Fetal Alcohol Exposure: Effects on the Developing Brain

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Objectives

After completing this article, readers should be able to:

1. Describe the primary central nervous system effects of prenatal alcohol exposure.
2. Describe the relationship of fetal alcohol syndrome and mental retardation.
3. Delineate proposed mechanisms of alcohol's adverse effects on the developing brain.
4. Identify key factors that increase the risk of alcohol-induced fetal brain damage.
5. Delineate proposed neuroprotective strategies to limit fetal brain damage.

Introduction

Fetal alcohol syndrome (FAS) was described initially in the American medical literature in 1973 by Jones and colleagues as a constellation of features in children born to alcoholic mothers. These features include facial and other physical anomalies, pre- and postnatal growth deficiency, and variable central nervous system (CNS) abnormalities. These latter may involve structural brain defects, cognitive abnormalities, delayed brain development, and signs of neurologic impairment, including lifelong behavioral and psychosocial dysfunction. In 1996, the Institute of Medicine further defined criteria for the diagnosis of FAS and also proposed a new term: Alcohol-related Neurodevelopmental Disorder (ARND). This latter term includes structural CNS and cognitive abnormalities in children in whom fetal exposure to alcohol has been confirmed. Unlike FAS, a diagnosis of ARND does not require the presence of facial or other physical abnormalities. In 2000, the American Academy of Pediatrics (AAP) Committee on Substance Abuse published these new definitions in *Pediatrics* (Figure).

The problem is enormous. FAS is estimated to occur in the United States at a rate of 1 to 3 per 1,000 live births and is higher in selected subgroups, such as Native Americans. The rate of ARND is estimated to be at least 10 times greater. Fetal alcohol exposure is estimated to be the leading cause of mental retardation in developed countries today. Although most children exposed to heavy alcohol in utero do not develop "full-blown" FAS, a significant percentage develop ARND, which may be just as disabling, if not more so.

This review article focuses on the effects of fetal alcohol exposure on the developing brain, including CNS abnormalities and the behavioral/psychosocial disorders that have been associated with fetal alcohol exposure as well as proposed mechanisms for alcohol's detrimental effects on the developing brain. Certain key risk factors that have been clearly associated with the development of alcohol-related CNS abnormalities are discussed. Finally, this review addresses treatment (including treatment of neonatal alcohol withdrawal) and early/late interventions designed to ameliorate alcohol's detrimental effects.

Clinical Findings of Alcohol-related CNS Abnormalities

In the majority of patients who have FAS/ARND, no gross brain abnormalities are seen either pathologically or by neuroimaging techniques. Pathologic studies have been limited because FAS is not typically fatal. Therefore, CNS abnormalities have been described more often in animal models. The few structural abnormalities that have been described after fetal alcohol exposure are listed in Table 1. Most of these structural abnormalities have been described relatively recently, based on sophisticated neuroimaging techniques such as magnetic resonance imaging (MRI).

Neurologic (Table 2) and neurobehavioral abnormalities (Table 3) have been associ-

