

Groene Hart Hospitals, oversaw data collection, analysed data, and jointly wrote the paper with FMH, KWMB, and MJNCK. FMH initiated and designed the study, supervised recruitment at Leiden University Hospital, supervised data collection, and analysed data. KWMB helped to develop the trial and collect data, and analysed data. FAMH and DEMM were responsible for completing data sheets and data entry. Marc Keirse helped in the study design; was responsible for power calculation, central randomisation, and termination of enrolment; reviewed data; and edited the paper.

Funding: Financial support was received from the participating institutions only.

Conflict of interest: None.

- 1 Sims JM. *Clinical notes on uterine surgery (with special reference to the management of the sterile condition)*. London: Robert Hardwicke, 1866.
- 2 Oei SG, Keirse MJNC, Bloemenkamp KWM, Helmerhorst FM. European postcoital tests: opinions and practice. *Br J Obstet Gynaecol* 1995;102:621-4.
- 3 Griffith CS, Grimes DA. The validity of the postcoital test. *Am J Obstet Gynecol* 1990;162:615-20.
- 4 Oei SG, Helmerhorst FM, Keirse MJNC. When is the postcoital test normal: a critical appraisal. *Hum Reprod* 1995;10:1711-4.
- 5 Glazener CMA, Coulson C, Lambert PA, Watt EM, Hinton RA, Kelly NJ, et al. The value of artificial insemination with husband's semen in infertility due to failure of postcoital sperm-mucus penetration-controlled trial of treatment. *Br J Obstet Gynaecol* 1987;94:774-8.

- 6 Te Velde ER, van Kooy RJ, Waterreus JJH. Intrauterine insemination of washed husband's spermatozoa: a controlled study. *Fertil Steril* 1989;51:182-5.
- 7 Friedman A, Haas S, Kredentser J, Stewart E, Schiff I. A controlled trial of intrauterine insemination for cervical factor and male factor: a preliminary report. *Int J Fertil* 1989;34:199-203.
- 8 Kirby CA, Flaherty SP, Godfrey BM, Warnes GM, Matthews CD. A prospective trial of intrauterine insemination of motile spermatozoa versus timed intercourse. *Fertil Steril* 1991;56:102-7.
- 9 Van de Berg-Helder A, Helmerhorst FM, Blankhart A, Brand R, Waegemaekers C, Naaktgeboren N. Comparison of ovarian stimulation regimens for in vitro fertilization (IVF) with and without a gonadotropin-releasing hormone (GnRH) agonist: results of a randomized study. *J Vitro Fertil Embryo Transfer* 1990;7:358-62.
- 10 Rowe PJ, Comhaire FH, Hargreave TB, Mellows HJ. *WHO manual for the standardized investigation of the infertile couple*. Cambridge: Cambridge University Press, 1993.
- 11 Allman RM, Steinberg EP, Keruly JC, Dans PE. Physician tolerance for uncertainty: use of liver-spleen scans to detect metastases. *JAMA* 1985;254:246-8.
- 12 Eisenberg JM, Schumacher HR, Davidson PK, Kaufmann L. Usefulness of synovial fluid analysis in the evaluation of joint effusions: use of threshold analysis and likelihood ratios to assess a diagnostic test. *Arch Intern Med* 1984;144:715-9.
- 13 Thibault GE. The appropriate degree of diagnostic certainty. *N Engl J Med* 1994;331:1216-20.
- 14 Putterman C, Ben-Chetrit E. Clinical problem solving: testing, testing, testing. . . . *N Engl J Med* 1995;333:1208-11.

(Accepted 13 May 1998)

Does moderate alcohol consumption affect fertility? Follow up study among couples planning first pregnancy

Tina Kold Jensen, Niels Henrik I Hjollund, Tine Brink Henriksen, Thomas Scheike, Henrik Kolstad, Aleksander Giwercman, Erik Ernst, Jens Peter Bonde, Niels E Skakkebaek, Jørn Olsen

Abstract

Objective: To examine the effect of alcohol consumption on the probability of conception.

Design: A follow up study over six menstrual cycles or until a clinically recognised pregnancy occurred after discontinuation of contraception.

