Fetal Alcohol Spectrum Disorders—Implications for Child Neurology, Part 2: Diagnosis and Management

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Abstract
In part 1, we discussed the mechanism of alcohol exposure, dosimetry, and the teratogenic pathways of damage to the fetus. In part 2, we review the diagnosis of fetal alcohol spectrum disorders and the developmental implications of prenatal alcohol exposure. Fetal alcohol spectrum disorders are associated with increased rates of mental retardation, seizure disorders, brain malformations, and premature mortality. The risk of comorbid disorders is increased among this population, which enhances phenotype severity and complexity of management. Recurrence rates are high and younger siblings tend to be more severely affected. Detection of prenatal alcohol use warrants substance abuse intervention, which can avoid exposure in subsequent pregnancies. Fetal alcohol spectrum disorders are common developmental disorders with a phenotype that is influenced by both age and development and require long-term management. Child neurologists are essential in the diagnosis and management of fetal alcohol spectrum disorders.

Keywords
fetal alcohol spectrum disorders, diagnosis, management, prevalence

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Discussion

Diagnosis
Children with fetal alcohol spectrum disorders typically present with delays, birth defects, a history of placement in foster care or adoptive homes, and whose mother has been in substance abuse treatment or in the corrections system. The initial diagnosis should be confirmed as early as possible, as early diagnosis and entry into intervention programs is associated with improved outcomes.1

Fetal alcohol spectrum disorders are composed of 4 diagnostic categories: (1) fetal alcohol syndrome; (2) partial fetal alcohol syndrome; (3) alcohol-related neurodevelopmental disorders; and (4) alcohol-related birth defects. Multiple diagnostic criteria are available.2–6 While the criteria have considerable overlap, guidance for clinicians in the selection of optimal criteria has been limited by a lack of comparison studies to evaluate the epidemiologic performance criteria for specificity, sensitivity, and accuracy.6 Diagnostic criteria from Burd et al and Hoyme are presented in Table 1.3,6 Currently, no diagnostic criteria are available for a prenatal diagnosis of fetal alcohol spectrum disorders.

The diagnosis of Fetal Alcohol Syndrome requires the presence of growth impairment, central nervous system damage and/or impairment, and at least 2 characteristic facial features. Current criteria utilize the 10th percentile as a cutoff for growth impairments for either height or weight, which can be assessed by evidence of past growth impairment at birth, during infancy,
or during childhood. Growth impairment is not stable and often attenuates during childhood and especially during adolescence.\textsuperscript{8} Figure 1 depicts the adverse developmental outcomes of fetal alcohol spectrum disorder. Characteristic facial features can be seen in Figure 2.

Evidence of central nervous system dysfunction is determined by the presence of an abnormal neurologic examination, imaging of structural abnormalities, or deficits identified by neuropsychological evaluation.\textsuperscript{9} Currently a 1.5 to 2 standard deviation deficit in 2 or more neuropsychologic functions are considered to be evidence of central nervous system damage consistent with prenatal alcohol exposure. The evaluation protocol is age and development dependent. For example, diagnosis of developmental disorders is difficult in early infancy but becomes much more identifiable as development proceeds. The developmental window for common impairments associated with fetal alcohol spectrum disorder continues through adolescence and into adult life (Figure 1). A multidisciplinary approach is recommended for the initial evaluation.

Most cases of fetal alcohol spectrum disorders are identified when the infant has reached a developmental stage to allow for an accurate neuropsychological assessment of delayed development. This time window is considered optimal from 2 through 16 years of age.\textsuperscript{10}

### Table 1. Criteria For Fetal Alcohol Spectrum Disorders: Revised from Hoyme et al.\textsuperscript{3}

| Fetal Alcohol Syndrome With Confirmed Maternal Alcohol Exposure (requires all features A-D) |
| A. Confirmed maternal alcohol exposure |
| B. Evidence of a characteristic pattern of minor facial anomalies, including \( \geq 2 \) of the following |
| 1. Short palpebral fissures \(( \leq 10\text{th percentile})\) |
| 2. Thin vermillion border of the upper lip (score 4 or 5 with the lip/philtrum guide) |
| 3. Smooth philtrum (score 4 or 5 with the lip/philtrum guide) |
| C. Evidence of prenatal and/or postnatal growth retardation |
| 1. Height or weight \( \leq 10\text{th percentile}, \) corrected for racial norms, if possible |
| D. Evidence of deficient brain growth or abnormal morphogenesis, including \( \geq 1 \) of the following |
| 1. Structural brain abnormalities |
| 2. Head circumference \( \leq 10\text{th percentile} \) |

