The Effects of Alcohol on Fetal Development

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Prenatal exposure to alcohol has profound effects on many aspects of fetal development. Although alterations of somatic growth and specific minor malformations of facial structure are most characteristic, the effects of alcohol on brain development are most significant in that they lead to substantial problems with neurobehavioral development. Since the initial recognition of the fetal alcohol syndrome (FAS), a number of important observations have been made from studies involving both humans and animals. Of particular importance, a number of maternal risk factors have been identified, which may well be of relevance relative to the development of strategies for prevention of the FAS as well as intervention for those who have been affected. These include maternal age >30 years, ethnic group, lower socioeconomic status, having had a previously affected child, maternal under-nutrition, and genetic background. The purpose of this review is to discuss these issues as well as to set forth a number of questions that have not adequately been addressed relative to alcohol's effect on fetal development. Of particular importance is the critical need to identify the full spectrum of structural defects associated with the prenatal effects of alcohol as well as to establish a neurobehavioral phenotype. Appreciation of both of these issues is necessary to understand the full impact of alcohol on fetal development. **Birth Defects Research (Part C) 93:3–11, 2011.** © **2011 Wiley-Liss, Inc.**

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INTRODUCTION

Although prenatal exposure to alcohol is now believed to be the most common recognizable cause of mental retardation, the discovery of the effects of alcohol on fetal development has occurred only relatively recently. In 1973, a pattern of malformation, set forth in Table 1 and Figure 1, referred to as the FAS, was reported by Jones et al. (1973) and Jones and Smith (1973) in 11 unrelated children all of whom were born to chronic alcoholic women who continued to drink heavily throughout pregnancy. Before 1973 Lancet publication, a 1968 article written by Dr. Paul Lemoine and colleagues of Nantes, France, had appeared in the French literature describing a group of children with prenatal alcohol exposure who had very similar features. Recognizing that these children likely had the newly described syndrome, Dr. Lemoine commented, "My French colleagues did not believe me then and they do not believe me to this day."

The purpose of this review is to evaluate what has been learned over the last 37 years about alcohol and its effect on fetal development and to identify a number of critical questions regarding this issue, which have not been adequately answered. The molecular mechanisms through which alcohol disrupts normal development in animal models have been recently reviewed elsewhere (Kaminin-Ahola et al., 2010a,b; Lipinski et al., 2010) and will not be discussed here.

WHAT WE HAVE LEARNED
A Specific Pattern of Malformation has been Identified

In addition to the studies referred to above by Lemoine et al. (1968) and by Jones et al., three additional studies have been published which are arguably of most importance relative to this issue.

- In 1996, an Institute of Medicine Report (IOM) was published in which criteria were set up to establish the clinical delineation of the fetal alcohol syndrome (FAS) (Stratton et al., 1996). Five categories were described. The first is virtually identical to that set forth 23 years earlier, the second is the same as the first but does not require a history of maternal alcohol exposure. The latter three categories, Partial FAS, Alcohol Related Birth Defects (ARBD), and Alcohol Related Neurodevelopmental Disorder (ARND) have somewhat non-specific parameters set forth for diagnosis in each category.

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- In 2000, Astley and Clarren described the four-digit diagnostic code which was developed to assure accurate and precise diagnosis of individuals with prenatal alcohol exposure. The four-digit code was developed to meet the need of a broad range of professionals in a broad range of settings to assure accurate and precise diagnosis of individuals with prenatal alcohol exposure.
- In 2005, Hoyme et al. published a clarification of the 1996 IOM criteria. The purpose of their report was to facilitate the prac-

tical application of the IOM criteria in clinical pediatric practice. One of the important contributions of this article was the assertion that prenatal exposure to alcohol leads to a much broader pattern of malformation referred to as Fetal Alcohol Spectrum Disorders (FASD).

A Number of Neurobehavioral Abnormalities have been Elucidated

Although at the present time confidence that a child has been exposed prenatally to alcohol requires documentation of the very specific pattern of minor structural abnormalities set forth in Table 1, the most important and primary effect of alcohol on fetal development is on brain development. The spectrum of cognitive and behavioral abnormalities seen in individuals who have been exposed prenatally to alcohol is broad including decreased IQ, hyperactivity, behavioral and adaptive difficulties, and deficits in motor function, attention, verbal language, executive function, and visuo-spatial skills (Mattson and Riley, 1998).

