, or functional (e.g., microcephaly, seizures, cognitive or learning deficits, and behavioral dysregulation), etc. (Fig. 2). This is a narrow set of criteria that may miss a number of patients who have other physical and neurocognitive effects from in utero alcohol exposure but do not have the classic triad essential for the diagnosis of FAS. In fact, children who experienced prenatal alcohol exposure but do not meet full criteria for FAS often have similar cognitive and behavioral characteristics.

Other disorders that have been identified within the spectrum include Alcohol-Related Neurodevelopmental Disorder (ARND), Partial Fetal Alcohol syndrome (PFAS), and Alcohol-Related Birth Defects (ARBD). ARND is characterized by evidence of CNS neurodevelopmental abnormalities, including at least one of...
the following: structural brain abnormalities, such as microcephaly or abnormalities on brain imaging; neurologic hard and soft signs such as deficits in fine motor skills; neurosensory hearing loss; poor tandem gait; and poor eye–hand coordination. The term Neurodevelopmental Disorder Associated with Prenatal Alcohol Exposure (ND-PAE) is the new terminology that has been proposed in the Diagnostic and Statistical Manual (DSM)-V and the criteria for the ND-PAE diagnosis are listed in the appendix of DSM-V under conditions for further study and under Other Specified Neurodevelopmental Disorder 315.8. The proposed criteria include that the patient was “exposed to alcohol at any time during gestation, including prior to pregnancy recognition and the exposure level was more than minimal” along with presence of neurocognitive impairment, impairment in self-regulation, and impairment in adaptive functioning. Partial FAS (PFAS) is diagnosed when there is confirmed alcohol exposure in utero and evidence of a characteristic pattern of facial anomalies as well as either growth retardation, CNS abnormalities, or cognitive abnormalities that are characteristic of full blown FAS. ARBDs are diagnosed when there is confirmed exposure to alcohol in utero and birth defects associated with alcohol exposure. It is now known that relying on facial features alone for the identification of children with an FASD underrepresents the population of all alcohol-exposed pregnancies and that severity of atypical facial features may not directly correlate with severity of neurobehavioral effects. A study by Mattson et al. showed that in children with history of heavy prenatal exposure to alcohol, similar levels and patterns of cognitive deficits were seen regardless of meeting facial criteria for FAS. In fact, it is now well known that the most devastating effect of alcohol exposure in utero is its impact on the brain.

**Epidemiology**

Prenatal alcohol exposure is the most common non-hereditary cause of intellectual disability in the United States. FAS has a prevalence rate of 0.2–1.5 cases per 1000 births across various populations in the United States.

