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Alcohol Alert

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Fetal Alcohol Spectrum Disorders: Understanding the Effects of Prenatal Alcohol Exposure

When pregnant women drink, they put their unborn babies at risk for a wide range of physical, cognitive, and behavioral problems. In fact, prenatal alcohol exposure is the leading preventable cause of birth defects in the United States.

Nearly 40 years ago, the effects of heavy alcohol exposure on the developing fetus were first recognized. And Drs. Smith and Jones, although not alcohol researchers, were the first to coin the term fetal alcohol syndrome or FAS.[1] Since then, scientists have defined a broad range of effects caused by prenatal alcohol exposure. We now refer to the disorders that fall within that broad range as fetal alcohol spectrum disorders (FASD). The following are the disorders under the FASD category:

- **FAS**—This diagnosis requires a characteristic pattern of facial abnormalities; growth deficits, prenatally and/or after birth; and central nervous system abnormalities.
- **Partial FAS**—This includes some signs and symptoms of full FAS but not all three of the characteristics noted in the previous bullet.
- **Alcohol-related birth defects** (ARBD)—This includes just alcohol-related physical abnormalities.
- **Alcohol-related neurodevelopmental disorder** (ARND)—This includes central nervous system abnormalities, as well as cognitive and behavioral problems.[1]

This *Alcohol Alert* explores the latest research on the full spectrum of alcohol-related developmental disorders, new diagnostic tools that can detect these disorders, and promising interventions and treatment options.

Is Any Amount of Alcohol Safe During Pregnancy?

There is no known safe amount of alcohol to drink while pregnant.[2] Studies show that even drinking small amounts of alcohol during

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pregnancy may affect fetal brain development.[3,4] This can result in deficiencies and dysfunction that can last a lifetime.[5]

Estimating FASD's Prevalence

FAS—a condition on the severe end of the spectrum of alcohol-related disorders—is estimated to occur in between 0.5 and 7.0 cases per 1,000 live births nationwide.[4,6] About 1 percent of newborns may suffer from FASD,[7] although this may be an underestimation.[6]

Unfortunately, FASD cases are chronically underdiagnosed. FASD can be difficult for practitioners to distinguish from other developmental disorders, such as Attention Deficit Hyperactivity Disorder (ADHD), because the two share some similar behavioral symptoms.

Critical Research Goal: Identifying FASD Earlier in Life

Pregnant women do not usually tell their health care practitioners if they drink alcohol. That makes recognizing babies and children with FASD a challenge, especially very early in life, when intervention can be most effective.

To develop better ways to identify children with FASD, researchers currently are focusing on more clearly defining three areas:[8]

- Structural abnormalities that distinguish children with FASD, including distinctive facial dysmorphology and brain differences
- Functional abnormalities
- Biomarkers

Facial Dysmorphology

Prenatal alcohol exposure can cause facial dysmorphology, or particular changes in facial features. Recognizing this specific pattern of facial features is a critical screening tool for diagnosing children with the full FAS. However, not everyone has access to a specialist who can identify these features, which are required for a diagnosis of FAS. In addition, fetal alcohol exposure affects many children who do not have these distinctive facial features. Because of this, recognizing FASD primarily on the basis of facial features misses many affected children.

Currently, researchers are developing computer systems and three-dimensional cameras to detect facial dysmorphology. This technology would automate diagnosis, reduce the need for consultation with specialists, and allow for more widespread FASD screenings.

For example, researchers from the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) are using a three-dimensional camera system to compare facial differences between children exposed prenatally to alcohol and those who were not exposed. Such cameras are making it possible to use telemedicine to identify children with FAS. And the computer system should enable scientists to interpret more subtle facial features found among individuals with FASD. Those computer-generated algorithms also may help to identify additional facial features to better characterize the full spectrum of FASD.