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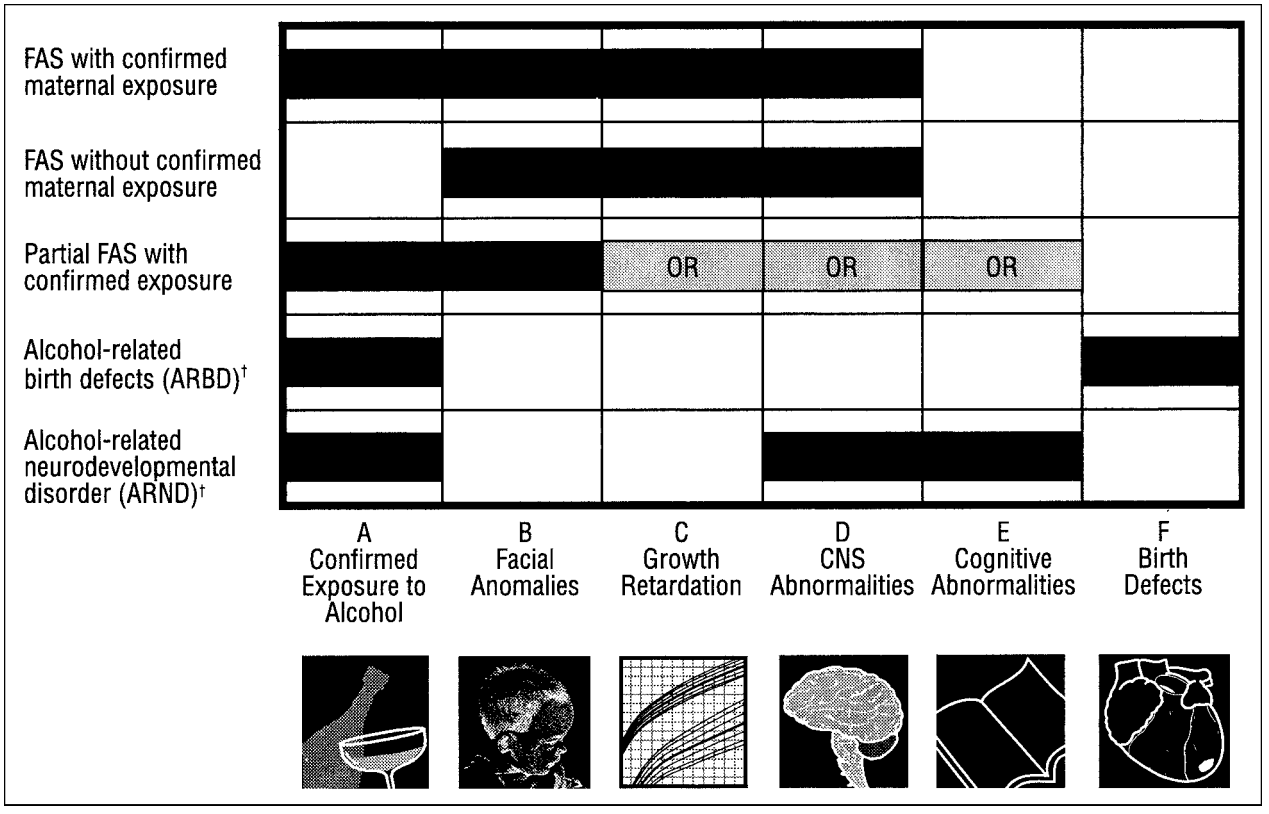

Figure. Diagnostic classification of fetal alcohol syndrome (FAS) and alcohol-related birth defects (ARBD). Reprinted with permission from *Pediatrics*. 2000;106:358–361.

ated with fetal alcohol exposure for a long time. Although these findings may not be as dramatic as a structural brain abnormality seen on MRI, they are at least as damaging and potentially disabling in the long term.

The behavioral and cognitive dysfunctions observed among persons who have FAS are exceedingly variable, but a common functional outcome is maladaptive behavior, a lifelong disability. Persons who have FAS or ARND are disproportionately overrepresented in United States jails.

Finally, certain alcohol-related birth defects (Table 4) are relevant to the developing CNS, both structurally and functionally. Ocular, auditory, and neuroendocrine abnormalities have been described.

Table 1. Structural CNS Abnormalities Associated With In Utero Alcohol Exposure

- Microcephaly (small head)
- Microencephaly (small brain)
- Decreased size of cerebrum, cerebellum, basal ganglia, diencephalon
- Partial or complete agenesis of the corpus collosum
- Neuroglial heterotopia
- Dendritic neuronal abnormalities
- Holoprosencephaly sequence
- Ventricular enlargement
- Dandy-Walker malformation

Table 2. Neurologic Abnormalities Associated With In Utero Alcohol Exposure

- Impaired fine motor skills
- Deficits in balance
- Poor tandem gait
- Neurosensory hearing loss
- Poor hand-eye coordination
- Hypotonia

Table 3. Neurobehavioral Abnormalities Associated With In Utero Alcohol Exposure

- Learning disabilities
- Decreased intelligence quotient (IQ) scores
- Mental retardation
- Attention deficit/hyperactivity disorder
- Poor impulse control
- Problems in memory, attention, or judgment
- Problems in social perception
- Deficits in higher level receptive or expressive language
- Poor capacity for abstraction or metacognition
- Autism
- Adult mental illness
  - –Alcohol or drug dependence
  - –Psychotic disorders
  - –Avoidant, antisocial, or dependent personality disorders
  - –Depression; suicide

Animal Research

Numerous questions about the mechanisms for the clinical CNS damage associated with prenatal alcohol exposure must be answered using animal models. These models frequently are designed to answer specific questions regarding CNS effects of fetal alcohol exposure, such as temporal and regional vulnerability, dose-response, and key risk factors (Table 5). In extrapolating results from these animal studies to the clinical realm, species differences in both the timing of brain development and the metabolism of alcohol must be considered.

