Infertility in Women and Moderate Alcohol Use

ABSTRACT

Objective. The purpose of this study was to investigate the relationship between moderate alcohol intake and fertility.

Methods. Interviews were conducted with 3833 women who recently gave birth and 1050 women from seven infertility clinics. The case subjects were categorized based on the infertility specialist's assignment of the most likely cause of infertility: ovulatory factor, tubal disease, cervical factor, endometriosis, or idiopathy. Separate logistic regression models were used to assess the relationship between alcohol use and each type of infertility, adjusted for age, infertility center, cigarette smoking, caffeine use, number of sexual partners, use of an intrauterine device (for tubal disease), and body mass index and exercise (for ovulatory factor).

Results. We found an increase in infertility, due to ovulatory factor or endometriosis, with alcohol use. The odds ratio for ovulatory factor was 1.3 (95% confidence interval [CI] = 1.0, 1.7) for moderate drinkers and 1.6 (95% CI = 1.1, 2.3) for heavier drinkers, compared with nondrinkers. The risk of endometriosis was roughly 50% higher in case subjects with any alcohol intake than in control subjects (OR = 1.6, 95% CI = 1.1, 2.3, at moderate levels; OR = 1.5, 95% CI = 0.8, 2.7, at heavier levels).

Conclusions. Moderate alcohol use may contribute to the risk of specific types of infertility. (*Am J Public Health.* 1994;84:1429–1432)

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Introduction

Although as many as 20% of married women in the United States have experienced infertility during their lifetime,[1] little attention has been given to the effect that many common exposures, including exposure to alcohol, have on a woman's ability to reproduce.

Much of the research that has been conducted involves studies of animals or alcoholic women. The animal research indicates that decreased steroid hormone levels,[2] reduced ovarian weight,[2,3] and amenorrhea[3] result from alcohol administration to rats or monkeys. Becker et al. reported that alcoholic women experienced higher frequencies of menstrual disturbance, abortion, and miscarriage than control subjects.[4] In a national survey of alcohol use habits and reproductive dysfunction in 917 American women, menstrual problems and gynecologic surgery were increased in women who reported high levels of alcohol intake.[5]

In this study, we examined the effect of moderate alcohol use on fertility in women. We compared self-reported history of alcohol consumption in case subjects who had primary infertility with that of control subjects who recently gave birth.

Methods

Originally, this case–control study was undertaken from 1981 through 1983 to examine the relationship between contraceptive practices and a woman's ability to conceive.[6,7] Case subjects were drawn from women who attended seven infertility clinics in the United States and Canada and who were accepted for work-up and evaluation. Infertility was defined as the inability to conceive after 12 months of unprotected intercourse or the failure to deliver a live-born child.

Case subjects were excluded if their infertility was due to congenital abnormalities, if they were seeking reversal of tubal ligations, or if their husbands had had vasectomies. Among the total number of case subjects who were eligible for interviewing, 5% refused, 10% were not interviewed due to a language barrier or other problem, 10% were lost to follow-up, and 10% had not completed their infertility work-up by the close of the study, leaving 1880 case subjects who were included. Work-ups in these subjects identified the following causes of infertility: ovulatory factor, tubal disease, cervical factor, endometriosis, male factor, or idiopathic infertility. Diagnostic protocols included, when indicated, measurement of basal body temperatures, hormonal studies, endometrial biopsies, postcoital test, hysterosalpingography, and diagnostic laparoscopy.

We assigned each woman to one infertility category based on her most likely cause of infertility, as indicated by the evaluating physician, and designated this cause as the case subject's "first diagnosis." However, infertility is often a multifactorial disorder. In a previous publication, we described in detail the distribution of second diagnoses (accom-

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TABLE 1—Profile of Case Subjects with Infertility and Control Subjects (in Percentages)