As evidenced by a study published (Coles et al., 1985) concerning the offspring of a group of heavily drinking, predominantly black women of low socioeconomic

status who were ascertained during the 2nd trimester of pregnancy, these problems can occur in association with drinking at any time during pregnancy and can often be diagnosed in the neonatal period. In that study, neurobehavioral evaluation with the Brazelton Neonatal Behavioral Assessment Scale was conducted at 3 days postnatal age. As a group, infants prenatally exposed to alcohol at any time during gestation had significant alterations in reflexive behavior, less mature motor behavior, and an increased activity level in comparison to unexposed infants. For those infants whose mothers stopped drinking in the second trimester, observed state control, need for stimulation, motor tone, tremulousness, and asymmetries in reflexive behavior were superior to those whose mothers continued to drink throughout pregnancy These results indicate that damage to the central nervous system can occur not only following exposure to alcohol throughout pregnancy but also during only the early part of pregnancy.

Coles et al. (1991) were able to perform a follow-up study of a subsample of 68 of those same children at school age who were at an average age of 5 years 10 months. Twenty-five of those children were born to women who drank throughout pregnancy [absolute alcohol (AA)/week: mean = 11.80 oz]. Their cognitive development was compared with outcomes of children born to women (n = 22) who stopped drinking (AA/week: mean = 11.46 oz) in the second trimester and to the offspring of women who did not drink during pregnancy and who drank little postnatally (n = 21). When current drinking reported by caretakers was controlled, the children who were exposed throughout pregnancy showed significant deficits in various areas of intellectual functioning including sequential processing (short-term memory and encoding) and overall mental processing. Alcohol-exposed children displayed significant deficits in

TABLE 1. Fetal Alcohol Syndrome
Growth
Prenatal growth deficiency
Postnatal growth deficiency
Microcephaly
Performance
Developmental delay
Fine motor dysfunction
Face
Short palpebral fissures
Long, smooth philtrum
Thin vermilion border
Other
Maxillary hypoplasia
Cleft plate
Joint anomalies
Altered palmar creases
Cardiac defects

Figure 1. Four-month-old child on the left and the same child at 8 years of age on the right. Note the short palpebral fissures, smooth philtrum, and thin vermillion border of the upper lip.

pre-academic skills when compared with children of non-drinkers, with both alcohol groups deficient in pre-math and reading skills. These data suggest that alcohol exposure throughout pregnancy is correlated with identifiable deficits in sequential memory processes and specific academic skills. However, significant deficits in academic skills were present even when alcohol use was limited to the first part of pregnancy.

Howell et al. (2006) evaluated the effect of prenatal alcohol exposure on ability, academic performance, and school functioning in adolescence using the same longitudinal cohort of children who at the time of evaluation had a mean age of 15 years and 1 month. School records were abstracted for grade point averages, standardized achievement test scores, conduct, attendance, and special education placement. Three groups of adolescents between 13 and 17 years of age were recruited from that cohort: an alcohol-exposed group who had features of FAS, an alcohol-exposed group who did not have features of FAS, and a group of adolescents who were not prenatally exposed to alcohol. With respect to ability and achievement, those with FAS had significantly lower IQ scores than those in either of the other two groups. Those adolescents with FAS had lower scores than those in the other groups on all the WISC-III summary scores with the exception of freedom from distraction. In addition, the processing speed index was lower in the FAS group. Relative to adaptive functioning, neither the FAS group nor the alcohol-exposed without features of FAS group differed from those adolescents who were not prenatally exposed to alcohol. With respect to academic performance, on the school-administered achievement tests, the FAS group performed significantly less well than the other groups on reading and math. Relative to the incidence of disrupted school experience, there were no differences between groups in minor and major conduct problems as defined by school system criteria.

This latter study is not consistent with a previous study by Mattson et al. (1997). They evaluated 47 alcohol-exposed children, 34 with FAS, and 13 children who lacked the characteristic physical features of FAS as well as prenatal and postnatal growth deficiency. Children in both groups displayed significant deficits in overall IQ when compared with normal control subjects. Although the IQ scores in the alcohol-exposed group without physical features of FAS were marginally higher than those in the FAS group, few significant differences were found between the two alcohol-exposed groups.

Although it is clear that prenatal exposure to alcohol is associated with a number of serious neurobehavioral problems, the extent to which these problems are associated with defects in brain structure and function are only recently becoming evident. These have been reviewed by Norman et al. (2009). Magnetic resonance imaging (MRI) studies have documented overall reduction in brain volume and central nervous system disorganization, with specific structural abnormalities of the corpus callosum, cerebellum, caudate, and hippocampus. More sophisticated neuroimaging techniques have led to detection of regional increases in cortical thickness and gray matter volume along with decreased volume and disorganization of white matter in individuals with FASD. In addition, functional imaging studies have found functional and neurochemical differences in those prenatally exposed to alcohol.