Table 4. Relevant Alcohol-related Birth Defects

Ocular

- Strabismus
- Retinal vascular abnormalities
- Optic nerve hypoplasia
- Refractive problems due to small globe size
- Coloboma

Auditory

- Conductive hearing loss
- Neurosensory hearing loss

Neuroendocrine

- Altered hypothalamic-pituitary-adrenocortical axis—heightened stress response
- Abnormal thyroid function

Mechanisms for Alcohol-related CNS Effects

The scientific literature regarding FAS is vast. Accumulated over 3 decades, there are now more than 5,000 articles in print. Many of these publications address possible mechanisms for alcohol's detrimental effects on the developing brain. No unifying hypothesis has emerged, nor is there likely to be one in the future. Rather, a picture has been drawn of a teratogen that has multifactorial effects at the molecular, cellular, and tissue levels. These may be direct effects because alcohol freely crosses the placenta and the blood-brain barrier, and they may be indirect effects via alcohol's metabolites or by alcohol's effects on placental or coronary blood vessels. Alcohol's effects also may interrelate with various hormonal, neurochemical, and neurophysiological systems that regulate normal brain growth. Furthermore, results vary according to species, dose, gestational age at exposure, specific brain region studied, and the frequent clinical occurrence of polydrug exposure.

Several reviews published recently have attempted to summarize the considerable progress made in the past decades toward unraveling the complexities of alcohol's detrimental effects on the developing brain. One of the best is by James West in 1994 (see Suggested Reading). Dr West categorizes progress toward determining the mechanisms for alcohol's neuroanatomical, neurotransmitter, neurotrophic, and signal transduction effects (Table 6). In addition, there has been considerable effort

Table 5. Neuropathologic and Neurophysiologic Abnormalities Observed in Animal Models of FAS

- Abnormal proliferation and migration of neurons
- Increased neuronal death
- Abnormalities in dendritic growth
- Transient cortical astrogliosis
- Decreased synaptic density
- Abnormal development of the cerebral microvasculature
- Holoprosencephaly spectrum
- Decreased number of pyramidal cells in hippocampus
- Hypomyelination
- Altered cerebrovascular responsivity
- Adenosine-mediated inhibition of fetal breathing movements

Table 6. Potential Mechanisms for Alcohol's Effects on the Developing Brain

Neuromorphologic Effects

- Altered proliferation and migration of neurons
- Increased neuronal cell death/apoptosis
- Altered dendritic growth
- Transient cortical astrogliosis with increased expression of glial fibrillary acidic protein
- Altered microvascular development (increased capillary diameter)
- Decreased protein synthesis
- Loss of pyramidal neurons in the CA1 region of the hippocampus
- Loss of Purkinje cells in the cerebellum
- Free radical toxicity
- Imbalance in prostaglandin levels
- Impaired DNA methylation
- Disordered fluidity and organization of membrane phospholipid bilayer
- Interference with ganglioside activity during critical periods of brain maturation
- Decreased availability of vitamin B6
- Folate deficiency
- Altered retinoic acid levels
- Increased intracellular calcium levels
- Altered unavailability and utilization of zinc or other trace elements
- Impaired cerebrovascular reactivity
- Hypoxia-ischemia induced indirectly via effects on umbilical vessels

Effects on Neurotransmitter Receptors

- Upregulation of *N*-methyl D-aspartate (NMDA) receptor function
- Altered gamma-aminobutyric acid (GABA)-mediated neurotransmission in cortical neurons
- Altered release of dopamine in the nuclueus accumbins, gender-related
- Excess endogenous nitric oxide (NO) formation leading to glutamate-mediated excitotoxic neuronal cell death
- Massive apoptotic neurodegeneration by interference with both NMDA and GABA receptor systems
- Abnormal development of the serotonergic system

Effects on Neurotrophic Support and Growth Factors

- Inhibition/depletion of neurotrophic activity in rat hippocampus and forebrain
- Diminished ability of sensory ganglion neurons to respond to nerve growth factor (NGF)
- Altered NGF-induced neurite outgrowth
- Abnormal thyroid function
- Reduced serum growth hormone levels

Effects on Signal Transduction

- Adaptive reduction in adenosine receptor-stimulated adenylate cyclase activity
- Altered levels of G-proteins which regulate adenylate cyclase activity
- Increased protein kinase C phosphorylation
- Upregulation of density of voltage-sensitive calcium channel sites
- Increased cytosolic calcium concentration in response to acute alcohol intoxication

devoted to study of alcohol's effects on the developing cerebral circulation and on alcohol's metabolic effects.

