Alcohol-Related Birth Defects: an Update

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Synopsis

Historically, mankind has at least suspected that alcohol was somehow connected with undesirable effects on progeny. In the 18th century, physicians became aware that maternal alcohol consumption resulted in excess fetal and neonatal mortality, low birth weight, and many other deleterious effects. Perhaps as a response to the temperance and Prohibition periods, scientists lost sight of or interest in the effects of alcohol in pregnancy. In the late 1960s and early 1970s, the issue surfaced again, and scientists began systematic and in-depth studies of fetal alcohol syndrome (FAS) and alcohol-related birth defects (ARBD).

Epidemiologic research now suggests that FAS has outranked Down's syndrome and spina bifida in prevalence and is now the leading known cause of mental retardation. Further, it is the only one of these three that is preventable. Because a safe limit of alcohol consumption in pregnancy is not defined, abstinence during pregnancy is the most prudent preventive measure.

Factors such as race, beer drinking, maternal weight gain, and low socioeconomic status are associated with a statistical increase in the incidence of FAS. In families where one child has been diagnosed as having FAS, the incidence rate can be as much as 405-fold higher than the worldwide average.

Neurobehavioral deficits can occur in the offspring of drinking mothers in the absence of a diagnosis of full FAS. The deficits differ with age and seem to persist into adulthood. Mental retardation or borderline mental retardation is a nearly ubiquitous neurological deficit in diagnosed FAS. In one study, it occurred in 75 percent of the non-FAS offspring of mothers who continued to drink heavily throughout their pregnancy.

From the mid-1970s, having established that alcohol is a teratogen, scientists have been trying to uncover the mechanism by which alcohol exerts its embryotoxic effects. Recent promising neuroanatomical studies have demonstrated that alcohol has a deleterious effect on neuronal migration and hence on the development of the cerebral cortex. Other studies have shown that prenatal alcohol exposure, by adversely affecting hippocampal development, may be responsible for the learning deficits so frequently encountered in FAS children. Other research has implicated prostaglandins in the mechanism of alcohol-related dysmorphology.

HISTORICALLY, there have been various cautions and proscriptions concerning alcohol and procreation. In the 18th century, London presented a unique opportunity to observe alcohol's effects on progeny. In a comprehensive review of historic literature, Coffey describes what is commonly known as the "Gin Epidemic," from 1720 to 1750 (*1*). In an effort to support the grain-producing gentry, Parliament reduced controls on distilling and selling of gin, expressly to promote its production and consumption. Public houses abounded, and the sale of gin flourished. Observations of excess fetal and infant mortality at ages less than 5 years were attributed to the consumption of alcohol (*2*). Birth rates declined, and death rates increased in a period of good wages, plentiful food, and relative freedom from epidemic diseases. More than a few reports and petitions by physicians, health care providers, and legislative committees speak of effects on children that correlate with some of the features of fetal alcohol syndrome (*2*). For example, in 1725 the College of Physicians in London warned the House of Commons that alcohol is " . . . too often the cause of weak and feeble, distempered children" (*3*).

Observations and reports of alcohol's effects on the growth and development of children continued throughout the 18th and 19th centuries; often they

were a mixture of medical science and temperance mortality (*1,2*). In one 1899 paper, a carefully elaborated study for that period, Dr. William Sullivan recorded his observations of 600 children born of 120 female alcoholic prisoners in a Liverpool prison (*4*). Sullivan's work represents one of the earliest descriptions of what was later to be called fetal alcohol syndrome.

With the advent of Prohibition in 1920, the issue of alcohol's effects on pregnancy outcome was largely ignored both in the United States and Britain for nearly 20 years—until 1940, when new research again began to emerge. Much of that research consisted of animal studies that ridiculed the moralistic studies of the pre-Prohibition era (*2*) and attempted to refute the "germ cell damage" caused by alcohol (*5*). Indeed, a great deal of the medical writing up to and into the sixties not only condoned maternal alcohol use, but even prescribed it for "sluggish digestion" (*6*) and frequently for delaying labor.

In 1967, a family practitioner from Rennes, France, Dr. Alexandre Lamache, spoke before the French Academy of Medicine concerning his observations—throughout his 37 years of practice—of 1,245 children of alcoholic parents (*7*). The importance of that report does not lie in its adherence to any scientific rigor, but in its signaling a renaissance of interest in alcohol-related birth anomalies. His observations included neurological dysfunction, mental retardation, behavioral disorders, genital malformations, facial anomalies, and excess infant mortality. In 1968, also in France, Lemoine and his coworkers published what seems to have been the first well-organized study of alcohol-related birth defects among humans in the modern era (*8*). In the United States, the era of interest in fetal alcohol effects was presaged by a report by Ulleland in 1970 on prenatal growth deficiencies in 10 children of alcoholic mothers (*9*). Eight of these children were examined by Jones and Smith, who recognized a distinct pattern of abnormalities, a syndrome, in four of them. In 1973, they and their colleagues reported their finding, which they called fetal alcohol syndrome (FAS) (*10*).