The ability to detect differences also depends on age.[9] Applying the three-dimensional camera technique to children at different ages may therefore lead to earlier detection of FASD. Researchers also have noted facial variability in dysmorphology among children of different ethnic backgrounds.[10]

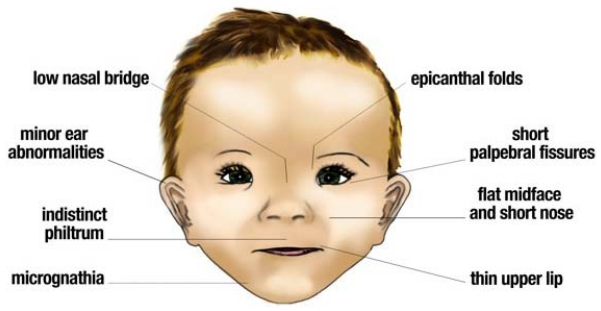
Structural Brain Development

Fetal alcohol exposure also can affect the development of brain structure. Advances in imaging techniques are allowing researchers to better understand this effect on the brain's structure and, consequently, its functioning.

The imaging techniques researchers use most often are magnetic resonance imaging (MRI) and functional MRI (fMRI). MRI studies of people exposed to alcohol prenatally show differences in the brain's size and volume, as well as in tissues within the brain[11–13] compared with people who were not exposed to alcohol. These structural differences in the brain may be related to the problems people with FASD experience on tests of various behaviors and cognitive skills, such as learning and memory.[3]

Another brain-imaging method, fMRI, uses a strong magnetic field to show how blood flows in the brain. In general, more blood flows toward an activated brain structure. Researchers can track this flow of blood to determine what part of the

Facial characteristics that are associated with fetal alcohol exposure



brain responds to particular stimuli and how different parts of the brain function.

For example, researchers used fMRI to determine that people with FASD showed different patterns of activity in various areas of their brains than those of people who were not exposed to alcohol.[14] The brain activation patterns were similar in both children and adults with FASD, showing that the brain changes associated with FASD do not necessarily improve with age.[15–17]

These brain changes have been linked with a constellation of effects that range from intellectual and learning disabilities and speech and language delays to behavioral and emotional difficulties, poor social skills, and motor deficits.

Biomarkers

Biomarkers are chemicals in fluids or tissues that change as a result of prenatal alcohol exposure. Alcohol can be measured in blood and urine, which health care practitioners can easily test. Such changes, however, are usually only detectable close to the time of intoxication. Researchers currently are investigating a variety of screening options that may serve as biomarkers for prenatal alcohol exposure:

- Phosphatidylethanol (PEth) —PEth is a product of alcohol metabolism that may indicate heavy maternal drinking levels.[18] It shows up in a newborn's blood.
- Fatty acid ethyl ester (FAEE) screening—FAEEs, which are products of alcohol metabolism, are present in humans exposed to alcohol prenatally, and they build up in hair and stool of the fetus and can be measured in the meconium or hair of the newborn.
- microRNA screening—Particular types of microRNA, or non–protein-coding RNAs, may change as a result of prenatal alcohol exposure.[18]
- Protein (or proteomic) screening—This method looks for a possible pattern of proteins that may change in the presence of alcohol.[18]

Researchers are working on ways to make detecting these biomarkers more accessible to allow for earlier identification of children at risk for FASD.[18,19] Other research efforts seek to increase the accuracy of the current biomarkers by developing panels of biomarkers that may prove useful.[20] In addition, researchers are examining biomarkers that can predict fetal alcohol–induced damage instead of merely signaling the presence of alcohol. For example, one study[21] compared proteins in the blood of a small number of children with FAS with children not exposed to alcohol. The study found differences in protein patterns between children with FAS and those without it. These proteins could one day help identify the extent of alcohol-induced damage in children at risk for FASD.

Factors Complicating Diagnosis

Distinguishing FASD from other developmental disorders is important for improving diagnosis and recognizing other accompanying disorders. Researchers estimate that more than 70 percent of children with FASD are diagnosed with ADHD.[22,23] As a result, another important research focus is on clearly distinguishing between the two conditions and other developmental disorders and recognizing comorbidities that affect developmental and behavioral outcomes.

