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REVIEW

MATERNAL ALCOHOL CONSUMPTION AND SPONTANEOUS ABORTION

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Abstract — This review examines the relationship between maternal alcohol consumption during pregnancy and spontaneous abortions. Although very high spontaneous abortion rates have been reported for alcoholic women, it is still uncertain if this is due to the direct effects of alcohol or the indirect effects of alcoholism-related disorders such as cirrhosis. The higher rates of spontaneous abortion among alcoholics may also be due to their higher pregnancy rates. Studies in animals indicate that blood alcohol levels >200 mg/dl can directly precipitate spontaneous abortion. The association between lower levels of maternal alcohol consumption and spontaneous abortion is much less clear. There is a definite effect of study site in these latter studies: those conducted in North America nearly always report statistically significant associations; those conducted in Europe or Australia nearly always report no significant associations. The reason for this difference is not related to differences in alcohol consumption. Possible explanations for this geographical difference include difference in the socioeconomic status of the women being studied and artefacts associated with the designs used to study these relationships.

INTRODUCTION

Alcohol's abortifacient potential dates back to ancient times. Pliny, a Roman historian, naturalist, and gossip, mentions a cucumber wine called 'miscarriage' (*Natural History*, 14: 108–112) and an Egyptian wine called 'delivery wine' which he says was used to induce abortions (*Natural History* 14: 21–22). Theophrastus, another contemporary naturalist–gossip, wrote about a wine from Greece that produced miscarriages in dogs and another that induced canine infertility (*History of Plants* 9.18.10). Theophrastus was subsequently misquoted and women, not dogs, became users of these wines (Athenaeus, *Dipnosophistae* I–31).

Nineteenth century medical texts and scientific articles paid little attention to alcohol's possible embryo- or fetotoxicity until the late 1800s and early 1900s, when birth rates in Europe began to decline. In 1876, Haddon commented on the frequency of early pregnancy and miscarriages among female alcoholics. A few years later, McDaniel (1883) conjectured that 'a succession of alcoholic debauches might . . . cause the death of the fetus *in utero*.' In 1909, Laitinen reported the results of a retrospective analysis of 5848 French families, which found that the number of spontaneous abortions was crudely related to the amount a woman said she drank, with an average of 1.07 abortions occurring among abstainers, 5.26 abortions among moderate drinkers (one glass of beer or less per day), and 7.11 abortions among 'immoderate' drinkers.

Experimental studies in animals supported such findings. French physician–scientist Charles Feré (1893, 1895) exposed chicken eggs to alcohol fumes in an incubator for the first week after fertilization and found that 15.5% of them failed to develop. Similar results were reported for fertilized sea urchin eggs exposed to 4% solutions of alcohol (Ridge, 1898).

Contemporary studies leave little doubt that alcoholic women have very high rates of sponta-

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neous abortions, but the relationship between alcohol consumption, in general, and spontaneous abortion is far less evident. This review examines the latter association and raises several issues concerning the interpretation of research relating to this potentially important relationship.

SPONTANEOUS ABORTION AMONG ALCOHOLIC WOMEN

Although alcohol consumption levels vary widely among alcoholics, the amounts consumed are generally far above those considered as 'heavy' drinking (e.g. minimum of two drinks a day) in most studies (Abel and Kruger, 1995). For instance, consumption levels for women being treated for alcoholism in a treatment facility are more of the order of an average of 16 drinks a day (Jones-Saumty *et al.*, 1981). In this review, the term 'alcoholic' is used to convey a comparable level of alcohol consumption, or when the authors of a study have used the term to describe their subjects. In either case, 'alcoholic' implies frequent consumption of intoxicating amounts of alcohol.