<table>
<thead>
<tr>
<th>TABLE 1. Criteria for FAS Diagnosis&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>A. Requires all three of the following findings:</td>
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<tr>
<td>1. Documentation of all three facial abnormalities (smooth philtrum, thin vermilion, and small palpebral fissures).</td>
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<td>2. Documentation of growth deficits.</td>
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<tr>
<td>3. Documentation of CNS abnormality.</td>
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<tr>
<td>B. Facial dysmorphia: Based on racial norms, individual exhibits all three characteristic facial features:</td>
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<tr>
<td>1. Smooth philtrum (University of Washington Lip–Philtrum Guide rank 4 or 5)</td>
</tr>
<tr>
<td>2. Thin vermilion border (University of Washington Lip–Philtrum Guide rank 4 or 5)</td>
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<tr>
<td>3. Small palpebral fissures (at or below tenth percentile)</td>
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<td>C. Growth problems: Confirmed prenatal or postnatal height or weight, or both, at or below the tenth percentile, documented at any one point in time (adjusted for age, sex, gestational age, and race or ethnicity).</td>
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<td>D. Central nervous system abnormalities:</td>
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<td>Structural Head circumference (OFC) at or below the tenth percentile adjusted for age and sex.</td>
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<td>Clinically significant brain abnormalities observable through imaging.</td>
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<td>Neurological Neurological problems not due to a postnatal insult or fever or other soft neurological signs outside normal limits. Functional Performance substantially below that expected for an individual’s age, schooling, or circumstances, as evidenced by the following:</td>
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<td>Global cognitive or intellectual deficits representing multiple domains of deficit (or significant developmental delay in younger children) with performance below the third percentile (2 standard deviations below the mean for standardized testing) OR Functional deficits below the 16th percentile (1 standard deviation below the mean for standardized testing) in at least three of the following domains:</td>
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<td>Cognitive or developmental deficits or discrepancies</td>
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<td>Executive functioning deficits</td>
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<td>Motor functioning delays</td>
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<td>Problems with attention or hyperactivity</td>
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<td>Poor social skills</td>
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<td>Other (e.g., sensory problems, pragmatic language problems, or memory deficits)</td>
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<td>E. Maternal alcohol exposure</td>
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<tr>
<td>1. Confirmed prenatal alcohol exposure</td>
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<td>2. Unknown prenatal alcohol exposure</td>
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</tbody>
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<sup>a</sup>Adapted with permission from Bertrand et al.5
Lip-Philtrum Guides 1 (A) and 2 (B) are used to rank upper lip thinness and philtrum smoothness. The philtrum is the vertical groove between the nose and upper lip. The guides reflect the full range of lip thickness and philtrum depth with Rank 3 representing the population mean. Ranks 4 and 5 reflect the thin lip and smooth philtrum that characterize the FAS facial phenotype. Guide 1 is used for Caucasians and all other races with lips like Caucasians. Guide 2 is used for African Americans and all other races with lips as full as African Americans. Copyright 2014, Susan Astley PhD, University of Washington. Copyright of the Picture(s) is not being released to the authors or publisher, only permission to incorporate it as described here.
Some researchers have estimated that the other disorders in the spectrum may be as high as to 9–10 per 1000 live births. Each year, about 40,000 babies are born in the United States with effects of prenatal alcohol exposure. Certain populations have higher reported rates of prevalence of FASDs. American Indians/Alaskan Natives have prevalence rates as high as 3–5 cases of FAS per 1000. FAS is highly prevalent among children in foster care, with reported rates of 15 cases per 1000 children. Burd et al. reported that among children diagnosed with an FASD, 70% are currently in foster care or went through the foster care system. Rates of FAS are even higher in the juvenile justice system and one study found that more than 200 per 1000 individuals (> 20%) have either FAS or another disorder in the spectrum. Countries that have high rates of alcohol consumption are also reported to have higher rates of FAS. For example, in Russia, the prevalence rate of FAS in orphanages is approximately 15 cases per 1000 children. In South Africa, the production and sale of alcohol is a vital part of the economy. It has the highest reported birth prevalence of FAS up to 41–46 cases per 1000 live births. Determining the true prevalence of FAS can be difficult, given that some primary care clinicians may have difficulty distinguishing the facial and neurodevelopmental features and lack the knowledge to be confident to diagnose and manage FAS. In addition, studies in the United States often use record review methodology. The direct evaluation method may be more accurate and a study in Italy reported rates of 4–7 cases per 1000 school children using a direct evaluation method for FAS.

**Costs to Individual, Family, and Society**

It has been estimated that the cost to raise one child with FAS is $2 million or more over a lifetime, not including costs related to incarceration, if applicable. Individuals with more severe challenges, which include profound intellectual disability, may incur even greater costs. The estimated annual costs related to FAS in the United States were $4 billion in 1998. The estimates for FAS alone are estimated to be from 1 to 5 million US dollars per child, and other indirect costs to society may also include the difficult challenges that are faced by families, the reduced quality of life of the affected individuals and the loss of the individual’s productivity. When an individual with an FASD goes undiagnosed and when appropriate interventions are not instituted, secondary disabilities (problems arising from the primary neurodevelopment disability) are common. Secondary disabilities include mental health problems (90%), substance abuse (30%), school problems (60%), criminal involvement (50%), dependent living (80%), and cognitive deficits (25%) in affected individuals. The neurobehavioral effects of alcohol exposure often result in significant developmental and behavioral challenges. Effects of the prenatal exposure can be devastating to both the child and his or her family. Given the significant effects on the child and his/her functioning, families often report high levels of stress. The affected individual may have problems in the home, playground, school, and workplace, and the family caring for the child often has to navigate the system of care without a diagnosis, not knowing how to...
parent their child and facing frustrations that arise from the child’s neurodevelopmental disability.