| Fetal Alcohol Syndrome Without Confirmed Maternal Alcohol Exposure |
| B, C, and D, as above |

| Partial Fetal Alcohol Syndrome With Confirmed Maternal Alcohol Exposure (requires all features, A-C) |
| A. Confirmed maternal alcohol exposure |
| B. Evidence of a characteristic pattern of minor facial anomalies, including \( \geq 2 \) of the following |
| 1. Short palpebral fissures \(( \leq 10\text{th percentile})\) |
| 2. Thin vermillion border of the upper lip (score 4 or 5 with the lip/philtrum guide) |
| 3. Smooth philtrum (score 4 or 5 with the lip/philtrum guide) |
| C. Evidence of prenatal and/or postnatal growth retardation |
| 1. Height or weight \( \leq 10\text{th percentile}, \) corrected for racial norms, if possible |
| 2. Evidence of deficient brain growth or abnormal morphogenesis, including \( \geq 1 \) of the following |
| a. Structural brain abnormalities |
| b. Head circumference \( \leq 10\text{th percentile} \) |
| 3. Evidence of a complex pattern of behavioral or cognitive abnormalities inconsistent with developmental level that cannot by explained by genetic predisposition, family background, or environment alone |
| a. This pattern includes marked impairment in the performance of complex tasks (complex problem solving, planning, judgment, abstraction, metacognition, and arithmetic tasks); higher-level receptive and expressive language deficits; and disordered behavior (difficulties in personal manner, emotional ability, motor dysfunction, poor academic performance, and deficient social interaction) |

| Partial Fetal Alcohol Syndrome Without Confirmed Maternal Alcohol Exposure |
| B and C, as above |

| Alcohol Related Neurodevelopmental Disorder (ARND) (requires both A and B) |
| A. Confirmed maternal alcohol exposure |
| B. At least \( \geq 1 \) of the following |
| 1. Evidence of deficient brain growth or abnormal morphogenesis, including \( \geq 1 \) of the following |
| a. Structural brain abnormalities |
| b. Head circumference \( \leq 10\text{th percentile} \) |
| 2. Evidence of a complex pattern of behavioral or cognitive abnormalities inconsistent with developmental level that cannot be explained by genetic predisposition, family background, or environment alone |
| a. This pattern includes marked impairment in the performance of complex tasks (complex problem solving, planning, judgment, abstraction, metacognition, and arithmetic tasks); higher-level receptive and expressive language deficits; and disordered behavior (difficulties in personal manner, emotional ability, motor dysfunction, poor academic performance, and deficient social interaction) |

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disorders can be identified at birth or during infancy, only the most severe cases typically are diagnosed during this time period, and high rates of false negatives have been reported. The optimal developmental window for assessment occurs when it is possible to evaluate cognitive development, speech and language development, attention, fine and gross motor skills, and other aspects of delayed or aberrant neuropsychological functioning. Imaging studies are not a routine component of evaluation unless clinically indicated.

Very limited information is currently available on the diagnosis of fetal alcohol spectrum disorders in adults and middle-age populations, and published studies of fetal alcohol spectrum disorders in the elderly do not yet exist. The current diagnostic criteria for fetal alcohol spectrum disorders have significant limitations when used with adults. This is relevant when considering fetal alcohol spectrum disorders in the parents of an affected child with a fetal alcohol spectrum disorder. In some cases, retrieval of prenatal care records and pictures during early childhood can facilitate an accurate diagnosis.

**Exposure Assessment**

We reviewed the issue of assessing exposure in detail in part 1 of this series. However, since this is an exposure-dependent diagnosis, we briefly summarize the relevant concepts. Most people with a fetal alcohol spectrum disorder (70%-80%) have early separation from their parents (foster care, adoption, maternal death or incarceration), compounding problems of confirmation of prenatal alcohol exposure and the assessment of dosimetry. A specific history of prenatal alcohol exposure is useful but not required for a diagnosis of fetal alcohol syndrome. However, confirmation of exposure (maternal reports or data from a knowledgeable informant) is required for the diagnoses of both alcohol-related neurodevelopmental disorder and alcohol-related birth defects.
Prevalence Rates of Fetal Alcohol Spectrum Disorders