Key Risk Factors for Alcohol-induced Brain Damage

Prenatal alcohol exposure affects the growth and development of the fetal brain. Furthermore, even heavy alcohol users produce offspring who have alcohol-related brain disorders ranging from no apparent adverse effects to severe mental and psychomotor retardation. Thus, the major questions confronting researchers today are the factors that increase the risk for alcohol-induced brain damage: alcohol dose, duration of exposure, temporal vulnerabilities, and associated drug and environmental interactions. These questions are exceedingly difficult to answer clinically for ethical, logistical, and sociological

reasons. Accordingly, animal models have been used extensively. When reviewing results from such studies, it is important to keep in mind the significant species differences in the timing of brain development. For example, the brain growth spurt in the human and sheep occurs in the third trimester of pregnancy; in the rat, it occurs postnatally. The rat has been the subject of most animal studies. It is also important to realize the differences between patterns of human alcohol consumption and laboratory alcohol administration protocols.

Given these caveats, following are partial answers to the difficult questions regarding alcohol's effects on the developing brain.

1. Peak blood alcohol concentration, not the length of alcohol exposure, is believed to be the critical variable in determining risk for adverse effects on brain development.

2. Cessation of drinking alcohol at any time during pregnancy is likely to be beneficial to the developing fetal brain, but particularly if cessation occurs prior to the second trimester.

3. Preimplantation embryos may not be as vulnerable to ethanol toxicity, and their development actually may be stimulated by moderate ethanol levels. This is a controversial area.

4. The cerebellum is particularly vulnerable to alcohol-induced growth restriction as well as neuronal loss following alcohol exposure during the brain growth spurt (third trimester in humans).

5. Heavy alcohol consumption during the first trimester is associated strongly with craniofacial abnormalities in humans and structural midline brain deformities in animal models.

6. Alcohol-associated microcephaly has been demonstrated to be dose-dependent late in gestation in animal models.

7. Chronic prenatal alcohol exposure causes hyperactivity in animal offspring that is dose- and age-related and that persists into adulthood.

Prevention of Alcohol-induced Fetal Brain Damage

In 2000, the AAP Committee on Substance Abuse published the following recommendations regarding prevention of FAS:

1. Abstinence is recommended for pregnant women and for those planning pregnancy.

2. High-quality educational programs should be developed for all levels of society regarding the deleterious effects of alcohol on the unborn child.

3. Health care professionals should increase their own awareness of FAS and ARND and their prevention.

4. The AAP supports federal legislation requiring the inclusion of health and safety messages in all alcohol advertisements that are based on the United States Surgeon General's warning: "Drinking during pregnancy may cause mental retardation and other birth defects. Avoid alcohol during pregnancy."

5. Parents of children diagnosed as having FAS or ARND should receive appropriate support services for themselves and their children, including careful anticipatory guidance directed toward preventing a similar problem in the future.

Despite considerable public health efforts directed at prevention of FAS by decreasing the use of alcohol by pregnant women, pregnant women continue to use and abuse alcohol. Therefore, research also has been directed toward preventive therapies that may be neuroprotective for the developing brain exposed to alcohol. Most of these studies have been designed based on results from animal studies that explored mechanisms for alcohol's effects on the developing brain. Preventive therapies include, but are not limited to, the following:

- Aspirin
- Neuropeptides
- Nitric oxide synthase (NOS) inhibitors
- Zinc supplementation
- Long-chain fatty acid supplementation
- Seratonergic receptor agonists

Neonatal Alcohol Withdrawal

An often-overlooked, but nevertheless important, adverse effect of maternal alcohol abuse is neonatal alcohol withdrawal. Although the literature on mechanisms and treatment of acute alcohol withdrawal in alcoholics is vast, virtually nothing exists on the subject in neonates. Yet, there have been anecdotal case reports in which alcoholic pregnant women have presented in labor after a binge when they had blood alcohol concentrations as high as 400 mg/dL. Clearly, as these women "detox," so do their newborns. Alcohol withdrawal induces significant cardiovascular, metabolic, and neurologic clinical signs. In neonates, the most important of these are:

- Hypoglycemia
- Irritability
- Tremors
- Seizures
- Autonomic dysregulation, including temperature instability

- Blood pressure abnormalities, including both hypotension and hypertension
- Excessive glucocorticoid release
- Altered behavioral state organization

Awareness of the potential for alcohol withdrawal in the newborns of alcoholic women is vital to prevention of further brain injury. Treatment generally is directed at the specific clinical signs.

