Fetal Alcohol Syndrome
Mechanisms of Teratogenesis

SAVITRI P. KUMAR, M.D.
Hospital of the University of Pennsylvania
Philadelphia, PA 19104

ABSTRACT
The mechanisms implicated in the fetal alcohol syndrome are described, with discussion on the effects of alcohol, acetaldehyde, and zinc deficiency on the fetal growth and development.

Introduction
The relationship between maternal alcohol abuse during pregnancy and adverse fetal outcome was suspected for centuries and established by the report of Jones et al in 1973, who noted the characteristic pattern of malformations in infants. Alcohol has been shown to be teratogenic in various animal models; the mechanism whereby alcohol produces the effect is still unclear, although several factors have been implicated. The purpose of this paper is to review the mechanisms by which alcohol produces its teratogenic effect.

Alcohol, like other drugs with a low molecular weight, passes freely across the placental barrier, and the concentration of alcohol in the fetus is almost as high as in the maternal blood. Acute doses of alcohol are metabolized almost exclusively in the cytosol fraction of the liver, with the rate-limiting step involving the oxidation of ethanol to acetaldehyde by a nicotinamide adenine dinucleotide (NAD) linked enzyme, alcohol dehydrogenase. The activity of the enzyme may be genetically dependent. A hepatic microsomal ethanol oxidizing system (MEOS) with characteristics similar to the microsomal drug detoxifying system is induced by chronic administration and may also be genetically determined.

One theory of the fetal alcohol syndrome is that alcohol functions like a teratogen similar to thalidomide, with induction of malformation in the embryo or fetus when exposure occurs at a critical stage of development. According to this theory, termination of pregnancy is the only option if a toxic dose is ingested at the "vulnerable" period of gestation.

The appearance of the children with fetal alcohol syndrome suggests a "genetic disorder" to some investigators. Acetaldehyde, the metabolite of alcohol, has been shown to be cytotoxic and mutagenic at high blood levels and interferes with structure and function of the microtubular system in the adult liver. A similar alteration of microtubular structure concerned with
the mitotic process could lead to chromosomal alterations.

Studies in different strains of mice\(^1\) have shown that prenatal death, malformations, and fetal weights were directly related to maternal blood alcohol levels. Fetal abnormalities and maternal blood alcohol levels varied with maternal strain and were inversely related to maternal alcohol dehydrogenase activity. It appears that maternal blood alcohol level is a better predictor of fetal outcome than the amount of dietary alcohol, as the latter can be influenced by the level of maternal alcohol dehydrogenase activity. This is supported by the frequent observation of varying degrees of insult in the offspring of women consuming similar amounts of alcohol.\(^1\)

**Effects of Alcohol**

Alcohol has been shown to disrupt directly the normal embryonic development in fish blastomeres, chicken and rat embryos exposed to alcohol. The positive relationship between fetal insult and blood alcohol level noted by Chernoff\(^3\) supports the direct mechanism of alcohol teratogenesis. However, in the same study, an indirect method of alcohol induced teratogenesis has been implicated by the positive relationship between fetal insult and the degree of MEOS induction, which may produce teratogenically active intermediates.

**Effects of Acetaldehyde**

Various authors have suggested that acetaldehyde, the primary metabolite of ethanol, rather than ethanol itself, may be responsible for the toxic dependency-producing and teratogenic properties of ethanol. Acetaldehyde has been shown to be intensely cytotoxic, mutagenic, and teratogenic at a blood level \(>30 \mu\text{mol per L}\), which is the maximum concentration found in healthy people ingesting alcohol. Veghelyi\(^16\) states that responsibility for fetal alcohol syndrome ascribed to acetaldehyde at maternal blood concentrations exceeding \(35\mu\text{mol per L}\) is probably due to an inherited or acquired defect of a specific aldehyde dehydrogenase. He suggests screening of prospective mothers for blood acetaldehyde levels after a drink, with advice against pregnancy if the levels are high.

O'Shea and Kaufman\(^13\) studied the effects of acetaldehyde on fetal growth and development of mice and noted a dose-dependent effect of acetaldehyde which was both teratogenic and embryotoxic when administered to pregnant mice during the early post-implantation period. A significant increase in embryonic and fetal losses was observed in acetaldehyde treated groups as compared to controls, both at mid-gestation and at term, with most anomalies observed in the central nervous system (CNS) resulting from failure of normal closure of the cranial and caudal regions of the neural tube.

Acetaldehyde appears to reproduce many of the general effects seen when ethanol itself is administered to pregnant laboratory animals. Kesaniemi and Sippel\(^19\) demonstrated that following administration of ethanol to pregnant rats, the ethanol content of intact placenta and fetus was the same as the maternal circulation. In contrast, only 25 percent of the acetaldehyde content present in maternal aortic blood could be found in the infant placenta and no acetaldehyde was found in the infant fetal tissue.

