

**Birthdefectsalcoholhypothesis.doc    July 24, 2002**  
**NATIONAL CHILDREN'S STUDY**  
**CORE HYPOTHESIS**

**I. Proposed Core Hypothesis**

The impact of prenatal alcohol exposure on birth defects, neurodevelopment, IQ and antisocial behavior in children is poorly understood and is likely to vary by dose and timing of exposure and by maternal and infant metabolizing enzymes.

**II. Workgroup**  
**Birth Defects**

**III. Contacts**

Paul A. Romitti, University of Iowa, Tel: 319-384-5012, Email: [paul-romitti@uiowa.edu](mailto:paul-romitti@uiowa.edu)

Ken Lyons Jones, University of California at San Diego, Tel: 619-543-2039, Email:

[klyons@ucsd.edu](mailto:klyons@ucsd.edu)

Godfrey P. Oakley, Jr., Emory University, Tel: 404-727-2656; Email:

[gpoakley@mindspring.com](mailto:gpoakley@mindspring.com)

**IV. Public Health Significance**

***Prevalence*** Alcohol consumption, and in particular, maternal consumption during pregnancy remains a significant public health problem. Data from the 2000 National Household Survey on Drug Abuse (SAMHSA 2001) estimated that 104 million persons age 12 and over consumed alcohol in the past year, and more than one-third (46 million) of these individuals reported binge drinking (five or more drinks on one occasion) in the month prior to the survey. Another recent U.S. survey (Schoenborn and Adams 2001) found that 54% of women 18-24 years of age reported they were current drinkers, and that these rates were most prevalent (66%) among women 25-44 years of age. Also noted in this survey was that about 20% of these women reported heavy consumption (seven or more drinks per week). Women who consume alcohol often continue such behavior following conception. The Centers for Disease Control and Prevention (CDC) estimate that annually in the U.S. more than 130,000 pregnant women consume alcohol at levels shown to increase risk of alcohol related adverse birth outcomes. Further, between 1991 and 1995, CDC reported a fourfold increase in frequent (seven or more drinks per week) and heavy (five or more drinks on any one occasion) drinking during pregnancy. Although the overall rate of any alcohol use (at least one drink) among pregnant women has declined since then, rates of frequent and heavy drinking have remained stable (CDC 2002).

Prenatal exposure to alcohol has been linked with growth retardation (e.g., low birth weight), structural malformations (e.g., craniofacial), neurodevelopmental abnormalities (e.g., mental retardation) and behavioral deficits (e.g., attention deficit disorder). In 1996, the Institute of Medicine (IOM 1996) developed five categories of outcomes related to prenatal alcohol exposure: Category 1-Fetal Alcohol Syndrome (FAS) with confirmed maternal alcohol consumption; Category 2-FAS without confirmed maternal alcohol consumption; Category 3-Partial FAS with confirmed maternal alcohol exposure; Category 4-Alcohol-Related Birth Defects (ARBD) and Category 5-Alcohol-Related Neurodevelopmental Disorder (ARND) (Table 1). The term FAS was introduced in 1973 by one of us (KLJ) and Smith (Jones and Smith 1973) and corresponds to a characteristic pattern of facial anomalies, growth retardation, and neurodevelopmental abnormalities (Table 1). FAS is estimated to impact between 1,200

and 8,800 births per year in the U.S., although the actual prevalence is not known due to lack of comprehensive surveillance and follow-up of such births. Even more frequent are the pregnancy outcomes estimated to be affected by alcohol exposure but which do not meet the complete criteria for FAS. These outcomes, originally termed fetal alcohol effects (Clarren and Smith 1978), are defined by IOM categories 4 and 5 (Table 1) and may account annually for up to ten times the number of infants born with FAS.