Today, alcohol is recognized as a teratogen, that is, a substance that is capable of producing birth defects (*11*). The consequences of alcohol use in pregnancy range from subtle neurological disturbances and reduced birth weight to the unique cluster of abnormalities that constitutes FAS. To meet the diagnostic criteria set by the Fetal Alcohol Study Group of the Research Society on Alcoholism (*12*), a diagnosis of FAS requires specific manifestations in three areas: (*a*) prenatal or postnatal growth retardation (below the 10th percentile), (*b*) central nervous system perturbations that may include tremulousness, poor sucking reflexes, abnormal muscle tone, hyperactivity, attentional deficits, or mental impairment, and (*c*) at least two characteristic facial anomalies including narrow eye width, ptosis, a thin upper lip, a short upturned nose with underdevelopment of the groove between the base of the nose to the top of the upper lip, and general underdevelopment (hypoplasia) of the midfacial area. Two other terms "alcohol-related birth defects (ARBD)" and "possible fetal alcohol effects (FAE)," have been used in reports on alcohol and pregnancy outcome to address the consequences of prenatal exposure to alcohol that do not meet the minimal FAS criteria. ARBD are complications of pregnancy or birth defects that are attributable to alcohol after statistical analysis has corrected for the contribution of other possible factors (*13*). Possible FAE are birth defects observed in children of women known to have consumed significant amounts of alcohol in pregnancy that are likely, though not definitively, attributable to alcohol use (*14*).

Prevalence

Exact prevalance figures for fetal alcohol syndrome are not available, but the best estimate—based on local reports from various U.S. and European studies—is a range from 1 to 3 cases per 1,000 live births (*11*). Abel and Sokol, basing their estimate on 20 studies from Australia, Europe, and North America, found a worldwide incidence of 1.9 cases of FAS per 1,000 live births (*15*). At this rate, FAS is the leading known cause of mental retardation, ranking ahead of Down's syndrome and spina bifida (*16*).

Certain factors seem to influence incidence rates for FAS. When one studies the population most at risk for FAS—children of pregnant women who abuse alcohol or are alcoholic—the incidence rate rises dramatically. Abel and Sokol found that the incidence rate of FAS among mothers who were alcohol abusers was 59 per 1,000 live births, based on 14 U.S. studies that identified the incidence of alcohol abuse during pregnancy (*15*).

Abel reviewed literature on more than 300 clinical case studies in which siblings were mentioned to determine the incidence of FAS and ARBD among younger and older siblings of an FAS patient (*17*). Among older siblings, he found an incidence rate of 170 per 1,000 live births for FAS and 417 per

1,000 for ARBD. Among younger siblings of the index patient, the incidence of FAS was 771 per 1,000 and 886 per 1,000 for ARBD.

From two studies of more than 13,000 pregnancies, it was found that, in addition to persistent exposure to alcohol, susceptibility to FAS and ARBD increases with these factors: black race, frequent beer drinking, lower maternal weight and weight gain, and low socioeconomic status (*15,18*). In a study on the epidemiology of FAS among Indians in the Southwest, May and his colleagues found that being part of a Southwest Plains Indian culture also may lead to increased susceptibility to FAS, with an incidence of 9.8 per 1,000 births (*19*). An even higher occurrence of FAS was reported by Robinson and his coworkers (*20*) for a small isolated Indian community in British Columbia. In contrast, May and coworkers found that FAS incidence rates among Pueblo and Navajo Indians were more in line with the worldwide figure of 1.9 cases per 1,000 live births (*19*).

In a study to determine the critical period in gestation when alcohol causes anomalies, data on 359 neonates who were prenatally exposed to alcohol were subjected to multivariate analysis. The analysis confirmed that the critical period for alcohol teratogenicity is around the time of conception (*21*).

Neurophysiological Effects

Examples of some of the neurological problems that exist and persist in some children of drinking mothers have been described by Streissguth and LaDue (*22,23*). Among them are learning disabilities, speech and language problems, hyperactivity, and attentional deficits. Children with a diagnosis of FAS have an average IQ of 68–70.

Neurological problems resulting from prenatal exposure to alcohol apparently array along a continuum throughout the life of the affected person. By analyzing data from a large number of epidemiologic studies that reported neurobehavioral outcomes associated with prenatal exposure to alcohol, Streissguth found that the following neurological deficits accrue to the neonatal period: poor sucking, disrupted sleep states, low levels of arousal, tremulousness, unusual body orientation, excessive mouthing, abnormal reflexes, hypertonia, and poor habituation to redundant stimuli (*24*). Progressing to older infancy, one finds disrupted sleep-wake patterns, poor visual recognition memory, and decrements in mental and motor development, spoken language, and verbal comprehension. Preschoolers exhibit attentional deficits, delayed reaction time, and decrements in fine and gross motor performance. Adolescents present psychosocial problems and more overt psychopathology, and adults have problems in adaptive living and self-sufficiency.