Very high spontaneous abortion rates among alcoholic women have been reported in Hungary (18.8%; Vitez and Czeizel, 1982), Germany (22%; Seidenberg and Majewski, 1978), Denmark (23%; Becker *et al.*, 1989), Scotland (46%; Beattie *et al.*, 1983), Russia (52%; Shurygin, 1974) and France (81%; Dehaene *et al.*, 1977). In some of these studies, these rates probably included multiple pregnancy losses by the same women. For example, in the United States, women with a clinical diagnosis of alcohol abuse were twice as likely as controls to have experienced three or more spontaneous abortions (Sokol *et al.*, 1980). A survey of the clinical literature relating to the fetal–alcohol syndrome (FAS) found that, out of 90 women with FAS children, 52% had had at least one spontaneous abortion, and the average rate of spontaneous abortion per mother was 2.2 (Abel, 1990).

Although alcoholic women and mothers of FAS children have high rates of spontaneous abortions, their pregnancy rates are not necessarily reduced as evidenced by the large numbers of children they often give birth to (Abel, 1984). The increased rate of spontaneous abortions among these women may therefore be due to a higher number of pregnancies. When spontaneous abortions were considered in terms of women, not individual pregnancies, differences between alcoholic women and controls were no longer significant (Becker *et al.*, 1989).

Most studies reporting high rates of spontaneous abortion among alcoholics are also problematic because the rates of spontaneous abortion among non-alcoholic women in the same studies (when presented) are often relatively high, e.g. 9.6% in Hungary (Vitez and Czeizel, 1982) and 8% in Denmark (Becker *et al.*, 1989). Since very little information is provided about the alcoholics in these studies, their high spontaneous abortion rates may be symptomatic of some other reproductive problem.

In contrast to the previously mentioned studies, a Swedish study found no differences in spontaneous abortion rates among a group of 92 alcoholic women whose daily alcohol consumption was about 12 drinks a day (Hollstedt *et al.*, 1983*a*, *b*). One of the reasons for the difference in outcome was that, unlike the previous studies, the alcoholics in the Swedish study did not differ from controls in socioeconomic status, marital status, previous diseases, or medical complications during pregnancies. The failure to find significant differences between alcoholics and non-alcoholics prompted the authors to conclude that, in the absence of various social and health differences, alcohol ingestion may not precipitate spontaneous abortions, even at levels associated with 'alcoholism'. This was also the conclusion of an earlier study, which found no differences in rates of spontaneous abortions between alcoholic women and those suffering from endogenous depression (Bark, 1979).

These latter two studies are noteworthy, not because they are out of line with the previously cited studies which did find significant associations, but because they imply that alcohol is not the only factor to consider in evaluating the high rate of spontaneous abortions among alcoholics. Many female alcoholics also suffer from depression (Bark, 1979), and there may be some inherent biological condition(s) these women share with depressive women that predispose(s) them for spontaneous abortions.

A medical disorder associated with both alcoholism and an increased risk for spontaneous abortion and other pregnancy complications, not

Table 1. Cross cultural comparison of studies reporting relationship between alcohol consumption and spontaneous abortion

Country	% drinkers	% drinking ⩾7 drinks/week	Significant increase	No significant increase	Type of study	Reference
Canada	30	4	✓		r	Armstrong *et al.* (1992)
USA	27	27	✓		p	Anokute (1986)
USA	49	3	✓		p	Harlap and Shiono (1980)
USA	57	6	✓		c	Kline *et al.* (1980)
USA		n.i.		✓	p	Little (1978)
USA	50	5	✓		r	Wilsnack *et al.* (1984)
USA	35	3	✓		c	Windham *et al.* (1992)
Australia	54	n.i.		✓	p	Walpole *et al.* (1989)
England	82	8		✓	p	Grisso *et al.* (1984)
England	51	n.i.		✓	p	Davis *et al.* (1982)
Finland	58	n.i.		✓	c	Halmesmaki *et al.* (1989)
Italy	65	n.i.		✓	c	Parazzini *et al.* (1991)
Italy	34	13		✓	c	Parazzini *et al.* (1994)
Italy	75	75		✓	p	Cavallo *et al.* (1995)
Scotland	92	6	✓		p	Plant (1985)
Spain	18	n.i.		✓	c	Dominguez-Rojas *et al.* (1994)

n.i. = no information; c = case control study; p = prospective study; r = retrospective study.

taken into account in any of the previous studies, is cirrhosis (Scholtes, 1979). As far as the outcome is concerned, it doesn't matter if a pregnancy is lost due to alcoholism or alcoholism-induced cirrhosis. But if the cause is being sought, the difference is important.