Current prevalence estimates for fetal alcohol spectrum disorders range from 0.3 (fetal alcohol syndrome only) to 9.1 total cases of fetal alcohol spectrum disorders per 1000 live births or about 109 new cases each day in the United States. Recent school-based prevalence studies using active case ascertainment strategies followed by comprehensive multidisciplinary evaluations have identified fetal alcohol spectrum disorder prevalence rate of 1% to 2%. In some populations, the rates of fetal alcohol spectrum disorder may be as prevalent as 10 to 89 per 1000. Fetal alcohol spectrum disorders are even more prevalent in certain at-risk populations; prevalence studies conducted in Western Cape, South Africa, found a fetal alcohol spectrum disorder rate of 4% to 8%. Thus, fetal alcohol spectrum disorder is one of the most common developmental disorders and may be the most identifiable known cause of mental retardation in the world.

The current prevalence estimates suggest that a significantly small number of people with fetal alcohol spectrum disorders are identified. In the United States, it is likely that several hundred thousand children and adolescents with fetal alcohol spectrum disorders are undiagnosed and rates would be expected to be high in children in foster care, residential care, juvenile corrections facilities, birth defect clinics, or those who present with neuropsychological impairments. Diagnosis of a fetal alcohol spectrum disorder would also be relevant in infant and child mortality reviews, since the mortality risk increases with this diagnosis. Prenatal alcohol exposure is associated with increased risk for preterm delivery.

Comorbidity

In our clinic, we have evaluated more than 600 infants and children with fetal alcohol spectrum disorders and followed many over the past 30 years. We have found comorbidity to be an important issue in the lives of most people with this diagnosis, especially as they mature into adolescence and adulthood. In Figure 3 we present a model of comorbidity and the potential effects on development. An often underappreciated aspect of fetal alcohol spectrum disorders is phenotype modification, where fetal alcohol spectrum disorders increase the severity or complexity of other conditions (ie, Rett syndrome, autism, schizophrenia, Noonan syndrome). In our experience, comorbidity is an important clinical issue in diagnosis and substantially increases the complexity of management over time. The most common comorbid conditions are listed by developmental time frame in Figure 1. This dictates the need for longitudinal follow-up of fetal alcohol spectrum disorders through infancy and into adult life.

Recurrence Risk

The recurrence rates of fetal alcohol spectrum disorders are high and are currently thought to exceed 50% and may approach 75%, if mothers continue to drink in subsequent pregnancies. In sibships, younger children are at greater risk than older siblings and manifest increased syndrome severity, presumably because of increasing severity of alcoholism over time. This highlights the need for assessment of all siblings of a child who has been diagnosed with a fetal alcohol spectrum disorder, even if they are in alternative placements or have been

Figure 2. Characteristic facial features in fetal alcohol spectrum disorders.
adopted. In addition, there is a strong transgenerational risk of fetal alcohol spectrum disorders.22,23

**Mortality**

Mortality risks (miscarriage, stillbirth, etc) associated with prenatal alcohol exposure are ongoing throughout pregnancy.19 Ethanol exposure impairs fertility, decreases implantations, increases miscarriages, and is associated with a 4-fold increase in stillbirths and mortality throughout childhood.25 Four- to 10-fold increases in rates of sudden infant death syndrome are associated with prenatal alcohol exposure.26,27 An increased mortality rate among siblings of children with fetal alcohol spectrum disorders is present, even if their fetal alcohol spectrum disorder diagnostic status is unknown.28 In addition, studies have reported an increased mortality among mothers of children with fetal alcohol spectrum disorder.23,29–31 This highlights the need for comprehensive clinical and public health programs to improve early identification of alcohol use during pregnancy, enhance entry and performance of substance abuse treatment programs, prevent the recurrence of exposure in subsequent pregnancies, and decrease postnatal risk associated with parental alcohol abuse for infants and children.