Maternal Risk Factors have been Identified

At the present time it is clear that we do not yet understand which women are truly at risk of having a child with FASD. However, a number of maternal risk factors have been proposed that may well confer susceptibility for having a child with FASD. These include the following:

- Maternal age >30 years: The extent to which this risk factor relates to the age of the mother or the severity and duration of maternal alcoholism is not clear. Majewski (1981) showed that with increasing severity of maternal alcoholism, there was a concomitant increase in frequency and severity of FAS among the offspring. He speculated that the difference in outcome might be determined by the increasing inability of the alcoholic mother to metabolize acetaldehyde. Similarly, using a rat model, Sanchis et al. (1987) suggested that the stage of maternal alcoholism, as indicated primarily by the extent of liver damage, plays an important role in the frequency and severity of in utero alcohol effects. Also, using a rat model, Abel and Dintchell (1985) identified that older age of the dam was a critical variable in determining pregnancy outcome. Although they did not speculate regarding the mechanism, they showed that the older the dam, the greater the adverse effect of alcohol treatment on pregnancy outcome. Finally, Church et al. (1990), again using a rat model, showed an age-related increase in blood alcohol concentration despite exposure to the same dose of alcohol administered. With increasing maternal age, they showed an increase in maternal peak blood alcohol concentration as well as prolonged presence of alcohol. It was concluded that this age-related phenomenon was due to changes in alcohol absorption and/or elimination.
- Lower socioeconomic status: Abel (1995) has appropriately suggested that FASD is not an equal opportunity birth defect. There are a myriad of problems that are associated with and apparently contribute to the incidence of FASD. Lower socioeconomic (SES) group appears to be one of them. The incidence of

FAS in the United States in sites with predominantly low SES and African American or Native American background is ~10 times higher than sites with a predominantly middle/upper SES and Caucasian background. However, Abel concluded that low SES is the critical factor for occurrence of FAS at most study sites evaluated.

- Ethnic group: Although it has been suggested that an African American and Native American background is more frequently associated with FAS, the basis for this association is elusive. However, what does seem clear is that the prevalence of this disorder seems to be high anywhere in the world where alcohol consumption is present in the culture, where poverty is common, and where hope for the future is almost nonexistent. In those situations people have looked for ways to escape from their situation. Alcohol has been one way to do so. Wherever and whenever that occurs, the prevalence of FASD will be high.
- Previous child with FASD: Women who have had one child with FASD and continue to drink have an equal or increased risk of their subsequent children being similarly or more severely affected by alcohol (Davis and Lipson, 1984; Abel, 1988) In a study of Native Americans, for mothers who had one child with FASD and continued to drink similar amounts of alcohol, their next pregnancy ended with a child who was equally (47%) or more severely affected (53%) than the previous child. (May et al., 1983).
- Maternal under nutrition: In a number of studies of FAS, the mothers of affected children have been described as undernourished reflected by low prepregnancy weight or poor maternal weight gain during pregnancy (Abel and Hannigan, 1995). In studies in South Africa, the degree of severity of the clinical phenotype of FASD correlated significantly with lower maternal body weight and body mass index (May et al., 2008).
- Genetic background: Alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase (ALDH) are the liver enzymes responsible for the majority of alcohol metabolism. ADH oxidizes alcohol to acetaldehyde and ALDH then oxidizes acetaldehyde to acetate. ADH, unlike ALDH, has a number of polymorphisms. The isoenzymes encoded by those polymorphisms have differing ability to metabolize alcohol. Because ADH1B encoded isoenzymes have significant differences in their kinetic properties, it has been suggested that ADH1B alleles have a greater impact on the rate of alcohol metabolism. There are four studies that have evaluated the impact of genetic polymorphisms on the risk of FASD in humans. In the first of these, Viljoen et al. (2001) demonstrated that the ADH1B2 allele (a rapid metabolizer of alcohol) was more common in control mothers than in mothers of children with FAS from a mixed ancestry South African population.