EPIDEMIOLOGICAL STUDIES

If the epidemiological literature relating to the effects of maternal drinking during pregnancy and spontaneous abortion is collectively scrutinized only from the standpoint of alcohol consumption levels, no consistent relationship between the two is evident. About half the studies report increased rates of spontaneous abortions related to drinking, whereas the other half report no significant association (see Table 1).

However, as indicated in Table 1, if the focus is shifted from alcohol consumption levels to study site, there is almost total consistency in outcome, regardless of consumption level, or study design, e.g. case–control, retrospective, or prospective strategy.

As indicated in Table 1, if the study was conducted in North America, the results point to a significant effect on spontaneous abortion; if done in Europe or Australia, the results indicate no adverse effect.

Since grouping studies in terms of drinking levels or design leads to inconsistency, whereas grouping studies by country leads to almost complete consistency, a likely inference is that while drinking levels are the same in these studies, the 'drinkers' are not. The corollary to this conclusion is that the women included in the drinking group in American studies differ from their respective control groups in a way that is related to the outcome being studied, whereas these groups are balanced much more evenly in the Australian and European studies. Although this conclusion cannot be proven or disproven as yet, there is some evidence to support such an inference. The following discussion of studies from these different sites highlights some of the important demographic differences, especially socioeconomic status, that may account for the disparity associated with study site.

AMERICAN AND CANADIAN STUDIES

In a very widely cited prospective study of alcohol's effects on spontaneous abortion, Harlap and Shiono (1980) reported a twofold increase in

spontaneous abortions for women consuming an average of one to two drinks a day during their second trimester of pregnancy. When the preliminary results of this study were first reported (Harlap *et al.*, 1979), maternal body weight was an important factor contributing to the rate of spontaneous abortions, and 'slender women' who drank were singled out as having a higher spontaneous abortion rate than others. When the final report appeared, maternal body weight was not even mentioned.

The absence of information about maternal body weight in the final report, given its fundamental relevance to pregnancy outcome and its apparent contribution in the original analysis, raises the obvious question: Why was maternal body weight ignored in the final redaction, especially since the decreased maternal body weights of the aborting women were probably the reason for their increased rate of spontaneous abortions? Omission of this information in the final publication, coupled with its apparent contribution in the original analysis, seriously compromises any conclusion one might draw from the reported findings.

This study is also problematical for other reasons. Whereas over 32 000 women were sampled, the authors did not originally intend to examine drinking patterns and there appears to have been considerable underreporting since the number of women consuming an average of two drinks a day was only 0.5%, far less than the norm (Sokol, 1980).

Another widely cited American study also reported a relatively low threshold for alcohol-related spontaneous abortions (Kline *et al.*, 1980), but is also problematic. In this latter study, women hospitalized for spontaneously aborting were compared with a control group in a prenatal outpatient clinic. Consumption of two to six drinks a week during pregnancy was estimated as producing a 2.35-fold increase in the likelihood of a spontaneous abortion. Although variables such as smoking, use of other drugs, and diet were taken into account, a larger percentage of the women in the alcohol group were on welfare. When the study was repeated with women in the alcohol group who were not on welfare, the previous relationship was no longer evident. The authors themselves also raised the likelihood that, in their own words, 'the group of women [who reported drinking twice a week in the first study may have] included those who on occasion drink a lot of alcohol' (Kolata, 1981). For instance, 62% of the cases drinking at least twice a week before pregnancy continued to drink at that level during pregnancy, although the typical trend is for most women (except very heavy drinkers) to decrease their alcohol consumption during pregnancy (Little *et al.*, 1976).