Table 1. Diagnostic Criteria for Fetal Alcohol Syndrome (FAS) and Alcohol-Related Effects

---

**Fetal Alcohol Syndrome**

- 1. FAS with confirmed maternal alcohol exposure**
  - A. Confirmed maternal alcohol exposure<sup>a</sup>
  - B. Evidence of a characteristic pattern of facial anomalies that includes features such as short palpebral fissures and abnormalities in the premaxillary zone (e.g., flat upper lip, flattened philtrum, and flat midface)
  - C. Evidence of growth retardation by one of the following:
    - low birth weight for gestational age
    - decelerating weight over time not due to nutrition
    - disproportional low weight to height
  - D. Evidence of CNS neurodevelopmental abnormalities as in:
    - decreased cranial size at birth
    - structural brain abnormalities (e.g., microcephaly, agenesis of the corpus callosum, cerebellar hypoplasia)
    - neurological hard or soft signs (as age appropriate), such as impaired fine motor skills, neurosensory hearing loss, poor tandem gait, poor eye-hand coordination
- 2. FAS without confirmed maternal alcohol exposure**
  - B, C, and D as above
- 3. Partial FAS with confirmed maternal alcohol exposure**
  - A. Confirmed maternal alcohol exposure<sup>a</sup>
  - B. Evidence of some components of the pattern of characteristic facial anomalies
  - Either C or D or E:
  - C. Evidence of growth retardation by one of the following:
    - low birth weight for gestational age
    - decelerating weight over time not due to nutrition
    - disproportional low weight to height
  - D. Evidence of CNS neurodevelopmental abnormalities as in:
    - decreased cranial size at birth
    - structural brain abnormalities (e.g., microcephaly, agenesis of the corpus callosum, cerebellar hypoplasia)
    - neurological hard or soft signs (as age appropriate), such as impaired fine motor skills, neurosensory hearing loss, poor tandem gait, poor eye-hand coordination
  - E. Evidence of a complex pattern of behavior or cognitive abnormalities that are inconsistent with developmental level and cannot be explained by familial background or environment alone, such as learning difficulties; deficits in school performance; poor impulse control; problems in social perception; deficits in higher level receptive and expressive language; poor capacity for abstraction or metacognition; specific deficits in mathematical skills; or problems in memory, attention, or judgment

**Alcohol-Related Effects**

- 4. Alcohol-related birth defects (ARBD)**
  - Cardiac
  - Skeletal
  - Renal
  - Ocular
  - Auditory
  - Other (Virtually every malformation has been described in some patient with FAS. The etiologic specificity of most of these anomalies to alcohol teratogenesis remains uncertain.)
- 5. Alcohol-related neurodevelopmental disorder (ARND)**

Presence of:

  - A. Evidence of CNS neurodevelopmental abnormalities, as in any one of the following:
    - decreased cranial size at birth
    - structural brain abnormalities (e.g., microcephaly, agenesis of the corpus callosum, cerebellar hypoplasia)
    - neurological hard or soft signs (as age appropriate), such as impaired fine motor skills, neurosensory hearing loss, poor tandem gait, poor eye-hand coordination

And/or:

  - B. Evidence of a complex pattern of behavior or cognitive abnormalities that are inconsistent with developmental level and cannot be explained by familial background or environment alone, such as learning difficulties; deficits in school performance; poor

---

---

impulse control; problems in social perception; deficits in higher level receptive and expressive language; poor capacity for abstraction or metacognition; specific deficits in mathematical skills; or problems in memory, attention, or judgment

---

Summarized from IOM 1996

<sup>a</sup> A pattern of excessive intake characterized by substantial, regular intake or heavy episodic drinking. Evidence of this pattern may include frequent episodes of intoxication, development of tolerance or withdrawal, social problems related to drinking, legal problems related to drinking, engaging in physically hazardous behavior while drinking, or alcohol-related medical problems such as hepatic disease.

