In 1973, Jones et al. described, in the American medical literature, a constellation of features in children born to alcoholic mothers, now known as fetal alcohol syndrome (FAS). In 1996, the Institute of Medicine further defined criteria of FAS and proposed a new term: alcohol-related neurodevelopmental disorder (ARND) and alcohol-related birth defects (ARBD) to include structural CNS and cognitive abnormalities in children in whom fetal exposure to alcohol has been confirmed. The incidence of FAS in the United States is estimated to be about 1–3 per 1000 live births. The incidence is higher in certain population, such as Native Americans.

GENETICS/BASIC DEFECTS

1. Genetics
   a. Genetic susceptibility
      i. Observation of differences in the severity and spectrum of FAS based on genetic background
      ii. Higher concordance of FAS in monozygotic twins than in dizygotic twins supports the concept of genetic factors in the fetal effects of alcohol
   b. Possible mechanism of heritable susceptibility to FAS: genetically encoded differences in alcohol dehydrogenase, the enzyme responsible for metabolizing alcohol in the liver
      i. Mother of children with FAS: possibly with less functional enzyme resulting in higher peak blood alcohol concentration after the ingestion of alcohol
      ii. Fetuses with FAS: possibly with deficient alcohol dehydrogenase activity and thus less able to tolerate elevated maternal alcohol levels

2. Pathogenesis
   a. Clinical features of FAS: result from exposure of the developing fetus to toxic levels of alcohol and its metabolites at critical periods in development
   b. Specific pathophysiology unknown: may involve free radical formation that causes cellular damage in the developing tissues of the fetus
   c. Exposure in the 1st trimester
      i. Affects organogenesis and craniofacial development, leading to minor and major malformations such as the characteristic facial features and ARBD
      ii. Excessive cell death in the midline of the developing embryo may account for the development of these facial features
   d. Continuous use of alcohol by the mother later in pregnancy resulting in low birth weight and affecting postnatal growth
   e. Alcohol exposure at varying times in pregnancy may result in similar CNS neurodevelopmental effects
   f. Detrimental defects on the fetus when there is concomitant maternal use of other drugs (marijuana, nicotine, caffeine)

3. Key risk factors for alcohol-induced brain damage
   a. Peak blood alcohol concentration rather than the length of alcohol exposure: the critical variable in determining risk for adverse effects on brain development
   b. Cessation of drinking alcohol at any time during pregnancy likely to be beneficial on developing brain
   c. Cerebellum particularly vulnerable to alcohol-induced growth restriction as well as neuronal loss following alcohol exposure during the brain growth spurt (3rd trimester in humans)
   d. Heavy alcohol consumption during the first trimester associated strongly with craniofacial abnormalities in humans

CLINICAL FEATURES

1. Characteristic craniofacial features in the young child
   a. Discriminating features
      i. Short palpebral fissures
      ii. Flat midface
      iii. Indistinct (smooth, flat) philtrum
      iv. Thin upper lip
   b. Associated features
      i. Epicanthal folds
      ii. Low nasal bridge
      iii. Minor ear anomalies
      iv. Short nose
      v. Micrognathia

2. Growth retardation
   a. Low birth weight for gestational age
   b. Decelerating weight over time not due to nutrition
   c. Disproportionate low weight to height

3. Alcohol-related birth defects (ARBD): birth defects associated with in utero alcohol exposure
   a. Ocular abnormalities
      i. Strabismus
      ii. Retinal vascular anomalies
      iii. Optical nerve hypoplasia
      iv. Refractive problems secondary to small globes
      v. Coloboma
   b. Cardiovascular abnormalities
      i. Atrial septal defect
      ii. Ventricular septal defect
      iii. Aberrant great vessels
      iv. Tetralogy of Fallot
   c. Hepatic abnormality: extrahepatic biliary atresia
   d. Skeletal abnormalities
      i. Hypoplastic nails
      ii. Shortened 5th digits
Fetal Alcohol Syndrome

3. Radioulnar synostosis
4. Flexion contractures
5. Camptodactyly
6. Clinodactyly
7. Pectus excavatum/carinatum
8. Klippel-Feil syndrome
9. Hemivertebrae
10. Scoliosis

e. Muscular abnormalities
   i. Hernias
      a) Diaphragm
      b) Umbilicus
      c) Inguinal
   ii. Diastasis recti
f. Renal abnormalities
   i. Aplastic/dysplastic/hypoplastic kidneys
   ii. Horseshoe kidneys
   iii. Ureteral duplications
   iv. Megaureter
   v. Hydronephrosis
   vi. Cystic diverticula
   vii. Vesicovaginal fistula

g. Genital abnormalities
   i. Hypospadias
   ii. Labial hypoplasia

h. Cutaneous abnormalities
   i. Hemangiomas
   ii. Hirsutism

i. Auditory abnormalities
   i. Conductive hearing loss
   ii. Neurosensory hearing loss