Although suggestive of direct effect, the teratogenic effects of acetaldehyde on mammalian embryos as shown by O'Shea and Kaufman\(^13\) may be due to a specific maternal or placentotoxic action with secondary effect on the fetus.

Alcohol has been shown to interfere with active transfer of amino acids across the placenta, reducing the availability of nutrients to the fetus.\(^12\) The effects of ethanol and acetaldehyde upon human placental uptake of actively transported
nonmetabolized amino acid, alpha amino isobutyric acid (AIB), was studied by Fisher et al., who demonstrated that no inhibition of uptake by term placental villi was seen in the presence or absence of alcohol even at 150 minutes of incubation. However, after 90 minutes of incubation with acetaldehyde, there was a significant inhibition of AIB uptake which could not be completely reversed, suggesting that in vivo metabolism of alcohol to acetaldehyde in the chronic pregnant alcoholic may impair placental transfer of essential amino acids contributing to the pathophysiology of fetal alcohol syndrome.

Recent evidence suggests that ethanol and acetaldehyde affect nucleic acid and protein synthesis. Incorporation of \(^3\)H thymidine into deoxyribonucleic acid (DNA) was significantly diminished by treatment with ethanol and acetaldehyde in regenerating rat liver, rat cells in culture, and rat fetal tissues. Reduced incorporation was especially marked in the fetal central nervous system. Treatment of dams specifically with acetaldehyde substantially reduced the uptake of the label into fetal DNA, particularly in animals receiving the larger dose and notably in the brain tissue. Fetuses from dams injected with acetaldehyde throughout pregnancy, and which survived, appeared to be normal, but the body weights of the animals were substantially lower than the controls. In addition, the incidence of fetal resorption sites rose appreciably, which suggests that, at the level used in the study, acetaldehyde was strongly embryotoxic. Resorption sites were found next to apparently healthy fetuses, which raises the possibility that the proposed barrier to acetaldehyde may be of varying effectiveness.

The demonstration that acetaldehyde severely depressed the incorporation of \(^3\)H thymidine into fetal DNA in the absence of accompanying ethanol serves to focus further attention on the possible involvement of this compound in fetal alcohol syndrome. All effects on DNA synthesis in the reported study occurred at concentrations of acetaldehyde considerably below the upper levels reported to occur in the blood of humans after drinking. Ethanol, on the other hand, affected the incorporation of \(^3\)H thymidine only when the intake was high, where the metabolic production of acetaldehyde would also be expected to be high.

**Effects of Zinc Deficiency**

Maternal dietary zinc deficiency in pregnant rats resulted in the development of congenital malformation in the pups, resembling those seen in the fetal alcohol syndrome. Increased urinary losses of zinc and hypozincemia have been noted in alcoholics. Over 70 metalloenzymes require zinc for their functions, and the metal is present in several dehydrogenases, aldolases, peptidases, and phosphatases. Alcohol dehydrogenase is a zinc-containing enzyme. Many studies have shown that zinc deficiency in animals impairs the incorporation of labeled thymidine into DNA, and that the decreased activity of deoxythymidine kinase may be responsible for reduction in DNA synthesis.

Flynn et al. studied the zinc status of alcoholic and nonalcoholic pregnant women and correlated it to fetal outcome. Alcoholic women had significantly lower plasma zinc levels than nonalcoholic women, and fetal cord plasma zinc levels were also lower in the offspring of alcoholic women. An inverse relationship was noted between plasma zinc levels and dysmorphic features in the offspring. However, the small sample size, the high incidence of birth defects in the nonexposed group, and a single determination of zinc level at delivery to assess the zinc status detracted from their study.

The effect of acute and chronic ethanol ingestion on placental zinc transport in pregnant rats was studied by Ghisham et
al$^5$ who noted that both acute and chronic ingestion led to a 40 percent and 30 percent reduction in $^{65}$Zn uptake in placental and fetal tissues, respectively. Chronic ethanol ingestion was also noted to result in a 30 percent decrease in fetal weight. Ghisham et al$^5$ concluded that alcohol interfered with placental transport of zinc and could partly explain the growth retardation seen in fetal alcohol syndrome.

In summary, while ethanol appears to be the principal agent responsible for fetal alcohol syndrome, a growing body of evidence suggests that acetaldehyde, with its inhibiting effect on DNA synthesis, placental amino acid transport, and morphologic alterations in the CNS of the developing mammalian embryo, could explain most of the abnormalities seen in fetal alcohol syndrome. The varying effects seen in the offspring of chronic alcoholic mothers ingesting a similar amount of alcohol is most likely dependent upon the differences in the ability to metabolize alcohol. Deficiencies of zinc, which is involved in a variety of metalloenzymes and protein synthesis, may also be contributory.

References