**Morbidity and Mortality** Morbidity and mortality associated with prenatal alcohol exposure are manifested initially in adverse birth outcomes and subsequently in behavioral and cognitive deficits throughout childhood and into adult life. Birth defects contribute to infant morbidity and are the leading cause of infant mortality. In addition to the specific pattern of malformation referred to as FAS, major malformations attributed to prenatal exposure to alcohol include central nervous system defects (Eckardt et al. 1998), craniofacial defects (Shaw and Lammer 1999); genitourinary defects (Mills and Graubard 1987) and heart defects (Tikkanen and Heinonen 1992). Infants with these defects often require surgical intervention, specialized health care and educational and social services that can total up to three-quarters of a million dollars per patient (Waitzman et al. 1996). Further some defects, such as heart defects, can contribute to mortality among children and adults.

Potential behavioral and cognitive deficits associated with prenatal alcohol exposure are numerous and continue to be elucidated. Children diagnosed with FAS, ARBD or ARND compared to those without prenatal alcohol exposure are more likely to exhibit hyperactive, disruptive, impulsive and delinquent behavior, including alcohol and drug abuse and crime (Streissguth et al. 1996; Roebuck et al. 1999; Mattson and Riley 2000). These children are also more likely to suffer from learning and memory deficits (Mattson et al. 1996) and have difficulty performing executive functions, such as problem-solving and abstract thinking (Kodituwakku et al. 1995). Although the extent to which prenatal alcohol exposure is associated with subsequent alcohol abuse among exposed offspring is unknown, alcohol abuse has been documented in some studies to have a genetic etiology.

**Quality of life** Infants with prenatal exposure to alcohol not only may face the clinical complications of adverse pregnancy outcomes, but also, a lifetime of health, behavioral, cognitive and social challenges.

**Economic and social burden** As mentioned, lifetime costs for individuals with an ARBD can total nearly three-quarters of a million dollars placing a considerable burden on personal and institutional resources (Tilford et al. 2001). In addition, behavioral and cognitive deficits attributed to prenatal alcohol exposure can have a substantial impact on our educational and legal systems.

**Perceived importance** Despite the fact that prenatal alcohol exposure is known to be associated with a specific pattern of malformation referred to as FAS, the disorder is frequently undiagnosed (particularly in the newborn period), prevention programs have been decidedly ineffective and strategies for helping affected children have been, for the most part, futile. By developing methods to more effectively diagnose FAS in the newborn period, such as by documentation of maternal alcohol consumption through development of effective biomarkers, it will be possible to enroll affected children early in life in programs to help them succeed in society. In addition, a better understanding of additional risk factors – genetic differences,

nutritional differences and maternal consumption patterns – that can impact pregnancy outcomes among women who consume alcohol will provide new insight into the diagnosis and prevention of FAS that can lead to a marked improvement in fetal, child and adult health and substantial reduction in the economic and social consequences of prenatal alcohol exposure.

***Preventability*** Prevention efforts to reduce prenatal alcohol exposure have included public service announcements, warning labels and educational campaigns to inform prospective mothers about fetal harm caused by alcohol exposure, although such efforts may be ineffective in reaching women at greatest risk. A review (Handmaker and Wilborne 2001) of more than 20 intervention programs and demonstration projects found that integration of a stepped intervention program into gynecologic and obstetric care might provide the most promise for prevention; however, with the overall ineffectiveness of current prevention programs, an alternative approach might be to better identify and target women whose offspring may be at highest risk (i.e., susceptible) to the adverse effects of prenatal alcohol consumption.

