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Alcohol and Pregnancy
An Epidemiologic Perspective

Dwight T. Janerich, DDS, MPH, and Susan Taylor Mayne, PhD

ABSTRACT *This article considers maternal use of alcohol during pregnancy, from an epidemiologic perspective. In general, maternal use of alcohol during pregnancy has been associated with a number of effects in offspring including fetal alcohol syndrome, a reduction in birth weight, effects on behavior, and other late effects. It is apparent from the existing literature that the epidemiologic dimensions of these effects are poorly defined and hampered by methodologic problems. Assessment of both outcome and exposure can be difficult, and there is great potential for uncontrolled confounding. Additionally, it is unclear whether the apparent teratogenicity of alcohol results from direct, acute effects of alcohol on the developing fetus, or results from chronic effects of excessive alcohol intake in the mother. This article concludes with recommendations for further research, which may help clarify the complexity of effects associated with maternal use of alcohol during pregnancy. Ann Epidemiol 1990;1:179–185.*

KEY WORDS: *Alcohol, pregnancy, fetal alcohol syndrome.*

INTRODUCTION

The notion that intemperate parents have defective offspring has been considered for centuries (1). Around the turn of the century, a number of investigators examined this issue in terms of inheritance of physical abnormalities and abnormal personality traits. At that time, results indicated that alcoholic parents produced children who were abnormal, but not abnormal in any highly specific way.

In the early 1970s, a series of reports identified a collection of clinical endpoints associated with maternal alcoholism. This syndrome included a more specific phenotype and was labeled the fetal alcohol syndrome (2–4). The characteristics of this syndrome include distinctive facial anomalies, prenatal and postnatal growth retardation, central nervous system defects including reduced head circumference and mental retardation, and various other congenital malformations.

In recent years, the literature on alcohol and pregnancy has expanded from maternal alcoholism and fetal alcohol syndrome to include a number of studies concerning effects of moderate alcohol use, or isolated instances of heavy drinking, during pregnancy. These more recent studies suggest that maternal alcohol use is associated with a number of fetal effects ranging from a reduction in birth weight (5, 6) to more subtle, late effects such as behavioral abnormalities (7, 8). As the abnormalities associated with maternal alcoholism have broadened, the problems associated with classification for epidemiologic studies have increased. The research problems are therefore twofold: misclassification associated with disease in the offspring, and difficulty in obtaining accurate data on alcohol ingestion.

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The literature on alcohol and fetal effects consists of well over 1000 publications. Fewer than 100 of these publications are epidemiologic studies. Despite this fairly large number of studies in epidemiology and other disciplines, there is a lack of detailed information regarding doses and timing required for an effect, and about the biologic mechanisms underlying this association. The purpose of this article is to summarize the state of epidemiologic investigations in this area, and to focus attention on areas that need further study.

DISEASE AND EXPOSURE MEASUREMENT PROBLEMS

Perhaps the largest obstacle to understanding this problem is the issue of measurement of exposure and of the adverse health effects associated with maternal alcohol ingestion. Historically, fetal defects associated with maternal alcohol ingestion were poorly characterized and lacked specificity. This may be in part due to the reliance on anecdotal reports in the early literature. The first solid evidence that a "specific" condition was associated with maternal alcohol ingestion were the reports in the 1970s that first described fetal alcohol syndrome (2–4). In retrospect, the selection of the term "fetal alcohol syndrome" may be unfortunate because the exposure is incorporated into the diagnostic description. It is therefore unlikely that a diagnosis of fetal alcohol syndrome would be assigned in offspring of a woman who did not use alcohol. This introduces difficulties in trying to measure the rate of fetal alcohol syndrome for nonexposed women, and also provides an obstacle for calculating odds ratios or relative risks. Conceivably, the odds ratio for fetal alcohol syndrome and maternal alcohol use is infinity, if the denominator equals zero. A similar condition may occur outside of alcohol use, but the background rate in nonexposed women appears to be unknown.

While odds ratios for fetal alcohol syndrome and alcohol are unavailable, odds ratios for all malformations and for major malformations by level of maternal alcohol consumption have been calculated in a study reported by Mills and Graubard (9). This study showed relatively small, statistically insignificant odds ratios even for women who drank as many as 5 to 6 drinks per day; however, the confidence intervals were quite large. Of the malformations that are typically reported to be increased in offspring with fetal alcohol syndrome, only malformations of the sex organs were significantly related to dose of alcohol (9).