Treatment/Interventions: Alcohol-induced Brain Damage

Children who have FAS and ARND demonstrate cognitive, behavioral, and psychosocial problems that cause lifelong disabilities. Treatment programs typically are directed at specific neurologic and neurobehavioral diagnoses. However, the most effective intervention programs generally are those that recognize and treat the unique patterns of disability common to children exposed to alcohol prenatally. One follow-up of a group of alcohol-affected children into adulthood demonstrated the profound, pervasive, and persistent nature of the disorder. In addition to the primary disabilities associated with alcohol exposure, affected individuals are at increased risk for secondary disabilities, such as mental health problems and chemical dependency (including alcoholism). Early diagnosis and intervention of affected infants hopefully will improve their outcomes and possibly reduce the occurrence of secondary disabilities.

Suggested Reading

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Stratton K, Howe C, Battaglia F, eds. *Institute of Medicine Report. FAS: Diagnosis, Epidemiology, Prevention and Treatment.* Washington, DC: National Academy Press; 1996

Streissguth A. *Fetal Alcohol Syndrome: A Guide for Families and Communities.* Baltimore, Md: Paul H. Brookes Publishing Co; 1997

West JR, Chen W-JA, Pantazis NJ. FAS. The vulnerability of the developing brain and possible mechanisms of damage. *Metab Brain Dis.* 1994;9:291–322

NeoReviews Quiz

1. A term newborn is admitted to the neonatal intensive care unit for observation. The maternal history is significant for consumption of alcohol throughout the pregnancy. Alcohol-related neurodevelopmental disorder is suspected based on a constellation of clinical features. Of the following, the infant is *most* likely to have:

   A. Congenital heart disease.
   B. Dandy-Walker malformation.
   C. Facial dysmorphism.
   D. Growth deficiency.
   E. Limb anomalies.

2. Fetal alcohol syndrome, which has an estimated incidence of 1 to 3 per 1,000 live births, is the leading cause of mental retardation in the United States. Of the following, the ethnic group with the *highest* incidence of fetal alcohol syndrome is:

   A. African-Americans.
   B. Asian Indians.
   C. Caucasians.
   D. Hispanics.
   E. Native Americans.

3. Numerous mechanisms have been proposed regarding the pathogenesis of the adverse effects of alcohol and its metabolites on the developing brain. Of the following, the mechanism *most* likely to explain the neurodevelopmental effect of alcohol on the fetus is:

   A. Cyanocobalamine deficiency.
   B. Decreased protein kinase C phosphorylation.
   C. Enhanced DNA methylation.
   D. Free radical toxicity.
   E. NMDA receptor downregulation.

4. Prenatal exposure to alcohol affects the growth and development of the fetal brain. Of the following, the *most* accurate statement regarding the adverse effects of alcohol on fetal neurodevelopment in humans is that:

   A. Alcohol-associated microcephaly is dose-dependent late in human gestation.
   B. Alcohol consumption during the first trimester is associated with midline brain deformities.
   C. Alcohol-induced growth restriction is observed most often in the cerebrum.
   D. Peak blood alcohol concentration is more critical than the length of alcohol exposure.
   E. Preimplantation embryos are vulnerable to alcohol toxicity.

5. The best strategy for the prevention of fetal alcohol syndrome is the promotion of abstinence from alcohol by pregnant women. Failure to accomplish this goal has led to research on other neuroprotective approaches. Of the following, the strategy *most* explored for neuroprotection against exposure to alcohol involves:

   A. Growth hormone.
   B. Iron supplementation.
   C. Nitric oxide synthase inhibition.
   D. Serotonergic receptor antagonism.
   E. Short-chain fatty acid supplementation.

6. A pregnant woman presents in advanced labor after a binge with alcohol and delivers a term neonate. The infant is observed for signs and symptoms of neonatal alcohol withdrawal. Of the following, the clinical feature *most* consistent with neonatal alcohol withdrawal is:

   A. Blood pressure abnormality.
   B. Hyperglycemia.
   C. Lethargy.
   D. Liver dysfunction.
   E. Respiratory distress.