## **V. Justification for a Large, Prospective, Longitudinal Study**

The number of potential adverse conditions associated with prenatal alcohol exposure makes it arguably the most common reproductive toxin. Although it is clear that heavy consumption during pregnancy can have profound effects on human development, there remain important uncertainties as the dose decreases. Current evidence (reviewed by Maier and West 2001) shows that risk for alcohol-related outcomes may differ by maternal drinking patterns (amount consumed per occasion, rather than total amount consumed during pregnancy). To illustrate, evidence from a cohort of about 10,000 births to middle-class women suggests that as little as one drink per day can have an important lowering of the distribution of IQ; therefore, improved and timely measurement of drinking patterns corroborated with relevant biologic markers are needed to understand the dose-response relationships that can lead to such conditions. Along with improved measurement of alcohol consumption, is the need to better understand maternal metabolic patterns for alcohol and the role of fetal susceptibility to alcohol exposure. Advances made by the Human Genome Project now permit efficient identification of a large number of variants in a comprehensive selection of candidate genes, a key to successful characterization of gene-environment interaction effects. Given the continuous nature of both maternal alcohol exposure and the outcomes associated with such exposure, no cohort could be considered to large. Examination of the biology of the adverse effects of maternal alcohol consumption in a cohort of 100,000 births will increase by 10-fold the size of previous samples and ameliorate the limitations in such studies, particularly timely questionnaire assessment of drinking patterns, biologic measurement and evaluation of maternal metabolic patterns and detailed examination of fetal susceptibility to alcohol exposure. Further, a cohort of 100,000 births will provide sufficient size to examine potential gene-alcohol interaction effects for susceptible subgroups. Lastly, planned follow-up of children will permit increased elucidation of the long-term effects of prenatal alcohol exposure and will provide the opportunity to evaluate pregnancy outcomes in these affected individuals.

## **VI. Scientific Merit**

Considerable animal data exist that prenatal alcohol consumption is teratogenic (reviewed by Maier and West 2001). As examples, a study using chick embryos (Cartwright 1998) demonstrated that alcohol exposure early in pregnancy can have direct impact on the development of fetal tissue, such as apoptosis of cranial neural crest cells that results in abnormal facial features found in humans diagnosed with FAS. Studies in rats have shown that higher alcohol doses result in lower brain weight (Bonthius and West 1988), and studies in both rats (Pierce and West 1986; Bonthius and West 1990) and monkeys (Astley et al. 1999)

suggest that binge-like alcohol exposure is more harmful than non-binge exposure. Results from human studies of prenatal alcohol exposure and adverse outcomes have been plagued by methodologic limitations, specifically, lack of reliable exposure assessment and categorization of maternal drinking patterns. Comprehensive and consistent measurement of such patterns will permit human studies to parallel the contributions made by animal studies to our understanding of the teratogenic effects of prenatal alcohol exposure.

## **VII. Potential for Innovative Research**

The opportunity to conduct a comprehensive and prospective evaluation of prenatal exposure to alcohol would be unprecedented. The ability to utilize well-developed clinical screening tools to identify at-risk mothers, validated questionnaires and biomarkers of exposure to record maternal drinking patterns, biomarkers of effect to investigate maternal metabolic differences and biomarkers of susceptibility to identify infant sensitivity will provide exposure assessment and risk identification for the effects of alcohol, relevant candidate genes and gene-alcohol effects. The ability to follow-up exposed infants into adulthood will permit detailed characterization of the epidemiology of FAS, ARBD and ARND currently not permitted by the structure and mandates of U.S. birth defect and developmental disability surveillance systems. Further, such follow-up will allow for increased understanding of behavioral and cognitive deficits associated with prenatal alcohol exposure. Lastly, given the suspected frequency of exposure, improvements in care and prevention efforts that can be realized from study findings will have enormous public health implications.

## **VIII. Feasibility**

**Critical period** Accumulating evidence indicates that timing and pattern of maternal alcohol consumption may be an important predictor of alcohol-related health and developmental effects (reviewed by Maier and West 2001). To illustrate, infants of pregnant monkeys exposed to binge-like patterns of alcohol consumption during the first three weeks, six weeks or all 24 weeks of gestation showed no differences in gross brain development and cognitive functioning, suggesting that early gestational exposure to binge-drinking may produce brain damage similar to that produced by exposure throughout gestation (Astley et al. 1999). Further, experimental evidence suggests that neuronal loss in the developing brain may occur after only a single episode of binge drinking (Goodlett and Eilers 1997; Pauli et al. 1995). In addition, early gestational exposure to alcohol has been associated with malformations of the cerebellum (Bonthius et al. 1996), eye (Clarren et al. 1990) and face (Astley et al. 1999). Combined, this evidence supports the need for establishment of maternal drinking patterns during early gestation requiring enrollment of couples prior to conception.