Current research developments are making these distinctions clearer. For example, we now understand the difference in one particular behavior called perseveration. Perseveration is an impaired ability to shift from one task to another. Children with FASD have much more difficulty making these transitions compared with individuals who have ADHD.[3]

In addition, the primary problem for children with ADHD is in focusing and sustaining attention and, to a certain extent, balancing and coordinating movement. By contrast, children with an FASD tend to have more problems with executive, or cognitive, functions such as:[24]

- Mental flexibility
- Problem solving
- Visual attention

Differentiating between FASD and ADHD when diagnosing a child with attention issues may be important when designing the most appropriate care.

Critical Research Goal: Understanding Maternal Characteristics That May Increase FASD Risk

Research demonstrates that children who are more significantly affected by FASD had mothers who not only drank alcohol during their pregnancy but who also share certain characteristics.

For example, women who drink and who are older and have had multiple pregnancies and births are at greater risk of having a child with FASD.[25] Women with poor nutrition and who have inadequate prenatal care also are at higher risk.[26–28]

The extent of FASD symptoms also can depend on the genetic makeup of the mother and her child. Mothers of children with FASD are less likely to carry a specific gene that is linked to

unpleasant side effects when drinking (i.e., nausea and flushing of skin). People who have that gene variant may be less likely to drink heavily.[29]

As with other children with behavioral problems, children with FASD are more likely to have unsettled home environments.[3] Women who have children with FASD also are more likely to be clinically depressed, to have heavy drinkers in their families, and to live with domestic partners who drink heavily.[26,29,30] Many children with FASD have lost a parent, experienced abuse or neglect, or live in foster homes. Others live in socio-economically disadvantaged conditions, or with family members who use drugs or display other types of antisocial behavior.[31] Clinicians need to take these additional details into account when trying to help children who are grappling with FASD.[3]

Interventions and Treatment

Parents often have great difficulty caring for children with FASD. In addition to problems with learning and remembering new material, children with FASD also face challenges with motor control, balance, visual perception, visual–motor coordination, and attention. They may also struggle with planning, organizational thinking, problem solving, and have difficulty interpreting and responding appropriately in social situations.[3] All of these areas influence the daily functioning of affected people as well as their academic and job performance.

Without intervention, these difficulties may only get worse as children with FASD age.[32] It is important for parents to understand that their children's behavior stems from prenatal alcohol exposure—not intentional disobedience.

A variety of interventions and treatment options can help both parents and children manage life with FASD.

Support Groups

Support groups and networks help parents understand the distinction between involuntary behavior and disobedience, and they provide guidance for parents and other adults who care for children affected by FASD. Participants in a trial of such a support system reported greater improvements in their sense of parenting effectiveness and in their understanding of their children's behavioral problems compared with those families receiving standard care.[33]

Stimulating Environments

Animal research also suggests that offering stimulating environments to animals exposed to alcohol prenatally may help reduce the symptoms of FASD. Providing rats with running wheels and toys, raising them in group settings, training them on motor learning tasks, and handling them often helped to offset the behavioral, social, learning, and motor coordination problems associated with prenatal alcohol exposure.[34,35] Interventions that foster environmental enrichment show promise in humans as well.[32]

Intervention at School

School-based therapies may be able to address a range of issues, from self-awareness, self-regulation and social skills to language, literacy, and mathematics training. Among school-age children, such interventions show promise for improving classroom behavior and even academic achievement. This is especially true for younger children, whose brains are more adaptable. [36] Though they may still lag behind children who are not exposed to alcohol prenatally, children with FASD can benefit from these interventions—both in terms of regulating their behavior and improving their academic performance. [33,36]