	Control Subjects (n = 3833)	Case Subjects: Ovulatory Factor (n = 431)	Tubal Disease (n = 230)	Cervical Factor (n = 105)	Endometriosis (n = 180)	Idiopathic (n = 104)
Center						
Boston	32.5	30.6	32.2	33.3	26.1	28.8
Vermont	8.3	11.6	21.7	8.6	12.2	15.4
Quebec	21.5	16.2	16.5	20.0	13.3	30.8
Washington, DC	8.4	10.0	10.9	0.9	11.7	12.5
Kentucky	13.1	13.0	3.9	10.5	25.6	1.0
Colorado	16.2	18.6	14.8	26.7	11.1	11.5
Age, y						
<25	40.2	44.3	41.7	33.3	32.2	28.8
25–29	40.1	36.9	36.2	41.0	41.1	38.6
30–34	17.6	14.6	19.1	23.8	25.0	28.8
>34	2.1	4.2	3.0	1.9	1.7	3.8
Education						
High school	29.4	29.5	35.2	29.5	27.2	26.0
College	70.6	70.5	64.8	70.5	72.8	74.0
Cigarette smoking						
Never	53.5	56.1	42.6	42.8	59.4	60.6
Former	16.5	11.4	16.1	14.3	13.9	11.5
Current	30.0	32.5	41.3	42.9	26.7	27.9
Number of sexual partners						
1	45.9	49.9	27.4	38.1	43.4	45.2
2–5	36.7	35.3	42.6	44.8	37.2	36.5
>5	17.4	14.8	30.0	17.1	19.4	18.3
Alcohol intake						
None	63.0	58.0	53.9	56.2	51.7	60.6
Moderate	30.1	33.0	34.4	34.3	38.9	33.7
Heavier	6.9	9.0	11.7	9.5	9.4	5.7

panying disorders that may have contributed to the infertility) among the women in each diagnostic category.[8] The group with ovulatory factor had the lowest percentage of women with an additional disorder (14.2%), whereas the group with a first diagnosis of tubal disease had the highest percentage (26.5%). Idiopathic infertility was always designated as a first and only cause.

Control subjects were recruited from women admitted for delivery of a live birth at hospitals adjacent to the infertility clinics. Adjacent hospitals were used to ensure both that the control subjects would have sought care at the hospital infertility clinic if they had been infertile and that the case subjects would have delivered at the hospital if they had become pregnant. All women admitted for delivery were eligible to be control subjects; among the potential control subjects, 5% refused to be interviewed, 8% had undergone infertility therapy, and 5% were not interviewed because of a language barrier or poor condition of the mother or infant, leaving 4023 control subjects for whom interviews were completed.

This report focuses on the 3833 White control subjects and 1050 White case subjects with no live-born children whose first diagnosis was ovulatory factor, tubal disease, cervical factor, endometriosis, or idiopathic infertility.

Information concerning reproductive history, medical and surgical history, and personal habits was collected by personal interview. Interviews of all case subjects were conducted before their infertility diagnosis. To ensure that all exposure information referred only to the time period before the likely onset of infertility, an "index date" was calculated for each case subject by subtracting the number of months during which she had been trying to conceive from the date on which she had first consulted an infertility specialist. Because the event that distinguished case subjects with primary infertility from control subjects was the first live birth, the index date for each control subject was the estimated date of conception of the first live-born child. If the control subject's pregnancy was planned, the index date was defined as the time at which the couple began attempting conception. Only exposures that occurred before the index date were considered relevant.

During the interview all subjects were asked "what was your average weekly consumption of each of the following beverages: beer (cans per week), wine (glasses per week), and liquor (ounces per week)" before the index date. To determine total alcohol intake per week, 13 g of alcohol was assigned per can of beer, 11 g per glass of wine, and 15 g per ounce of liquor.[9] Women consuming 100 g or less of alcohol per week (approximately one drink or less per day) were considered "moderate" drinkers, whereas those drinking more than 100 g per week were categorized as "heavier" drinkers.

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for each level of alcohol intake were calculated by using multiple logistic regression.[10] Separate models were used for each type of infertility. Variables evaluated included age, infertility center, religion, education, body mass index (weight in kilograms/height in meters squared), exercise, cigarette smoking, number of sexual partners, type of contraceptive used, and caffeine intake. Because the study included few non-White women, the analysis was restricted to Whites to control for race as a potential confounder. In all of the final models, age (<25, 25–29, 30–34, >34 years), center (Boston; Vermont; Quebec; Washington, DC; Kentucky; Colorado), cigarette smoking (current, former, never), number of sexual partners (1, 2–5, >5), and caffeine consumption (0–3.0, 3.1–5.0, 5.1–7.0, >7.0 g/week) were included. For analyses of tubal disease, we also controlled for use of an intrauterine device (yes or no); body mass index (<19.0, 19.0–20.9, 21.0–22.9, >23.0 kg/m^2) and exercise (0, 1–6, >6 h/week) were controlled for in models of ovulatory factor.

All tests of significance of the odds ratio were two-tailed. For the analyses involving tests of trend, we categorized alcohol use as explained above, assigned scores to each level of intake, and treated the scored factor as a continuous variable in the logistic regression model. All significant associations were indicated by $P \leq .05$ or a 95% confidence interval excluding 1.