**Sampling needs** Based on current estimates, between 30 and 200 pregnancies affected by FAS and up to 2,000 pregnancies with lesser effects related to prenatal alcohol exposure will be expected from the study cohort. Given that the teratogenic effects of alcohol exposure may differ by ethnicity, samples selected should include mothers of major ethnicities, particularly those of African-American, Asian-American, Mexican-American and Native American heritage.

**Contact** Since drinking patterns may vary prior to and following conception, women will need to be enrolled ideally prior to conception and contacted at various time intervals before conception and during pregnancy. To evaluate alcohol-related effects at birth, a detailed newborn exam will need to be conducted. To evaluate long-term effects, annual pediatric exams and neurobehavioral evaluation will need to be conducted.

***Measurement tools*** Numerous measurement tools are available to conduct comprehensive assessment of maternal prenatal alcohol consumption. These include: well-developed clinical screening tools to identify at-risk mothers (reviewed by Chang 2001), questionnaires to record maternal drinking patterns (reviewed by Dawson and Room 2000), and biomarkers (reviewed by Bearer 2001) to determine maternal drinking patterns, metabolic differences and infant susceptibility. Data requested from mothers would include questionnaire information for screening and determining alcohol drinking patterns and biologic samples for biomarker analysis. Collection of questionnaire data would be time-intensive but pose minimal risk to the participant. Collection of biologic samples, such as bloods and urine, could be conducted at preconception and prenatal visits, and in part, be acquired from leftover material from clinical tests limiting the burden on participants.

## **IX. References**

Astley SJ, Magnuson SI, Omnell LM, Clarren SK. Fetal alcohol syndrome: Changes in craniofacial form with age, cognition and timing of ethanol exposure in the macaque. *Teratology* 59(3):163-172, 1999.

Bearer CF. Markers to detect drinking during pregnancy. *Alcohol Res Health* 25(3):168-74, 2001.

Bonthius DJ, Bonthius NE, Napper RM, et al. Purkinje cell deficits in nonhuman primates following weekly exposure to ethanol during gestation. *Teratology* 53(4):230-6, 1996.

Bonthius DJ and West JR. Blood alcohol concentration and microencephaly: A dose response study in the neonatal rat. *Teratology* 37(3):223-31, 1988.

Bonthius DJ and West JR. Alcohol-induced neuronal loss in developing rats: Increased damage with binge exposure. *Alcohol Clin Exp Res* 14(1):107-18, 1990.

Cartwright MM, Tessmer LL, Smith SM. Ethanol-induced neural crest apoptosis is coincident with their endogenous death but it is mechanistically distant. *Alcohol Clin Exp Res* 22(1):142-9, 1998.

Centers for Disease Control and Prevention. Alcohol use among women of childbearing age-United States, 1991-1999. *MMWR* 51(13):273-6, 2002.

Chang G. Alcohol-screening instruments for pregnant women. *Alcohol Res Health* 25(3):168-74, 2001.

Clarren SK, Smith DW. Fetal alcohol syndrome. *New Engl J Med* 298 (19):1063-1067, 1978.

Clarren SK, Astley SJ, Bowden DM, et al. Neuroanatomic and neurochemical abnormalities in nonhuman primate infants exposed to weekly doses of ethanol during gestation. *Alcohol Clin Exp Res* 14(5):674-83, 1990.