In two additional studies, the ADH1B3 (a rapid metabolizer of alcohol) allele was more highly represented in control mothers than in mothers of children with neurobehavioral abnormalities seen in association with prenatal alcohol exposure from two different studies involving US African-American populations (McCarver et al., 1997; Jacobson et al., 2006). In a study by Das et al. (2004), facial photographs were taken at 1 year of age of children initially evaluated for neurobehavior by McCarver et al. (1997). They showed that a report of alcohol use by pregnant women prior to the first prenatal visit was associated with a significantly lower frequency of various alcohol-related facial features identified on the photograph in cases in which neither the mother nor the infant carried an ADH1B3 allele. On the basis of these four studies, it is hypothesized that because the heightened metabolic activity of ADH1B2 and ADH1B3 results in higher levels of the noxious and unpleasant metabolic intermediate, acetaldehyde, women possessing these alleles drink less and thereby do not attain as high a blood alcohol concentration, reducing the risk of FASD.

Animal Models have Added New Information to our Understanding of FASD

- Similarity of structural defects: Primarily based on the work of Kathie Sulik and her group at the University of North Carolina, a number of similarities have been identified between the face and brain of humans with FAS and animal models with prenatal alcohol exposure. Alcohol administration to C57B1/6J mice at gastrulation stages of embryonic development resulted in facial features characteristic of FAS (Sulik, 1984). These included microcephaly, microphthalmia, short palpebral fissures, deficiencies of the philtral region, and a long upper lip. Scanning electron microscopy of embryos 24 hr after alcohol administration at 7 days gestation revealed a decreased size of the neural plate, particularly in the forebrain resulting in abnormal brain and eye formation (Sulik, 2005). Analysis at later stages revealed the development of closely placed olfactory placodes resulting in deficiencies of the medial nasal prominences. (Sulik and Johnston, 1983).

Magnetic resonance microscopy is more recently being used to more meticulously identify the spectrum of brain defects resulting from prenatal exposure to alcohol and has permitted the identification of structural brain defects resulting from ethanol exposure at various stages of embryonic development. For example, acute ethanol administration to C57B1/6J mice at gestational day 7 results

in median facial and forebrain deficiencies which fall into the spectrum of holoprosencephaly, a structural defect that has been seen at one end of the spectrum of FASD, as well as cerebral cortical dysplasia/heterotopias, which have also been seen at the severe end of the spectrum in at least one newborn with FASD (Godin et al., 2010). On the other hand, ethanol administered to C57B1/6J mice on gestational day 8 resulted in volume reduction in all areas of the brain examined with the exception of the pituitary and the septal region. Several regions of the brain were disproportionally affected, that is, they were most severe on the right side and were significant for the olfactory bulb, hippocampus, and cerebellum (Parnell et al., 2009).

- Similarity of behavioral effects: Driscoll et al. (1990) compared the neurobehavioral effects of moderate prenatal alcohol exposure in humans and animals. With respect to qualitative endpoints, hyperactivity, attentional problems, inhibitory deficits, impaired learning, perseveration errors, feeding difficulties, gait anomalies, motor impairments, and hearing anomalies were similarly affected in both humans and animals. Of additional importance, the blood alcohol levels required to produce an effect were similar in animals and humans and were not necessarily associated with structural defects and the magnitude of the effects were apparently dose-related for both humans and animals.
- Genetic factors: One of the first animal studies to evaluate the impact of genetic differences on risk for prenatal alcohol risk was by Chernoff (1980). Females from three different inbred mouse strains maintained on the same diet made up of 20% ethanol derived calories were mated in a diallele cross. Fetal abnormalities were directly related to maternal blood alcohol levels, which differed based on the maternal strain. He concluded

that the maternal genotype was responsible for the fetal phenotype despite the fact that females of each strain were administered the same diet with the same percent of ethanol-derived calories. Boehm et al. (1997) studied the effect of prenatal alcohol exposure on three different inbred mouse strains. As opposed to the study by Chernoff, the same blood alcohol concentration was maintained in all three strains. Strain differences for both the extent and pattern of malformations as well as fetal mortality were documented. In two other studies, Thomas et al. (1998, 2000) evaluated the impact of strain differences on behavioral endpoints in rats bred for high-alcohol-sensitivity (HAS) versus low-alcohol-sensitive (LAS) lines. She observed increased motor activity and severe motor coordination deficits in the HAS line but not in the LAS line in rat pups who had received alcohol intragastrically in the neonatal period, equivalent to the third trimester of pregnancy in humans.