Nutritional Supplements

Another promising area of research is on nutrition as a therapeutic intervention for offsetting the problems associated with FASD. For example, animal studies show that certain nutrients, such as zinc, folate, and choline, may protect the developing fetus from the harmful effects of alcohol.[37]

One study monitored pregnant animals that were given supplemental choline and that also were exposed to alcohol. As a result of the choline, the newborns had less severe alcohol-related birth weight reductions, physical defects, and changes in behavior.[38] Choline and other nutrients also may help improve the symptoms of FASD, even when administered after being exposed to alcohol prenatally and during postnatal development.[37] For example, researchers found that animals treated with choline postnatally had less severe alcohol-related memory problems later in adulthood than animals who did not receive the supplements.[39]

Conclusions

Prenatal alcohol exposure can have devastating effects on the affected children and their families. Because of the lifelong consequences for individuals, families, and society, it is a significant public health priority to better identify pregnant women who drink and children who experienced prenatal alcohol exposure. Researchers are investigating new diagnostic techniques and developing a deeper understanding of the risk factors related to alcohol consumption in pregnancy. In addition, family support, school interventions, and new therapies will help individuals already grappling with FASD. Educating clinicians, parents, and educators about such treatments will help those with FASD lead more productive and satisfying lives.

References

[1] Warren, K.R.; Hewitt, B.G.; and Thomas, J.D. Fetal Alcohol Spectrum Disorders: Research Challenges and Opportunities. *Alcohol Research & Health* 34(1):4–14, 2011. [2] U.S. Surgeon General. Surgeon General's Advisory on Alcohol and Pregnancy. Washington, D.C.: U.S. Department of Health and Human Services, 2005. Available at http://www.surgeongeneral.gov/pressreleases/sg02222005.html. Accessed September 23, 2010. [3] Coles, C.D. Discriminating the effects of prenatal alcohol exposure from other behavioral and learning disorders. *Alcohol Research & Health* 34(1):42–50, 2011. [4] May, P.A., and Gossage, J.P. Estimating the prevalence of fetal alcohol syndrome: A summary. *Alcohol Research & Health* 25:159–167, 2001. [5] Nuñez, S.C.; Roussotte, F.; and Sowell, E.R. Update on Brain Pathology. Focus On: Structural and functional brain abnormalities in fetal alcohol spectrum disorders. *Alcohol Research & Health* 34(1):121–131, 2011. [6] May, P.A.; Gossage, J.P.; Kalberg, W.O.; et al. Prevalence and epidemiologic characteristics of FASD from various research methods with an emphasis on recent in-school studies. *Developmental Disabilities Research Reviews* 15(3):176–192, 2009. [7] Sampson, P.D.; Streissguth, A.P.; Bookstein, F.L., et al. Incidence of fetal alcohol syndrome and prevalence of alcohol-related neurodevelopmental disorder. *Teratology* 56(5):317–326, 1997. PMID: 9451756. [8] Wilson, S.E., and Cudd, T.A. Focus On: The use of animal models for the study of fetal alcohol spectrum disorders. *Alcohol Research & Health* 34(1):92–98, 2011. [9] Wetherill, L.; Hoyme, H.E.; Robinson, L.K; et al. Longitudinal changes in facial measurements from 3D images in children with heavy prenatal alcohol exposure. *Alcoholism: Clinical and Experimental Research* 34(Suppl. S2):101A:P361, 2010. [10] Wetherill, L., and Foroud, T. Understanding the effects of prenatal alcohol exposure using three-dimensional facial imaging. *Alcohol Research & Health* 34(1):38–41, 2011. [11] Archibald, S.L.; Fennema-Notestine, C.; Garnst, A.; et al. Brain dysmorphology in individuals with severe prenatal alcohol exposure. *Developmental Medicine and Child Neurology* 43(3):148–154, 2001. PMID: 11263683 [12] Mattson, S.N.; Riley, E.P.; Sowel, E.R.; et al. A decrease in the size of the basal ganglia in children with fetal alcohol syndrome. *Alcoholism: Clinical and Experimental Research* 20(6):1088–1093, 1996. PMID: 8892532 [13] Sowell, E.R.; Mattson, S.N.; Kan, E.; et al. Abnormal cortical thickness and brain–behavior correlation patterns in individuals with heavy prenatal alcohol exposure. *Cerebral Cortex* 18(1):136–144, 2008. [14] Malisza, K.L.; Allman, A.A.; Shiloff, D.; et al. Evaluation of a spatial working memory function in children and adults with fetal alcohol spectrum disorders: A functional magnetic resonance imaging study. *Pediatric Research* 58(6):1150–1157, 2005. PMID: 16306185 [15] Fryer, S.L.; Tapert, S.F.; Mattson, S.N.; et al. Prenatal alcohol exposure affects frontal-striatal BOLD response during inhibitory control. *Alcoholism: Clinical and Experimental Research* 31(8):1415–1424, 2007. PMID: 17559542 [16] O'Hare, E.D.; Lu, L.H.; Houston, S.M.; et al. Altered frontal-parietal functioning during verbal working memory in children and adolescents with heavy prenatal alcohol exposure. *Human Brain Mapping* 30 (10):3200–3208, 2009. PMID: 19263420 [17] Sowell, E.R.; Lu, L.H.; O'Hare, E.D.; et al. Functional magnetic resonance imaging of verbal learning in children with heavy prenatal alcohol exposure. *NeuroReport* 18(7):635–639, 2007. PMID: 17426589 [18] Steward, S.H.; Law, T.L.; Randall, P.K.; and Newman, R. Phosphatidylethanol and alcohol consumption in reproductive age women. *Alcoholism: Clinical and Experimental Research* 34(3):488–492, 2010. PMID: 20028353 [19] McDade, T.W.; Williams, S.; and Snodgrass, J.J. What a drop can do: Dried blood spots as a minimally invasive method for integrating biomarkers into population-based research. *Demography* 44(4):899–925, 2007. PMID: 18232218 [20] Bakhireva, L.N., and Savage, D.D. Focus On: Biomarkers of fetal alcohol exposure and fetal alcohol effects. *Alcohol Research & Health* 34(1):56–63, 2011. [21] Robinson, M.K.; Myrick, J.E.; Henderson, L.O.; et al. Two-dimensional protein electrophoresis and multiple hypothesis testing to detect potential serum protein biomarkers in children with fetal alcohol syndrome. *Electrophoresis* 16(7):1176–1183, 1995. PMID: 7498162 [22] Burd, L.; Klug, M.G.; Martsolf, J.T.; and Kerbeshian, J. Fetal alcohol syndrome: Neuropsychiatric phenomics. *Neurobiology and Teratology* 25(6):697–705, 2003. PMID: 14624969 [23] Dalen, K.; Bruaroy, S.; Wentzel-Larsen, T.; and Legreid, L.M. Cognitive functioning in children prenatally exposed to alcohol and psychotropic drugs. *Neuropediatrics* 40(4):162–167, 2009. PMID: 20135573 [24] Vaurio, L.; Riley E.P.: Mattson S.N. Differences in executive functioning in children with heavy prenatal alcohol exposure or attention-deficit/hyperactivity disorder. *Journal of the Neuropychological Society* 14(1):119–129, 2008. PMID: 18078538 [25] May, P.A.; Gossage, J.P.; Marais, A.S.; et al. Maternal risk factors for fetal alcohol syndrome and partial fetal alcohol syndrome in South Africa: A third study. *Alcoholism: Clinical and Experimental Research* 32:738–753, 2008. PMID: 18336634 [26] Bingol, N.; Schuster, C.; Fuchs, M.; et al. The influence of socioeconomic factors on the occurrence of fetal alcohol syndrome. *Advances in Alcohol & Substance Abuse* 6:105–118, 1987. PMID: 3425475 [27] May, P.A.; Hamrick, K.J.; Brooke, L.E.; et al. Nutrition: Its