Dawson DA, Room R. Towards agreement on ways to measure and report drinking patterns and alcohol-related problems in adult general population surveys: the Skarpö Conference. *J Subst Abuse* 12:1-21, 2000.

Eckardt MJ, File SE, Gessa GL, et al. Effects of moderate alcohol consumption on the central nervous system. *Alcohol Clin Exp Res* 22(5):998-1040, 1998.

Goodlett CR and Eilers AT. Alcohol-induced Purkinje cell loss with a single binge exposure in neonatal rats: A stereological study of temporal windows of vulnerability. *Alcohol Clin Exp Res* 21(4):738-44, 1997.

Handmaker NS and Wilbourne P. Motivational interventions in prenatal clinics. *Alcohol Res Health* 25(3):219-29, 2001.

Institute of Medicine. *Fetal Alcohol Syndrome Diagnosis, Epidemiology, Prevention, and Treatment*. Washington, DC: Institute of Medicine, National Academy Press, 1996.

Jones KL, Smith DW. Recognition of the fetal alcohol syndrome in early infancy. *Lancet* 2(7836):999-1001, 1973.

Kodituwakku PW, Handmaker NS, Culter SK, et al. Specific impairments in self-regulation in children exposed to alcohol prenatally. *Alcohol Clin Exp Res* 19(6):1558-1564, 1995.

Maier SE, West JR. Drinking patterns and alcohol-related birth defects. *Alcohol Res Health* 25(3):168-74, 2001.

Mattson SN, Riley EP. Parent ratings of behavior in children with heavy prenatal alcohol exposure and IQ-matched controls. *Alcohol Clin Exp Res* 24(2):226-231, 2000.

Mattson SN, Riley EP, Delis DC, et al. Verbal learning and memory in children with fetal alcohol syndrome. *Alcohol Clin Exp Res* 20(5):810-16, 1996.

Mills JL, Graubard BI. Is moderate drinking during pregnancy associated with an increased risk for malformations? *Pediatrics* 80(3):309-314, 1987.

Pauli J, Wilce P, Bedi KS. Acute exposure to alcohol during early postnatal life causes a deficit in the total number of cerebellar Purkinje cells in the rat. *J Comp Neurol* 360(3):506-12, 1995.

Pierce DR, West JR. Blood alcohol concentration: A critical factor for producing fetal alcohol effects. *Alcohol* 3(4):269-272, 1986.

Roebuck TM, Mattson SN, Riley EP. Behavioral and psychosocial profiles of alcohol-exposed children. *Alcohol Clin Exp Res* 23(6):1070-1076, 1999.

Schoenborn CA, Adams PF. Alcohol use among adults: United States, 1997-98. National Center for Health Statistics. *Vit Health Stat* 324, 2001.

Shaw GM, Lammer EJ. Maternal periconceptional alcohol consumption and risk for orofacial clefts. *J Pediatr* 134(3):298-303, 1999.

Streissguth AP, Barr HM, Kogan J, Bookstein FL. Final Report: *Understanding the occurrence of secondary disabilities in clients with Fetal Alcohol Syndrome (FAS) and Fetal Alcohol Effects (FAE)*. Seattle, WA: University of Washington Publication Services, 1996.

Substance Abuse and Mental Health Services Administration (SAMHSA). *Summary of Findings from the 2000 National Household Survey on Drug Abuse*. Office of Applied Studies, NHSDA series H-13, DHHS Publication No. (SMA)01-3549. Rockville, MD, 2001.

Tilford JM, Robbins JM, Hobbs CA. Improving estimates of caregiver time cost and family impact associated with birth defects. *Teratology* 64(Supplement 1):S37-S41, 2001.

Tikkanen J, Heinonen OP. Risk factors for atrial septal defect. *Eur J Epidemiol* 8(4):509-15, 1992.

Waitzman NJ, Scheffler RM, Romano PS. *The cost of birth defects-Estimates of the value of prevention*. Lanham, MD: University Press of America, Inc., 1996.