- Nutritional factors:
  - Zinc: Almost immediately following the identification of FAS in 1973, it was suggested by Lucille Hurley of the University of California, Davis that maternal zinc status was an important predictor of the risk for FASD (Hurley et al., 1971). It has been suggested that alcohol mediates significant changes in zinc status in the mother and fetus through induction of metallothionein (MT)-I and −II isoforms (zinc-binding proteins) in the maternal liver. Excessive production of MT results in sequestration of zinc in the liver with subsequent reduction in maternal plasma zinc (Taubeneck et al., 1994). Two studies of maternal ethanol exposure associated with decreased plasma zinc and increased fetal defects in MT knockout mice link the teratogenic effect of alcohol to the

induction of maternal MT and the limitation of fetal zinc supply from the plasma (Carey et al., 2000a,b). In these studies, it was demonstrated that liver zinc levels were increased and plasma zinc levels were decreased in MT+/+ mice exposed to alcohol. Conversely, liver zinc levels were decreased and plasma zinc levels were increased in MT−/− mice exposed to alcohol. Finally, increased fetal abnormalities were noted in the MT+/+ mice when compared to the MT−/− knockouts after prenatal exposure to alcohol. A final study confirming the fact that zinc deficiency plays an important role in alcohol teratogenesis was published by Summers et al. (2009). They acutely exposed C57BL/6J mice to alcohol on gestational day 8 and treated them with zinc supplementation from gestational day 0–gestational day18. They had four treatment groups: a saline plus control diet containing 35 mg zinc/kg in which there were 10 ± 0.4 % abnormal fetuses/litter; a saline plus dietary zinc supplementation containing 200 mg zinc/kg in which there were 9.1 ± 2.2 abnormal fetuses/litter; an ethanol plus control diet containing 35 mg zinc/kg in which there were 26.4 ± 3.5 abnormal fetuses per litter; and an ethanol+dietary zinc supplementation containing 200 mg zinc/kg in which there were 12.2 ± 3.3 abnormal fetuses per litter. The investigators concluded that dietary zinc supplementation throughout pregnancy can protect against fetal defects caused by ethanol exposure on gestational day 8.
  - Choline: Recent studies in rats indicate that perinatal choline supplementation is effective in attenuating behavioral effects resulting from alcohol exposure during the early neonatal period which is

equivalent to the period of brain growth spurt that occurs in the third trimester in humans. In addition, they showed that choline supplementation was effective in reducing the behavioral alterations later in the postnatal period after the ethanol-induced damage had occurred (Thomas et al., 2004, 2007). More recently, the same group has evaluated the extent to which prenatal choline supplementation mitigates the adverse effects of prenatal alcohol exposure on development in rats. Comparing pregnant dams exposed to 6.0 g/kg/day ethanol from gestational days 5–20 to two different control groups, they showed that choline administered at the same time as ethanol significantly attenuated most of ethanol's effects (Thomas et al., 2009, 2010).

- Intervention: Several reports have shown that rearing rats in an enriched environment after prenatal alcohol exposure can mitigate fetal alcohol effects on behavior. One of these seems particularly relevant. Hannigan

Figure 2. Railroad track configuration of ear. Note the prominent median crus of the helix in combination with the inferior crus of the antihelix leading to parallel ridges.

and Berman (2000) compared the offspring of pregnant rats exposed to high binge levels of alcohol from gestational day 8–20 to offspring of untreated pregnant rats. Both exposed and controls were housed for 8 weeks in either an enriched environment in which 12 rats were housed in large areas filled with various objects with which they could play or they were housed in isolation in steel/wire cages. Relative to non-exposed controls, rats exposed prenatally to alcohol and raised in isolation had locomotor gait dysmetrias indicative of a functional ataxia. After environmental enrichment, there was no longer any evidence of ataxia in the prenatally alcohol exposed group.

Questions Remaining to be Answered

- Spectrum of defects: Recognition of the full spectrum of defects associated with the prenatal effects of alcohol is necessary to understand the full impact of alcohol on development as well as to appreciate the true incidence of this disorder. Jones et al. (2010) evaluated 831 children from the collaborative initiative on fetal alcohol spectrum disorders with a structured protocol for diagnosis of FASD using the cardinal facial and growth features and assessment of additional structural features thought to occur more frequently in children with prenatal alcohol exposure. These additional features, initially set forth by Hoyme et al. (2005), include a "railroad track" configuration of the ears (see Fig. 2), ptosis of the eyelids, a "hockey stick" palmar crease (see Fig. 3), other palmar crease abnormalities, lack of complete extension of one or more digits, decreased supination/pronation at the elbows, other joint contractures, and heart murmur. With the exception of "other

joint contractures," there was a dose/response relation with FASD category ($p < 0.05$), with the children in the FAS group having the highest prevalence of each feature and those in the No FAS having the lowest prevalence.