**Developmental Course**

**Infancy.** High rates of vision and hearing disorders, seizures, and abnormal electroencephalography results are common.32–34 Surprisingly, data on the prevalence of alcohol withdrawal syndrome in infants is limited. The available studies have reported a relatively mild withdrawal symptomatology for children with fetal alcohol spectrum disorders, including characteristics such as jitteriness, increased respiratory rates, hyperacusis, exaggerated reflexes, and sleep disturbances.21

**Childhood and adolescence.** By adolescence and early adulthood, high rates of mental retardation, neurocognitive impairment, substance use, impaired peer relationships, increased vulnerability to exploitation, and deficits in judgment and decision making are widely expressed. These adverse outcomes have serious life consequences, leading to school failure, multiple foster home placements, peer exploitation, and frequent contact with law enforcement. Fetal alcohol spectrum disorders appear to have a very long developmental window, extending at least to age thirty. Streissguth and colleagues evaluated 415 patients, ranging in age from 6 to 51 years, diagnosed with either fetal alcohol syndrome or fetal alcohol effects and found increased lifetime prevalence of adverse outcomes (Table 2).1 Deficits in mathematical calculation and comprehension, and problems with adaptive behavior are common in childhood.1,35–37 Recent follow-up studies of adolescent and adult patients with fetal alcohol spectrum disorders have found high rates of attention-deficit hyperactivity disorder, depression, mental disorders, low rates of independent living, and aberrant decision making.10,38

**Figure 3.** Fetal alcohol spectrum disorders: outcomes from prenatal exposure. Note: ADHD = attention-deficit hyperactivity disorder.
accompanying academic failure, injury, and mortality. Childhood and into adolescence increases the risk of abuse, adversity. Persistence of these adverse conditions through exposure and increased risk for postnatal environmental exposure is useful to acknowledge the link between prenatal alcohol depression, violence, and suboptimal living conditions. It entering, other drug use, inadequate nutrition, high rates of exposure to multiple teratogens, including alcohol, smoking, other drug use, inadequate nutrition, high rates of depression, violence, and suboptimal living conditions, and substance abuse treatment programs.

Developmental assessments and linkage to intervention strategies and resources should begin as early as possible, ideally occurring jointly with diagnosis. These strategies should start with a careful assessment of the home environment, including a systematic inquiry about alcohol and substance abuse and safety of infants in the home environment. Early intervention decreases the likelihood of adverse outcomes. Multiple foster home placements are common and extremely detrimental to development. Early guidance about the severity of these disorders and appropriate interventions may decrease risk for multiple foster home placements and have great potential to improve developmental outcome. It is important to note that the early prenatal environment for children with a fetal alcohol spectrum disorder is often one of exposure to multiple teratogens, including alcohol, smoking, other drug use, inadequate nutrition, high rates of depression, violence, and suboptimal living conditions. It is useful to acknowledge the link between prenatal alcohol exposure and increased risk for postnatal environmental adversity. Persistence of these adverse conditions through childhood and into adolescence increases the risk of abuse, neglect, academic failure, injury, and mortality.

When developing treatment programs, it is imperative that schools, foster homes, and residential care programs understand that the neurobehavioral phenotype of fetal alcohol spectrum disorders is a mix of impairments and behaviors. Behaviors are variably modifiable, and impairments will often require modification of programmatic objectives and psychosocial expectations. Wide fluctuations in day-to-day levels of performance are common in fetal alcohol spectrum disorders and may represent a distinctive neurocognitive feature of fetal alcohol spectrum disorders. This issue often leads to problematic program expectations. The child’s ability to perform a task on one day is often not representative of his or her ability over time, which can lead to unrealistic expectations set on days of peak performance. The attribution of subsequent failure to perform at that level as being due to willful defiance is common. This issue may be more appropriately managed by acknowledging the role of impairments, which are less likely to be improved by intervention but are responsive to accommodation and a more narrow focus on behavior.

A primary goal when working with patients diagnosed with a fetal alcohol spectrum disorder is to provide anticipatory guidance about future developmental abnormalities and to provide appropriate therapeutic interventions. Equally important is a long-term plan that includes prospective risk reduction. Three common goals are to (1) prevent multiple foster home placements, which are extremely detrimental for optimal development; (2) maximize parent or caretaker understanding of the age-related changes in behavior and age-related risk; and (3) anticipation of future development of age-related impairments common in fetal alcohol spectrum disorders. For example, at our center we use a 10-year plan where at each contact we review current problems and provide anticipatory guidance about potential upcoming issues. During late childhood and adolescence, we emphasize the need to plan for the fetal alcohol spectrum disorder tetrad of peer exploitation, substance abuse, decreased potential for independent living, and increased risk for incarceration.