The probability that the relationships between the drinking levels reported in the previous two studies and an increase in spontaneous abortions is spurious and is, instead, related to health status and undernutrition of the mothers being studied is also suggested in a third study. This case-control study (Windham *et al.*, 1992) likewise found an increase in spontaneous abortions associated with relatively low levels of consumption, e.g. an average of one or more drinks a day during the first trimester; but the association was strongest among 'uninsured women' (a circumlocution for poverty-stricken).

While a prospective study from Oklahoma City (Anokute, 1986) reported an increase in spontaneous abortions associated with drinking during pregnancy among mainly white women not differing in socioeconomic status, the data presented in Table 3 of that study do not support the author's conclusion. Nor do they support another of the author's conclusions that the smokers in his study had a 100% chance of non-live births compared to non-smokers.

The Canadian study listed in Table 1 is also problematical, because the overall spontaneous abortion rate in previous pregnancies was almost 22% while the rate among abstainers was 20.5%. These very high baseline rates of spontaneous abortion suggest inherent problems in ascertainment or an unexplained but important bias in the study overall.

One of the most thorough attempts to assess drinking among women also included questions regarding spontaneous abortions and still births. A concerted effort was made to obtain valid self-reports of drinking behaviour through use of specially trained interviewers and specially worded questions regarding high levels of consumption. On the basis of retrospective study, the threshold for spontaneous abortion or still births was estimated at six or more drinks per day, consumed at least three times per week (Wilsnack

et al., 1984). Although the authors did not distinguish between spontaneous abortions and still births, these results suggest a relatively high threshold for these effects, which is more in line with the data from studies relating to alcoholic women than to women who drink an average of one drink a day.

Interestingly, the one exception to the general pattern in North American studies linking drinking and an increase in spontaneous abortion involved women enrolled in a health maintenance organization (Little, 1978). This exception is similar to Hollstedt *et al.*'s (1983*a*) study mentioned earlier, in which no significant association was found between maternal alcoholism and spontaneous abortion rates when alcoholic women did not differ from non-alcoholics in health. Although participation in a health maintenance organization does not preclude differences in health or socioeconomic status between women participating in the study; if this were so, it would support the inference that the relationship between drinking during pregnancy and an increase in spontaneous abortions is not due to the direct effects of alcohol.

EUROPEAN AND AUSTRALIAN STUDIES

In contrast to the populations examined in the American studies, the populations studied in Europe and Australia seem to be much more socioeconomically homogeneous. Interestingly, when there appear to be class differences between subjects, there is a stronger association between drinking and spontaneous abortions.

Four case-control studies, two from Italy (Parazzini *et al.*, 1991, 1994), one from Spain (Dominguez-Rojas *et al.*, 1994) and the other from Finland (Halmesmaki *et al.*, 1989), did not find any relation between alcohol consumption and spontaneous abortions.

The Parazzini *et al.* (1994) study is noteworthy because all miscarriages were confirmed by uterine curettage and pathological examinations. Women in the control group were recruited from those who delivered at term. All cases and controls were interviewed by trained interviewers using a standard questionnaire, which included items concerning number of days per week each type of alcoholic beverage was consumed in the week prior to pregnancy and during the first trimester of pregnancy, average number of drinks per day, and duration of drinking in years. None of these alcohol-related indices was significantly related to spontaneous abortion rates.

Nearly all of the European and Australian prospective studies have likewise found no significant associations between drinking and spontaneous abortion. Thus the prospective study by Walpole *et al.* (1989) from Australia also did not find any increase in the rate of spontaneous abortions related to total alcohol intake, but when women who miscarried were considered in terms of different alcoholic beverages, those who were 'heavy' beer drinkers (an average of two or more a day) were more likely to have had a spontaneous abortion than those who were not. The above authors pointed out that these heavy beer drinkers were more likely than wine drinkers to smoke more than one packet of cigarettes a day, and were likely to be of different ethnic origins, unmarried, and in a lower socioeconomic class. The fact that these women differed significantly from control women in several ways, in addition to their alcohol consumption, is congruent with the previous argument that it is the 'drinker' and her living conditions, as much as the drink, that accounts for the significant epidemiologically increased spontaneous abortion rates associated with drinking during pregnancy.