Central nervous system (CNS) deficits were the subject of two Swedish studies of children born to alcoholic mothers. Aronson and Olegard studied 8- and 9-year-old children of alcoholic mothers and found that 25 percent attended special schools for the mentally retarded, and 35 percent had borderline mental retardation that required special help in school (*25*). Forty-three percent of the children of mothers who stopped drinking by midpregnancy and 75 percent of the children of mothers who continued to drink were mentally retarded or borderline mentally retarded. In a study by Larsson and Bohlin, 80 percent of children from alcohol abusing mothers presented behavioral disturbances or retarded psychomotor development or both (*26*).

Coles and coworkers conducted a series of studies on 103 neonates without FAS who were born to black mothers of low socioeconomic status (*27*). The infants were divided into groups whose mothers did not drink, who drank an average of 12 ounces of absolute alcohol (24 drinks) per week throughout their pregnancies, and who drank that amount but quit by the second trimester. Both alcohol groups were less optimal in neurobehavioral responses when examined at 3 days, but those whose mothers continued to drink throughout pregnancy were significantly lower in their orientation toward auditory and visual stimuli, motor performance, and autonomic regulation than those whose mothers did not drink. A subsample followed up at 30 days showed persistent behavioral deficits in the continued drinking group in reflexive behavior and autonomic control. An examination at 6 months of 60 of the infants found that differences in orientation, motor performance, reflexive behavior, and autonomic control at 3 days were predictive of mental development and motor performance at 6 months.

Streissguth likewise found persistent behavioral deficits in her cohort of children of heavier-drinking mothers to at least age 4 (*28*). The 4-year-old children whose mothers were heavier drinkers during pregnancy show clear performance decrements in tests requiring vigilance and fast reaction. This suggests that although the children of the heavier-drinking mothers may be clinically normal, their lowered vigilance and longer reaction time may represent minor alcohol-related CNS

perturbation along the same continuum that includes the severe neurological and behavioral deficits that occur only at alcoholic levels of consumption among mothers, that is, in FAS.

Mechanisms of Effects on the Fetus

Research on the possible teratogenic mechanism involved in FAS and ARBD has centered around direct alcohol toxicity, placental dysfunction, nutritional deficits, fetal hypoxia, and acetaldehyde toxicity. For a review of this research, see Randall (*29*). This paper briefly examines several potential mechanisms of certain ARBD that have been explored recently.

Because CNS deficits are such an important and tragic aspect of FAS, considerable research has addressed potential mechanisms of CNS-derived injury. One brain structure that has been a focus of attention is the hippocampus. The importance of the hippocampus in learning (*30,31*), a behavior manifestly affected in FAS, contributed to the attention given to the potential fetal alcohol-induced injury of this structure. A number of studies have demonstrated neuroanatomical abnormalities in the hippocampus following prenatal exposure to alcohol (*32–34*). Some evidence also suggests that alcohol exposure during the period that in the rodent model is the developmental equivalent of the human third trimester of pregnancy (the first 10 days after birth of the rat pup), exerted a greater adverse impact on hippocampal development than exposure during the equivalent of the first or second trimesters (*35*).

In addition to the hippocampus, prenatal exposure to alcohol also causes profound disruptions in the development of the cerebral cortex. Growth and development of the cerebral cortex requires the generation of neurons within the germinal zones and their subsequent migration to specific anatomic sites. Miller observed that alcohol alters the period for neuronal generation and the migration of newly born neurons (*36*). Further, the number, size, and shape of neurons were altered by prenatal exposure to alcohol.

An issue with significant public health importance is whether the extent of fetal injury relates more to the absolute quantity of alcohol to which a fetus is exposed, or to the maximal concentration of alcohol attained within the fetus. This issue was approached by West and his colleagues (*37*) in a study with young rat pups. Identical total amounts of alcohol were administered to two groups of rat pups. For one group the alcohol was divided into 12 even doses distributed over the course of a day; for the other group, the same daily amount was provided in 4 doses. Therefore, the latter animals, though administered the same total amount of alcohol, attained higher blood alcohol concentrations. The animals receiving alcohol in 4 doses had smaller brains for body size (microcephaly) than either the animals receiving alcohol in 12 doses or control animals receiving no alcohol. These decrements persisted past age 90 days. Further deficits in balance and hindlimb coordination were observed. That study indicated (a) the importance of alcohol concentration in relation to alcohol dose, and (b) exposure to alcohol in the third trimester results in persistent injury to the CNS.

An important finding arising from research is that prostaglandins may be involved as a mechanism of alcohol-induced birth defects. Prostaglandins are a class of lipids that exert hormone-like activities. Randall and Anton have observed that aspirin, a drug that functions as an inhibitor of prostaglandin synthesis and that can cross the placental membrane, antagonizes the teratogenic effects of alcohol (*38*). Though aspirin did not totally eliminate pathology caused by alcohol exposure, it did significantly reduce the number of fetal malformations.

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