- Neurobehavioral phenotype: Although a number of neurobehavioral deficits have been associated with prenatal exposure to alcohol, they are non specific. A major focus of research at the present time is the identification of a behavioral phenotype specific for prenatal alcohol exposure that would allow diagnosis of FASD in the absence of the specific pattern of structural anomalies that has been identified (Table 1). Toward that end, Mattson et al. (2010) have set forth a preliminary profile using data from two sites of a multisite study and a broad neuropsychological test battery. The profile was successful in distinguishing between FAS and non-exposed controls without FAS with 92% overall accuracy. Measures of executive function and spatial processing were particularly sensitive to prenatal alcohol exposure.

- Physical features most predictive of neurobehavioral abnormalities: It is becoming increasingly clear that alcohol is a behavioral teratogen. The importance of the physical features of FASD rests for the most part on their

Figure 3. Hockey stick palmar crease. Note that the distal palmar crease curves distally and terminates between the index and middle fingers.

ability to predict abnormalities in neurobehavioral development. Only one study, a PhD thesis (2002) by Del Campo, has looked critically at this issue. On the basis of 61 patients with heavy prenatal alcohol exposure who received complete dysmorphology exams and neurobehavioral evaluations, features most predictive of abnormal neurobehavioral function were decreased head circumference and a hockey stick palmar crease; less predictive were postnatal growth deficiency, a smooth philtrum, thin vermillion border of the upper lip, ptosis, and abnormal palmar creases (other than hockey stick crease); and not predictive of abnormal neurobehavioral function were birth weight, short palpebral fissures, and length of the philtrum.

- Genetic factors: Although various genetic polymorphisms of ADH and ALDH have been studied with respect to susceptibility for and/or protection against the development of FASD, no genome-wide association or linkage studies have been done. Lombard et al. (2007) have highlighted a list of candidate genes from the TGF-β, MAPK, and Hedgehog signaling pathways that are all potential targets for the teratogenic effects of alcohol on humans.
- Nutritional factors: Data primarily from animal studies suggest that nutritional issues are important risk factors that may well confer protection against and/or susceptibility for the prenatal effects of alcohol. An ongoing prospective study in Ukraine is potentially of importance relative to this issue and is the first study to evaluate the maternal blood levels of various micronutrients as a potential risk factor for FASD (Keen et al., 2010). Preliminary data from that study show that plasma zinc and copper concentrations are lower in pregnant women who report high alcohol intakes versus women who drink lightly or not at all. It has long been hypothesized that zinc can interact with maternal alcohol exposure to influence the risk for FASD (Keen et al., 2010).
- Intervention: Although few programs to successfully intervene with affected children are available, a number are being developed and tested. A conference which brought together a number of investigators involved in developing innovative interventions was held recently. (FASD Fall Conference, 2010, Atlanta, GA). The Math Interactive Learning Experience (MILE), one such program, utilizes parent training, teacher training, and individualized math instruction with the goal of improving math skills and children's behavior in school and at home (Kable et al., 2007). In randomized clinical trials of this program, children with FASD demonstrated gains on standardized math tests and improved behavior that persisted at a 6 month follow-up assessment (Coles et al., 2009).
- Prevention: By virtue of the variable causes and manifestations of alcoholism, alcohol misuse, and heavy alcohol drinking, Waterson and Murray-Lyon (1990) have pointed out that effective prevention strategies for FASD must include a variety of approaches played out in a variety of different settings utilizing many different techniques. Discussing the same issue, May (1995) outlines three levels of prevention as they apply to women and their level of drinking:
  - Primary prevention which involves elimination of the root causes of heavy alcohol consumption in a community. The goal is that no children are born with FASD;
  - Secondary prevention which involves making measures available to individuals and populations for early detection and effective intervention to correct departures from good health, and
  - Tertiary prevention which involves providing measures to decrease the results of prenatal exposure to alcohol on the newborn infant and to help the mother adjust to those problems.

May (1995) recognized that issues related to culture, society, behavior, belief systems, and medicine must all be considered for both etiology and prevention.

CONCLUSION

The effects of alcohol on fetal development represent a major problem for which prevention continues to be evasive. It is critical to recognize that prevention of FASD will require that we, as a society, take responsibility to establish programs that go far beyond the education of pregnant women. Only by looking at this problem within a broad social and economic context will it be possible to understand the reason for drinking alcohol during pregnancy and to begin to develop strategies that might prevent it.

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