Pharmacologic Management

For many children with a fetal alcohol spectrum disorder, attention-deficit hyperactivity disorder is an initial presenting problem and early recognition appears to be associated with a positive response to developmental interventions and pharmacologic interventions. In a summary review of use of stimulants, 5 studies reported on 94 subjects. In these studies, 88% (83/94) of the subjects were reported to have a positive response to pharmacologic treatment of attention-deficit hyperactivity disorder. However, there is controversy over the appropriate intervention methods used for the treatment of attention-deficit hyperactivity disorder. As development progresses, surveillance for common comorbid disorders such as epilepsy, depression, anxiety disorders, sensory impairments, and cognitive impairments is imperative as early intervention decreases the likelihood of adverse outcomes. Thus, fetal alcohol spectrum disorders are most appropriately considered to be a developmental disorder with a changing phenotype in response to age and development. This suggests that long-term management by knowledgeable providers will be essential for optimal outcomes.

Cost of Care

The public health burden for cases of fetal alcohol spectrum disorder is significant with lifetime costs of care at

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**Table 2. Prevalence of Adverse Outcomes in Fetal Alcohol Spectrum Disorders**

<table>
<thead>
<tr>
<th>Adverse Outcome</th>
<th>Prevalence, %</th>
<th>Age 6-11</th>
<th>Age 12-20</th>
<th>Age 21-51</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inappropriate sexual behavior</td>
<td></td>
<td>39.1</td>
<td>47.5</td>
<td>51.7</td>
</tr>
<tr>
<td>Disrupted school experiences</td>
<td></td>
<td>14.3</td>
<td>62.3</td>
<td>59.1</td>
</tr>
<tr>
<td>Trouble with the law</td>
<td></td>
<td>14.3</td>
<td>61.1</td>
<td>58.4</td>
</tr>
</tbody>
</table>
approximately $2 million to $2.8 million. These rates are similar across the United States and Canada. Several studies have been conducted on prevalence rates and costs associated with fetal alcohol spectrum disorders in South Africa. The rates of fetal alcohol syndrome and partial fetal alcohol syndrome in South Africa are the highest reported worldwide. Subsequently, Crede and colleagues reported that annually $70,960,053 is spent on managing health care needs of children with fetal alcohol syndrome/partial fetal alcohol syndrome in the Western Cape, South Africa. The burden of care seems disproportionate to the resources spent on prevention.

Prevention

Prevention of fetal alcohol spectrum disorders will require improved screening strategies to detect substance abuse during the early stages of prenatal care. Early diagnosis of alcohol abuse or fetal alcohol spectrum disorder can lead to the prevention of future cases if the mother can enter an effective substance abuse treatment program. Thus, prevention of fetal alcohol spectrum disorders offers an important opportunity to decrease infant, child, and adolescent morbidity and mortality. Similarly, early recognition has the potential to decrease the need for subsequent developmental interventions and reduce the rates of residential placement and entry into substance abuse treatment programs and corrections systems. This would accrue huge cost savings to state and federal governments. Current prevalence estimates in the United States of 40,000 new cases each year suggest that it is likely most child neurologists have and will see large numbers of infants and children with fetal alcohol spectrum disorders throughout their career.

Conclusion

The diagnosis and management of fetal alcohol spectrum disorders requires a multifaceted approach. Criteria for diagnosis of fetal alcohol spectrum disorders include growth impairment, varied central nervous system damage, and characteristic facial features collectively requiring a team of clinicians to properly diagnose. Long-term management of fetal alcohol spectrum disorders requires specialized care and therapy. Language and speech therapists, special education services, occupational and physical therapists, psychiatrists, assisted living programs, and substance abuse treatment programs may all be utilized for a child with fetal alcohol spectrum disorder. Many of these services will be needed throughout life, and it is recommended that 10-year management plans are developed to review the current situation and anticipate upcoming problems.

With a prevalence rate of nearly 9.1 cases of fetal alcohol spectrum disorders per 1000 live births, it is likely many children and adolescents are left undiagnosed. Identifying a fetal alcohol spectrum disorder at an early age is essential to providing the best care for the child. Early identification can lead to early enrollment into benefits such as special education and speech and language therapy. Diagnosing a fetal alcohol spectrum disorder early in life also provides the benefit of starting a life-long management plan and coordination of services for the child. Early entrance into services may also reduce the risk of substance abuse, contact with the corrections system, and other adverse outcomes later in life.

Authors’ Contributions

AP and LB are responsible for the main design and concept of this article. AP is responsible for the literature review. AP, ADW, and LB all contributed important intellectual content to this article.

Declaration of Conflicting Interests

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Ethical Approval

The Institutional Review Board of the University of North Dakota has approved the research cited in this review.

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