Results

In general, with the exception of women with an ovulatory factor, case subjects tended to be somewhat older than control subjects (Table 1). Educational status was similar in the case and control groups, although those with tubal disease were slightly less educated than control subjects. Similarly, cigarette smoking and sexual habits were comparable in all women, but case subjects with infertility due to tubal disease or cervical factor were more likely to be smokers and to have had multiple sexual partners than were control subjects.

Case subjects who were diagnosed with tubal disease reported the highest levels of alcohol intake. Those with ovulatory factor, cervical factor, or endometriosis also consumed more alcohol than control subjects, although the majority of women in all of the groups reported no alcohol use.

After we adjusted for risk factors, significantly increased odds ratios were observed for infertility due to a first diagnosis of ovulatory factor or endometriosis (Table 2). For ovulatory factor, the odds ratio was 1.3 (95% CI = 1.0, 1.7) for moderate drinkers and 1.6 (95% CI = 1.1, 2.3) for heavier drinkers compared with nondrinkers. This trend of increasing risk of ovulatory infertility with increasing alcohol consumption was statistically significant (test for trend, $P = .005$). There was also a similar trend among women diagnosed with cervical factor (OR = 1.3, 95% CI = 0.8, 2.1 for moderate drinkers; OR = 1.6, 95% CI = 0.8, 3.3 for the heavier drinkers); however, relatively few women with cervical factor reported using alcohol and these estimates were thus unstable. The odds ratio for endometriosis was 1.6 (95% CI = 1.1, 2.3) for moderate drinkers and 1.5 for heavier drinkers (95% CI = 0.8, 2.7) compared with women who did not drink.

Approximately 4% of case subjects with a first diagnosis of an ovulatory factor also had endometriosis, and 12% of those with endometriosis as a first diagnosis were found to have an ovulatory dysfunction. To examine whether the presence of women with both an ovulatory factor and endometriosis had an effect on the risk of infertility observed in these two diagnostic groups, the data were reanalyzed after removing women with both diagnoses (Table 2). The risk of an ovulatory factor associated with alcohol use remained the same (OR = 1.3 for women drinking moderately and OR = 1.6 for those drinking more heavily), whereas the risk increased slightly in women with endometriosis (from an OR of 1.6 to 1.7 at moderate levels and from an OR of 1.5 to 1.8 at higher levels).

TABLE 2—Case Subjects' Risk of Infertility, by Alcohol Use and Type of Infertility

Infertility Type	Moderate Alcohol Use		Heavier Alcohol Use	
	OR[a]	95% CI	OR[a]	95% CI
First diagnosis				
Ovulatory factor[b] (n = 431)	1.3	1.0, 1.7	1.6	1.1, 2.3
Tubal disease (n = 230)	1.0	0.7, 1.4	1.2	0.7, 1.9
Cervical factor (n = 105)	1.3	0.8, 2.1	1.6	0.8, 3.3
Endometriosis[c] (n = 180)	1.6	1.1, 2.3	1.5	0.8, 2.7
Idiopathic (n = 104)	0.9	0.5, 1.4	0.7	0.3, 1.6
Ovulatory factor, excluding women with the additional diagnosis of endometriosis (n = 413)	1.3	1.0, 1.7	1.6	1.1, 2.4
Endometriosis, excluding women with the additional diagnosis of ovulatory factor (n = 158)	1.7	1.2, 2.5	1.8	1.0, 3.2

Note. OR = odds ratio; CI = confidence interval.
[a]Adjusted for infertility center, age, number of sexual partners, cigarette smoking, and caffeine intake. For ovulatory factor, hours of vigorous exercise and body mass index were included as confounders; for tubal disease, intrauterine device use was included. Women who reported no alcohol use were used as the reference group.
[b]Test for trend: $P = .005$.
[c]Case subjects who were diagnosed with endometriosis before their infertility evaluation and control subjects who reported a history of endometriosis were excluded.

Discussion

This study demonstrates an association between reported consumption of alcohol and infertility due to ovulatory factor or endometriosis. A small, but significantly increased, risk of ovulatory infertility was observed for women reporting moderate alcohol intake, whereas this risk rose considerably in those women drinking at heavier levels compared with nondrinkers. Increased risks of endometriosis were found at both levels of alcohol intake examined.