**Pathophysiology**

When a woman consumes alcohol, the ethanol contained in the drink is absorbed in her stomach. The rate of absorption depends on factors such as stomach contents and the rate at which the alcoholic beverage is consumed. Peak blood alcohol is attained an hour after intake. In a pregnant woman, the capillaries that contain maternal blood and those containing fetal blood are separated only by a very thin barrier in the placenta. This enables exchange of oxygen and nutrients from the mother to the fetus and carbon dioxide and wastes from the fetus to the mother. Although the placenta is a selective barrier, it does not discriminate among certain substances such as drugs and viruses, and alcohol easily diffuses from the maternal blood into fetal blood. Therefore, when a mother drinks alcohol, alcohol freely crosses the placenta and the embryo or fetus is exposed to the same blood alcohol level as the mother. Unfortunately, the fetal liver and other organs are underdeveloped and cannot detoxify the alcohol before it affects developing cells, tissues, and organs.

The facial features of FAS are replicable in a mouse model that corresponds to the third and fourth week of gestation. The third to eight week of gestation (embryonic period) is a critical time when alcohol may affect the development various organs of the body including the eyes, ears, heart, palate, teeth, limbs, and external genitalia. However, there is continued development of the various organs throughout pregnancy. For example, the central nervous system is developing the entire 9 months and is vulnerable to the effect of alcohol throughout gestation. Prenatal alcohol exposure during the critical or sensitive periods of development may result in structural or functional abnormalities common in FAS or FASDs.

What determines how alcohol can affect an organism in utero? Dose, pattern of consumption, timing of exposure, genetics, and metabolism are all important considerations. The greater the amount of absolute alcohol consumed, the greater the risk for FAS. In 2005, the US Surgeon General advised that there is no known safe amount of alcohol during pregnancy. This advice was based on numerous scientific articles on the effect of alcohol on the brain. Prenatal alcohol exposure to at least one drink per day is associated with reduced birth weight and intrauterine growth retardation, spontaneous abortion, preterm delivery, and stillbirth. While dosage of absolute alcohol is important, the pattern of drinking is also a very important consideration. In general, when the pattern of drinking produces very high blood alcohol levels, the risk is greater. Binge drinking (consumption of four or more alcoholic drinks per day) confers a high degree of risk. The National Institute of Alcohol Abuse and Alcoholism defines one drink as 12 oz of beer or 5 oz of wine, 4 oz of sherry, or 1.5 oz of liquor per day. Another determinant of how alcohol may affect a fetus is the timing of exposure. First trimester exposure may cause damage to developing organs (e.g., heart, eyes, ears, kidney, and extremities). Second trimester exposure increases the risk of spontaneous abortion. Imbibing alcohol in the third trimester has the greatest impact on height/length and weight. The brain is vulnerable to the effects of alcohol in all trimesters of pregnancy. There is no period of pregnancy that appears to be safe for drinking since alcohol can cause damage at any point after conception. Another determinant of how alcohol may affect the fetus is the genetic sensitivity of the organism. For example, dizygotic twins are affected differently, and women metabolize alcohol differently. The fetus has a limited ability to metabolize alcohol and alcohol levels in the fetus are thought to be higher and present for a more prolonged, variable time when compared to maternal levels. There may also be genetic, racial, or ethnic differences in a woman's metabolism of and sensitivity to alcohol exposure. The effect of maternal nutrition may also be a factor in women who chronically abuse alcohol and suffer from undernutrition either from a poor diet or because of alcohol's interference with the absorption or processing of nutrients like folate. Women with higher maternal age, gravidity (number of previous pregnancies), or parity (number of previous births) have a higher likelihood of having a more severely affected child compared with younger women who drink similar amounts of alcohol. Studies show that the risk of having a child with FAS increases with each successive pregnancy. The rate increases from 0.5–2/1000 to 771/1000 live births for the younger sibling of a child born with fetal alcohol syndrome.