An interesting study from Finland examined the effects of alcohol administration on women in treatment for threatened first or second trimester abortion. A total of 239 women were routinely treated with beta-mimetics; 136 of these women also received oral and intravenous alcohol. Alcohol was administered as brandy (30–40 ml) four to five times a day and 'additional doses were liberally offered if a patient sensed uterine contractions.' Some women also received intravenous infusions of alcohol. Treatment lasted from 3 to >22 days. Alcohol-treated patients received an average of 3.8 drinks a day. After discharge, 53% of the women who received alcohol treatment in the hospital continued to drink at home to arrest uterine contractions. Alcohol treatment had no significant effects on abortions (Halmesmaki and Ylikorkala, 1988).

The one European study which did find a significant association between spontaneous abortions and drinking during pregnancy was correlational in nature (Plant, 1985). When the relationship was re-examined after controlling

for diet and smoking, the correlations which were weak initially remained very weak, e.g. 0.09.

STUDIES IN ANIMALS

Studies in non-human primates and dogs enable researchers to examine questions about causality in a more direct way than is possible in clinical or epidemiological studies. These studies have been reviewed in depth elsewhere (Abel, 1984; Blakley, 1988). In general, these studies support the conclusion that very high blood alcohol levels, such as one might expect in conjunction with alcoholism, are capable of producing spontaneous abortions. The blood alcohol threshold for these increases is ~200 mg/dl, although in some cases, blood alcohol levels have been considerably higher (Ellis and Pick, 1980; Altshuler and Shippenberg, 1981; Scott and Fradkin, 1984; Stuckey and Berry, 1984; Clarren *et al.*, 1987; Catlin *et al.*, 1993). To achieve a blood alcohol level of ~200 mg/dl, comparable to that producing spontaneous abortions in animals, a 120 lb pregnant women would have to drink about eight drinks over a 3 h period. A blood alcohol level this high would be associated with extreme stupor in someone not accustomed (i.e. tolerant) to this level of intoxication (animals are rendered comatose), and hence unlikely to be achieved by the overwhelming majority of drinkers.

SUMMARY, GENERAL CONCLUSIONS AND COMMENTS

While maternal alcoholism is associated with an increased risk for spontaneous abortion, it is uncertain whether this association is directly due to alcohol, a secondary effect of maternal illness, e.g. cirrhosis, or some other underlying reproductive problem variously described as 'habitual', 'recurrent', or 'repetitive' abortion, which is only coincidentally, not causally, related to drinking itself.

'Recurrent' abortion is defined as two or more consecutive abortions (Glass and Golbus, 1978) and is also associated with increased rates of perinatal mortality and morbidity (Funderbunk *et al.*, 1976). Conceivably, women who experience recurrent abortion, increased rates of perinatal mortality, etc. may have a particular underlying physiological constitution that predisposes them to these outcomes. In fact, many alcoholic women have ovarian dysfunction and menstrual disorders (see, e.g., Wilsnack, 1973; Moskovic, 1975; Beckman, 1979; Jones-Saumty *et al.*, 1981; Becker *et al.*, 1989; Russell and Bigler, 1979). In many cases, these disorders preceded, and may in fact have precipitated, heavy drinking on the part of women who became alcoholic (see, e.g., Lisanky, 1957; Curlee, 1969). Similarly, alcoholic women, or women who drink 'heavily', might be at increased risk for spontaneous abortions, in spite of their drinking, due to a family history of recurrent spontaneous abortions (Parazzini *et al.*, 1991). Heavy drinking for this group may be symptomatic of physiological problems related to spontaneous abortions, rather than causal, although studies in animals clearly indicate that toxic levels of alcohol are capable of interrupting pregnancies.