Ascertainment of the more subtle effects associated with maternal alcohol ingestion is also problematic. Learning disabilities and behavioral abnormalities not only may be the most common debilitating consequence of maternal alcohol ingestion, but also are probably the most difficult endpoints to study because they may not develop until well after birth. The epidemiologic tools available to examine these associations include case-control studies and cohort studies. Case-control studies may have difficulties associated with either differential or nondifferential misclassification of exposure (10). Considerable time separates the pregnancy and diagnosis of these conditions; therefore, accurate recall of exposure may be a problem. Differential misclassification could result if mothers of children with behavioral abnormalities recall alcohol use during pregnancy differently than do mothers of normal children. This effect can either increase or reduce the magnitude of the odds ratio (10). On the other hand, nondifferential misclassification (e.g., random recall error) results in an attenuation of the odds ratio toward the null value (10).

Cohort studies offer another approach for examining the effect of maternal alcohol ingestion, although they have their own set of difficulties. The logistics and

expense of long-term follow-up are problematic, and selective loss to follow-up can influence the estimate of the odds ratio. The primary advantage of this study design is that it avoids differential misclassification of exposure data, and may reduce nondifferential misclassification.

The problems inherent in estimating exposure to alcohol based on self-report have led some investigators to examine laboratory measures as indicators of exposure (11). However, results suggest that laboratory tests for alcohol, as with self-reports, are associated with problems including assay variability and error, subjective categorizing of continuous variables in order to make classifications, idiosyncratic responses of humans to alcohol, and a short plasma half-life for alcohol (11). In general, laboratory tests relate poorly to self-reported alcohol use when use is sporadic or infrequent (11). Thus, while laboratory tests can be used in conjunction with self-report to estimate exposure status, they are clearly inadequate to be used as a standard against which self-reports are to be judged (11).

CONFOUNDING

Many studies have reported that moderate maternal alcohol ingestion during pregnancy leads to a reduction in birth weight. Birth weight is an outcome that is simply and accurately measured, unlike the diagnosis of fetal alcohol syndrome or behavioral abnormalities. However, there are many possible determinants of birth weight such as maternal age and stature, parity, nutrition, tobacco use, maternal exercise, caffeine use, and recreational drug use. An association between maternal use of alcohol and other factors that influence birth weight introduces the potential for confounding. Kuzma and Kissinger (12) reported that the drinking habits of over 12,000 California women were associated with age; ethnicity; marital status; income; education; prenatal care; and use of tobacco, caffeine, or illicit drugs. Failure to adequately control for these and other factors could call into question positive results regarding moderate alcohol use during pregnancy and a decreased birth weight. This concept is supported by studies that failed to find an association between moderate alcohol consumption and birth weight, after controlling for a number of potentially confounding factors (13–15).

ALCOHOL TERATOGENESIS

The term teratogen originated from the Greek word *teratos* (monster) to describe agents that could cause gross congenital malformations in offspring. Teratogenesis has been gradually broadened to include agents that can cause any type of morphologic, biochemical, or functional abnormality produced during gestation. The broader concept of teratogenesis applies when the absence or deficiency of an agent (e.g., zinc) results in malformations, and may also be applicable to more subtle endpoints such as birth weight and behavior.

During the embryonic period, lasting from weeks 2 to 8 of gestation, most major morphologic abnormalities are produced, whereas physiologic defects and minor morphologic abnormalities generally are produced during the period of fetal development (beyond 8 weeks' gestation). Thus, susceptibility to teratogenic agents varies greatly with the timing of exposure. For many teratogens, a critical period of exposure during gestational development has been observed. For example, thalidomide was shown to be teratogenic when it was taken during gestational days 34 through 50 (16).

A critical period of exposure for alcohol teratogenesis is more difficult to define. Since facial anomalies associated with fetal alcohol syndrome can be quite subtle, it is not entirely clear that the critical period of exposure for fetal alcohol syndrome is restricted to the embryonic period. This association may be difficult to sort out epidemiologically, since exposure to significant quantities of alcohol during embryogenesis is frequently associated with significant exposure prior to conception, as well as during the fetal period. The critical period of exposure may not be the embryonic period for other physical effects of alcohol and pregnancy. Fetal weight gain is greatest during the late fetal period; therefore, the critical period of exposure for a decrement in birth weight may be during the later stages of gestation. This is consistent with the observation that growth retardation was not observed in infants born to women who reduced heavy drinking prior to the third trimester of pregnancy (17).

Experimental teratology suggests that teratogenesis is related to dose, with a teratogenic dose falling between that which is embryolethal, and that which has no effect (threshold). For example, at dosages below 50 mg/kg, cleft palates are not observed in the offspring of mice exposed to diphenylhydantoin in utero (16). At dosages of 50 mg/kg and above, a dose-response relationship is observed (16). Whether or not a threshold exists for alcohol teratogenesis remains to be determined, probably because of the methodologic difficulties in assessing exposure, as previously described. Scientific evidence of a threshold for alcohol is lacking; therefore, maternal abstinence during pregnancy is certainly prudent.