j. Neuroendocrine abnormalities
   i. Altered hypothalamic-pituitary-adrenocortical axis-heightened stress response
   ii. Abnormal thyroid function

k. Other abnormalities: include virtually any malformation

4. Alcohol-related neurodevelopmental disorder (ARND)
a. Structural CNS abnormalities associated with in utero alcohol exposure
   i. Microcephaly
   ii. Microencephaly
   iii. Decreased size of cerebrum, cerebellum, basal ganglia, diencephalons
   iv. Partial or complete agenesis of the corpus callosum
   v. Neuroglial heterotopia
   vi. Dendritic neuronal abnormalities
   vii. Holoprosencephaly sequence
   viii. Anencephaly
   ix. Porencephaly
   x. Ventricular enlargement
   xi. Dandy-Walker malformation
b. Neurologic abnormalities associated with in utero alcohol exposure
   i. Impaired fine motor skills
   ii. Deficits in balance
   iii. Poor tandem gait
   iv. Neurosensory hearing loss
   v. Poor hand-eye coordination
   vi. Hypotonia
c. Neurobehavioral abnormalities associated with in utero alcohol exposure
   i. Learning disabilities
   ii. Decreased IQ scores
   iii. Mental retardation
   iv. Attention deficit/hyperactivity disorder
   v. Poor impulse control
   vi. Problems in memory, attention, or judgment
   vii. Problems in social perception
   viii. Deficits in higher level receptive or expressive language
   ix. Poor capacity for abstraction or metacognition
   x. Autism
   xi. Adult mental illness
   xii. Alcohol or drug dependence
   xiii. Psychotic disorders
   xiv. Avoidant, antisocial, or dependent personality disorder
   xv. Depression
   xvi. Suicide

5. Neonatal alcohol withdrawal signs
   a. Hypoglycemia
   b. Irritability
   c. Tremors
   d. Seizures
   e. Autonomic dysregulation, including temperature instability
   f. Blood pressure abnormalities
      i. Hypotension
      ii. Hypertension
   g. Excessive glucocorticoid release
   h. Altered behavioral state organization

6. Medical risks for women who drink alcohol
   a. Increased mortality and breast cancer in women who drink more than two drinks daily
   b. Increased menstrual symptoms, hypertension, and stroke in women with higher levels of alcohol consumption
   c. Increased infertility and spontaneous abortion in women who drink heavily
   d. Adverse fetal effects after variable amounts of alcohol consumption, making any alcohol use during pregnancy potentially harmful

DIAGNOSTIC INVESTIGATIONS
1. Diagnosis of FAS based on clinical features in the setting of maternal alcohol use
2. Radiography for skeletal abnormalities
3. CT and MRI imagings for CNS abnormalities
4. Echocardiography for cardiovascular anomalies
5. Ultrasound for renal abnormalities
6. Neurologic and neurobehavioral evaluations

GENETIC COUNSELING
1. Recurrence risk
   a. Patient’s sib: high if the mother abuse alcohol during the pregnancy
   b. Patient’s offspring: high if the affected woman abuse alcohol during her pregnancy
2. Prenatal diagnosis
   a. Low maternal serum alpha-fetoprotein and low pregnancy-specific beta 1-glycoprotein observed in one report possibly reflecting primary or secondary effects of ethanol abuse in pregnancy and possibly useful in predicting fetal alcohol syndrome
   b. Prenatal ultrasound examination recommended for pregnant women who drinks to detect fetal growth retardation and various birth defects associated with in utero alcohol exposure

3. Management
   a. Beneficial effects of early diagnosis of FAS on medical intervention of affected infants and children
   b. Management of issues (medical and surgical interventions) regarding specific birth defects
   c. Implementation of resource programs for developmental delay, functional abilities, speech abilities, and social/behavioral interactions
   d. Appropriate interventions with educational evaluation and support and community resources such as The National Organization on Fetal Alcohol Syndrome (NOFAS)
   e. Evaluate and manage the siblings who also have FAS
   f. Prevention of alcohol-induced fetal brain damage
      i. Abstinence recommended for pregnant women and for those planning pregnancy since there is no known safe amount of alcohol consumption during pregnancy
      ii. High-quality educational programs regarding the deleterious effects of alcohol on the unborn child
      iii. High awareness of FAS and ARND and their prevention by health care professionals
      iv. Appropriate support services including prevention of recurrence for parents and children diagnosed as having FAS or ARND

REFERENCES
Fig. 1. Two brothers with fetal alcohol syndrome showing prenatal and postnatal growth deficiency and characteristic facial features (short palpebral fissures, flat nasal bridge, flat midface, smooth philtrum, and thin upper lip).

Fig. 2. Another boy with fetal alcohol syndrome showing short stature and similar characteristic facial appearance.