On the other hand, the consistency of the studies in non-human primates and dogs as to threshold blood ethanol concentrations for spontaneous abortion is impressive. If these studies have any bearing on humans, they give a certain validity to Wilsnack's estimated threshold in humans of 6 drinks a day for several days a week.

A further indication that alcohol consumption, at least at levels not associated with alcoholism or this level of drinking, is an unlikely cause of spontaneous abortions comes from a study which found that alcohol consumption affected the chances of a couple conceiving their first child; if, however they did conceive a child, drinking did not affect their subsequent likelihood for having another child. In other words, alcohol may interfere with conception, possibly by affecting sexual performance, but not maintenance of pregnancy, i.e. it did not increase spontaneous abortions (Olsen *et al.*, 1983). Given the increased parity of alcoholic women and women with FAS children (e.g. Abel, 1984; Sokol *et al.*, 1986), alcoholism does not have a major impact on spontaneous abortions.

Since most spontaneous abortions go unrecognized (Simpson, 1990), the relationship between drinking and spontaneous abortion may be a methodological artefact of when the 'cases' are collected. For instance, 'cases' may differ from 'controls' not in how often they abort, but in when they abort. In other words, women who abort during their second trimester (e.g. those studied by

Harlap and Shiono, 1980, and Kline *et al.*, 1980) are more likely to be hospitalized than are women who abort early in their pregnancies. Women in the former group will be examined for drinking ('cases') and they will be compared with women who gave birth ('controls'), not with women who aborted earlier and therefore did not give birth. Even though there may be no effect of drinking during pregnancy, alcohol may be identified as a risk factor for spontaneous abortion because the proper 'controls', i.e. women who habitually abort in their first trimester and do not drink, are not included in the study.

As indicated by Table 1, epidemiological studies reporting increases in spontaneous abortion rates associated with very low levels of drinking during pregnancy are singular in that virtually every study reporting such a relationship was conducted in the United States or Canada; those that did not find a significant link between the two were conducted in Europe or Australia. These differences in outcome cannot be simply explained as a difference in the percentage of heavy drinkers in North America compared to other countries (Abel, 1996). The health or socioeconomic status of the women included in the drinking groups must be given greater consideration in making inferences about alcohol's effects for this and other perinatal outcomes.

Finally, the influence of smoking has not been adequately taken into account in most of the studies listed in Table 1. Smoking is positively correlated with drinking, and in studies in which alcohol and smoking are both examined with respect to spontaneous abortion, smoking typically has a greater impact than drinking (see, e.g., Grisso *et al.*, 1984; Anokute, 1986; Parazzini *et al.*, 1991; Armstrong *et al.*, 1992; Dominguez-Rojas *et al.*, 1994; Cavallo *et al.*, 1995). For example, on the basis of their case–control study, Dominguez-Rojas *et al.* (1994) estimated that smoking 11 or more cigarettes a day produces a 3.35-fold increase in the likelihood of spontaneous abortion.

Epidemiological studies which look for interactions between smoking and drinking (e.g. Harlap and Shiono, 1980; Kline *et al.*, 1980) are very unlikely to uncover a statistically significant relationship between these dual activities because smoking and drinking do not occur independently of one another. Since most heavy drinkers are also heavy smokers, and most abstainers are also nonsmokers, there will be no interaction to examine, unless the sample size is large enough to include various combinations of smokers and drinkers, e.g. women who drink heavily and do not smoke, or women who do not drink and smoke heavily. Caffeine is another substance highly correlated with drinking, which also independently increases the risk of spontaneous abortion (see, e.g. Dominguez-Rojas *et al.*, 1994; Cavallo *et al.*, 1995). Only by stratifying drinkers on the basis of smoking and coffee consumption can the relationship between drinking and spontaneous abortion be properly tested. This is a recurrent problem in all epidemiological evaluations of fetal alcohol effects.

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