Many teratogens are associated not only with critical periods of exposure and thresholds, but also with a relatively specific outcome. As previously mentioned, there is a broad specificity of effect associated with alcohol teratogenesis. When a teratogen has a broad critical period, or very little specificity, or a highly variable threshold, it can be difficult to measure its effect or to characterize its biologic action, even in the face of strong evidence that the agent has teratogenic effects.

BIOLOGIC MECHANISMS

The biologic mechanisms by which maternal alcohol use or abuse could cause abnormalities and other effects in the offspring may be direct, indirect, or both. Direct mechanisms would be simple teratogenesis or fetotoxicity by alcohol and/or acetaldehyde. However, the strong evidence that maternal alcohol use does have an adverse effect on the fetus, together with the lack of evidence that there is a critical period that produces a specific adverse response in the fetus, seems to argue for the existence of multiple or indirect effects on the fetus. Indirect mechanisms could range from the generalized malnutrition that frequently accompanies alcoholism to other long-term side effects of alcohol, such as maternal hepatic damage. The latter is supported by the report that a high percentage of mothers and fathers of children with fetal alcohol syndrome die of hepatic cirrhosis (18). In addition to hepatotoxicity, ethanol can also be placentotoxic, impairing the normal transfer of essential fetal nutrients, resulting in selective fetal malnutrition (19). The observation that maternal plasma zinc levels are low in alcoholic women (20), due to hyperzincuria (1), may be important since rodent studies have clearly demonstrated that zinc deficiency results in congenital malformations or other serious defects in the central nervous system and brain (21).

The resolution of direct versus indirect effects of alcohol during pregnancy has important implications for prevention. The direct effects of alcohol can presumably be

avoided by alcohol cessation. However, alcohol may have persistent effects, as suggested by the results of Little and colleagues (22), which showed that women who abstained from alcohol during pregnancy but were previously heavy drinkers had an elevated risk for having offspring with a reduced birth weight. These results suggest that prevention of alcohol teratogenesis resulting from chronic alcohol use may require strategies that go beyond simple avoidance of alcohol during pregnancy.

IMPLICATIONS FOR FURTHER RESEARCH

Despite the widespread attention that the subject of alcohol and pregnancy has received, there are a number of issues that remain to be resolved, as reviewed by others (23). This section will highlight key areas where epidemiology could contribute to a better understanding of this issue.

As discussed earlier, when the cause of a disease or syndrome is incorporated into the diagnostic description (e.g., fetal alcohol syndrome, thalidomide defect or syndrome), the epidemiologist is faced with the nearly unsolvable problem of attempting to calculate a relative risk or odds ratio. Assuming that the condition now known as fetal alcohol syndrome does sporadically occur in the absence of maternal alcohol consumption, it is important to try to conduct well-designed studies where the outcome is assessed without knowledge of exposure history. Adequate control for confounding variables is absolutely necessary to estimate the odds ratio or relative risk of effects associated with maternal alcohol ingestion. In addition, recent studies that implicate beer, but not wine or liquor, in alcohol effects (15, 24–27) suggest that epidemiologists should pay attention not only to the amount of alcohol, but also to the source.

Alcohol abuse can cause lingering, chronic health effects in women who are in their reproductive years. For example, Mena and colleagues (18) reported that the eldest siblings of children with fetal alcohol syndrome appeared well, later siblings showed some clinical features suggesting fetal alcohol syndrome, and the youngest child was the most afflicted. These and other results suggest that the cumulative effects of long-term alcoholism which may affect host status may be important in the cause of fetal alcohol syndrome. A related issue concerns paternal alcohol use and risk for alcohol teratogenesis. Fetal alcohol syndrome has been reported to occur in children whose fathers, but not mothers, were alcoholics (18, 28, 29). This points to the possibility that elements of the syndrome might be passed genetically from the father through alcohol-induced chromosomal aberrations. Future epidemiologic studies in this area should be constructed to provide a clearer understanding of the mechanisms of alcohol teratogenesis for prevention purposes, because the risk may not be ameliorated by maternal abstinence during pregnancy.

Additionally, some studies have attempted to examine the issue of possible teratogenic windows that make the timing of use of alcohol during pregnancy especially risky (30). This question has been well studied for classic teratogens such as rubella and thalidomide, but clear evidence of this issue is not yet available for alcohol.

Finally, there have been no studies into the important issue of health effects in adolescents and adults who were exposed to alcohol in utero. Long-term follow-up of offspring previously evaluated in prospective cohort studies may provide one mechanism for examining this research question in greater detail. This area of research may be particularly challenging in that it will be difficult, but not impossible, to separate

the in utero effects of alcohol from potential effects associated with the postnatal home environment.

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