Several limitations of these data need to be considered. Because information on exposure history was obtained by self-report, misclassification of alcohol use may have occurred. In particular, approximately 50% to 60% of the women in the case and control groups reported no alcohol intake, slightly more than the 48.3% of women in a national survey of drinking and reproductive dysfunction.[5] To minimize information bias, data were collected during personal interviews that were conducted by trained nurses. Although we were not able to verify the self-reported alcohol use in this population, Willett et al. found that self-report of alcohol intake was highly reproducible in a study of 173 women (Spearman correlation coefficient = 0.90).[11] Our study population was composed exclusively of women of relatively high socioeconomic status, as indicated by the large majority of college-educated participants (approximately 70%). It is possible that their alcohol intake was lower than that of the general population, although to our knowledge no pertinent data have been published. Although this issue may affect the generalizability of our results, it would not affect the validity of our comparison of alcohol intake in case and control subjects, because several measures indicate a similar socioeconomic status in the two groups (education, cigarette smoking, and number of sexual partners were comparable).

This similarity is particularly important in a study such as this one, because the case subjects were recruited from women referred to a specialized medical clinic. Such women may be different, particularly with respect to socioeconomic status, even from the "typical" hospital patient. And alcohol intake could vary with social class. However, as we noted, several socioeconomic indicators are similar among the case and control groups here. In addition, the total household income was similar for case and control subjects, with approximately 50% of both groups falling into the highest income category, suggesting a lack of referral bias in this study.

An additional bias could have resulted from the fact that all the case

subjects were attempting their first pregnancy, whereas some control subjects were multiparous and had to recall exposures before their first pregnancy. In fact, the recall period (i.e., the mean difference between the index date and the interview date) was similar for both groups (approximately 3 years). Although it is possible that subjects' recall of alcohol use 3 years in the past may not have been completely accurate, the recall period was similar for case and control subjects; thus, any potential bias would be nondifferential and lead to an underestimation of the actual risks of infertility associated with alcohol use.[12]

Although the control subjects were instructed to report alcohol use before their first pregnancy, their more recent intake could have been reflected in their report. We reanalyzed the data for the primiparous control subjects only (approximately 50% of the control group) and found risk estimates corresponding to those obtained with the entire control group: for ovulatory factor, the OR was 1.1 (95% CI = 0.9, 1.5) for moderate alcohol use and 1.6 (95% CI = 1.0, 2.6) for heavier alcohol use; for endometriosis, the OR was 1.3 (95% CI = 0.9, 1.9) for moderate intake and 1.4 (95% CI = 0.7, 2.6) for heavier intake.

Still, all the control subjects would have been advised to abstain from alcohol during pregnancy, perhaps leading to an underreport of their alcohol use. If this underreporting were true, we would expect to see increased alcohol intake among all the case subjects. Alcohol was associated with an increased risk of ovulatory factor, cervical factor, and endometriosis; but there was little risk of tubal disease among alcohol users, and a slightly decreased risk of idiopathic infertility was observed.

Because infertility is often a multifactorial disorder, it is also possible that the increased risks of infertility associated with a first diagnosis of ovulatory factor or endometriosis were due to the presence of women with both of these diagnoses. However, when we removed women from each group who were diagnosed with both disorders, a reanalysis of the data did not lead to any appreciable change in the results.

There may be a biological basis for the association that we observed between alcohol use, ovulatory infertility, and endometriosis. Research on the chronic effects of alcohol use on menstruation indicates that alcoholism is associated with early menopause[13] and reduced levels of follicle-stimulating hormone,[13,14] although it remains unknown whether these consequences would also result from the more moderate levels of alcohol use reported in this study. In a cross-sectional study of drinking and reproductive dysfunction, heavy menstrual flow and dysmenorrhea were associated with moderate and high levels of alcohol intake.[5] Both of these factors have been related to an increased risk of endometriosis.[15]

It is possible that women with symptoms of endometriosis (specifically, pain in the pelvic area) drink alcohol to help alleviate their pain. However, when we examined use of alcohol by the case subjects with endometriosis, we found no significant difference between women reporting none to mild dysmenorrhea and those reporting moderate to severe dysmenorrhea. Approximately 50% of case subjects in both those groups were alcohol users.

There is presently little information available on the specific effects of moderate alcohol intake on reproductive capacity. This is one of few investigations that has examined the consequences of moderate alcohol use on distinctive types of fertility problems. We found the largest effect of alcohol use to be on the hormonally associated fertility disorders. It is of interest that an increased risk of breast cancer has also been associated with moderate alcohol use.[16,17] No mechanism has been established yet to explain this association, but breast cancer is most likely an estrogen-dependent neoplasm,[18] and both ovulatory function and endometriosis are related to estrogen levels. □

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