possible contribution to fetal alcohol syndrome among Coloured women in the Western Cape Province of South Africa. *Alcoholism: Clinical and Experimental Research* 28(5):125A, 2004. [28] May, P.A.; Gossage, J.P.; Brooke, L.E.; et al. Maternal risk factors for fetal alcohol syndrome in the Western Cape Province of South Africa: A population-based study. *American Journal of Public Health* 95:1190–1199, 2005. PMID: 15933241 [29] Khaole, N.C.; Ramchandani, V.A.; Viljoen, D.L.; and Li, T.K. A pilot study of alcohol exposure and pharmacokinetics in women with or without children with fetal alcohol syndrome. *Alcohol and Alcoholism* 39:503–508, 2004. PMID: 15351745 [30] Flynn, H.A., and Chermack, S.T. Prenatal alcohol use: The role of lifetime problems with alcohol, drugs, depression and violence. *Journal of Studies on Alcohol and Drugs* 69:500–509, 2008. PMID: 18612565 [31] Hussong, A.M.; Huang, W.; Curran, P.J.; et al. Parent alcoholism impacts the severity and timing of children's externalizing symptoms. *Journal of Abnormal Child Psychology* 38(3):367–380, 2010. PMID: 20084453 [32] Paley, B., and O'Connor, M.J. Behavioral interventions for children and adolescents with fetal alcohol spectrum disorders. *Alcohol Research & Health* 34(1):64–75, 2011. [33] Bertrand, J. Interventions for children with fetal alcohol spectrum disorders: Overview of findings for five innovative research projects. *Research in Developmental Disabilities* 30:986–1006, 2009. PMID: 19327965 [34] Hannigan, J.H.; O'Leary-Moore, S.K.; and Berman, R.F. Postnatal environmental or experiential amelioration of neurobehavioral effects of prenatal alcohol exposure in rats. *Neuroscience and Biobehavioral Reviews* 31:202–211, 2007. PMID: 16911827 [35] Klintsova, A.Y.; Scamra, C.; Hoffman, M.; et al. Therapeutic effects of complex motor training on motor performance deficits induced by neonatal binge-like alcohol exposure in rats: II. A quantitative stereological study of synaptic plasticity in female rat cerebellum. *Brain Research* 937:83–93, 2002. PMID: 12020866 [36] Adnams, C.M.; Sorour, P.; Kalberg, W.O.; et al. Language and literacy outcomes from a pilot intervention study for children with Fetal Alcohol Spectrum Disorders in South Africa. *Alcohol* 41:403–414, 2007. PMID: 17936509 [37] Idrus, N.M., and Thomas, J.D. Fetal Alcohol Spectrum Disorders: Experimental treatments and strategies for intervention. *Alcohol Research & Health* 34(1):76–85, 2011. [38] Thomas, J.D.; Abou, E.J.; and Dominguez, H.D. Prenatal choline supplementation mitigates the adverse effects of prenatal alcohol exposure on development in rats. *Neurotoxicology and Teratology* 31:303–311, 2009. PMID: 19616089 [39] Thomas, J.D.; La Fiette, M.H.; Quinn, V.R.; and Riley, E.P. Neonatal choline supplementation ameliorates the effects of prenatal alcohol exposure on a discrimination learning task in rats. *Neurotoxicology and Teratology* 22:703–711, 2000. PMID: 11106863

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Resources

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- ***Alcohol Research & Health,* 34(1) "Fetal Alcohol Spectrum Disorders" examines the latest research on prenatal alcohol exposure. Articles explore what is known about the harmful effects of drinking during pregnancy. Includes a look at the latest technology and how it is helping scientists to better understand the effects of alcohol on the developing brain. Articles also describe new diagnostic tools for identifying children at risk for FASD as well as the latest findings in the treatment, intervention, and prevention of these harmful effects.**

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