**Neurobiological Effects**

Alcohol affects the brain on a cellular and vascular level with decreased neurogenesis, disrupted neuronal migration, increased neuronal cell death, and even
altered microvascular development. Approximately 25% of children with FAS have been found to have intellectual disability. Intelligence quotient (IQ) ranges from 20 to 120 in FAS and 49–142 for the other FASDs. However, even in the absence of mental retardation, there may be adverse effects on memory, processing speed, motor control, abstract reasoning, language, nonverbal reasoning, sensory integration, and executive function. These brain-based deficits make it critical for clinicians, educators, and families to understand the link between central nervous system pathology and behavioral problems.

Alcohol is a teratogen that has direct toxic effects on cells and can interfere with the actions of endogenous growth factors such as cell adhesion molecules that are important in brain development. Alcohol can induce the formation of free radicals that can cause cell death and tissue damage, producing birth defects that involve the brain, face, heart, and genitourinary tract. Areas of the brain found to be affected in animal models include the hippocampus, cerebellum, caudate nucleus, corpus callosum, and cortex.

Evaluation and Management in the Medical Home

There is now an algorithm for evaluation of FAS and FASDs in the medical home and this is referenced in the sections on diagnosis and management. The complex medical and developmental needs of children with FASD require evaluation by various disciplines. Like any chronic condition of children with special health care needs, their needs are best served by coordinated care within the medical home. Research shows that availability of appropriate social and educational services can reduce the chance of long-term negative outcomes. Many experts agree that the development and behavior of children with an FASD need to be monitored and developmental/behavioral supports or interventions provided based on need. When there is developmental delay or risk of delay in a child under the age of 3 years, the child should be referred to early intervention services such as physical therapy, occupational therapy, and or speech pathology. In Part C of the Individuals with Disability Educational Act (IDEA), FAS is a "presumptive eligibility" diagnosis, which will allow them to obtain services based on their risk of developmental delay. Considering the profile of the child with an FASD, a unique set of parenting skills are needed and caregivers need to be educated about their child's neurobehavioral needs. Families may need parenting classes and even family counseling. Children often struggle academically, and parents, teachers, and counselors need to collaborate to create a plan that can meet the child's needs, based on educational evaluation. This may lead to an Individualized Education Plan (IEP), a written document that outlines goals and objectives for the child's progress at school. Children who do not meet the strict criteria for an IEP may still be able to receive help under the Section 504 of the Federal Rehabilitation Act of 1973 under a "504 plan" that allows for some classroom modifications to meet the child's needs. Transition needs for an adolescent with an FASD may include helping them obtain supported employment/job coach, transportation, assisted living, respite care, Social Security disability benefits, Supplemental Security Income, and/or legal advocacy.

Since prenatal alcohol exposure affects the brain, it must be understood that behaviors seen in FASDs are often related to or influenced by abnormal brain function, with inherent difficulty with problem-solving in difficult and novel situations, learning from past experiences, applying what one has learned from one setting to another, predicting cause and effect and regulating one's emotions once frustrated, overstimulated, or unduly challenged. Of course, just as one would provide glasses to those with near-sightedness or a hearing aid for a child who is hard of hearing, there should be accommodations for the specific neurobehavioral challenges found in individuals with an FASD. But children cannot be helped unless they are identified. Therefore, it is incumbent upon clinicians to identify children exposed to alcohol during pregnancy and to have these infants/children evaluated by professionals who are trained to diagnose the physical and/or neurobehavioral problems seen in FASD.

The diagnostic and identification process opens up access to existing resources that include the new American Academy of Pediatrics (AAP) FASD Toolkit (aap.org/fasd), with resources for medical and behavioral health providers, educators, and families. This toolkit also includes the AAP algorithm that can assist clinicians in the evaluation and initial management of children with fetal alcohol spectrum disorders within the medical home and resources for further study, such as the AAP Pedialink course on FASD. The FASD toolkit offers scripts that can be used when communicating with families and information on evidence-based interventions.
developed for children and families affected by FASD.\textsuperscript{42} Within the toolkit, health care professionals are challenged to participate in the continuum from FASD prevention to identification/diagnosis and to management strategies, including supportive services for families in order for clinicians to make a difference in this 100% preventable disorder.

The following articles in this issue will discuss screening and behavioral interventions for women with respect to alcohol use during pregnancy, diagnosis, and differential diagnosis of FAS and related conditions, treatment strategies, and ethical principles in FASD prevention, diagnosis, and treatment.

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References