Subjects: 430 Danish couples aged 20-35 years trying to conceive for the first time.

Main outcome measures: Clinically recognised pregnancy. Fecundability odds ratio: odds of conception among exposed couples divided by odds among those not exposed.

Results: In the six cycles of follow up 64% (179) of women with a weekly alcohol intake of less than five drinks and 55% (75) of women with a higher intake conceived. After adjustment for cycle number, smoking in either partner or smoking exposure in utero, centre of enrolment, diseases in female reproductive organs, woman's body mass index, sperm concentration, and duration of menstrual cycle, the odds ratio decreased with increasing alcohol intake from 0.61 (95% confidence interval 0.40 to 0.93) among women consuming 1-5 drinks a week to 0.34 (0.22 to 0.52) among women consuming more than 10 drinks a week ($P=0.03$ for trend) compared with women with no alcohol intake. Among men no dose-response association was found after control for confounders including women's alcohol intake.

Conclusion: A woman's alcohol intake is associated with decreased fecundability even among women with a weekly alcohol intake corresponding to five or fewer

drinks. This finding needs further corroboration, but it seems reasonable to encourage women to avoid intake of alcohol when they are trying to become pregnant.

Introduction

The incidence of infertility is high and expected to increase. Intake of alcohol is a possible causal factor of public health importance as consumption is widespread and increasing in many countries. In experimental animals alcohol is known to decrease steroid hormone concentrations, inhibit ovulation, and interfere with sperm cell transportation through the fallopian tube.¹ Alcohol given to rats and monkeys reduces ovarian weight and causes amenorrhoea.²⁻³

The concentration of sulphated steroids has been found to be lower in alcoholic women than in controls.^{3,4} Furthermore, chronic alcohol misuse in women has been associated with changes in hepatic oestrogen receptors.⁵ Women with high or frequent alcohol intake have been found to have higher rates of menstrual disorders, including amenorrhoea, dysmenorrhoea, and irregular menstrual periods.⁶⁻⁸ Pregnant women with a high alcohol intake have a higher incidence of miscarriages, placental abruption, preterm deliveries, and stillbirths than control women.^{6,9} Alcohol in high doses is also known to be teratogenic and is responsible for fetal alcohol syndrome.¹⁰ The effect of moderate alcohol intake on reproduction, however, is less well examined.

Department of Growth and Reproduction, National University Hospital, Rigshospitalet, Section GR 5064, 9-Blegdamsvej, DK-2100 Copenhagen, Denmark

Tina Kold Jensen, *postdoctoral fellow*
Aleksander Giwercman, *physician*
Niels E Skakkebaek, *professor*

Department of Occupational Medicine, Aarhus University Hospital, Nørrebrogade, 8000 Aarhus C, Denmark
Niels Henrik I Hjollund, *physician*
Henrik Kolstad, *physician*
Jens Peter Bonde, *chief doctor*

continued over

BMJ 1998;317:505-10

Perinatal
Epidemiological
Research Unit,
Department of
Obstetrics and
Gynaecology,
Aarhus University
Hospital

Tine Brink
Henriksen,
physician
Erik Ernst,
physician

Department of
Biostatistics,
University of
Copenhagen, 2200
Copenhagen N
Thomas Scheike,
*associate professor of
biostatistics*

Danish
Epidemiology
Sciences Centre,
Aarhus University,
Hoegh-Guldbergs
Gade 10, 8000
Aarhus C

Jørn Olsen,
professor

Correspondence to:
Dr Kold Jensen
tk.jensen@
wiiisloew.ou.dk

Fecundability is defined as the probability of achieving conception or a recognised pregnancy in a menstrual cycle. The time (number of months) to pregnancy or cycles to pregnancy it takes a sexually active couple to conceive and carry the pregnancy to clinical recognition has been used as a measure of fecundability. Time to pregnancy has been associated with lifestyle factors such as the woman's smoking and caffeine intake,¹¹⁻¹⁵ but few studies have investigated the relation between fecundability and alcohol intake in either partner.¹⁶⁻²⁰ Most studies have found no effect of moderate alcohol intake in women, whereas a high intake has been associated with reduced fecundability.¹⁷⁻¹⁸ None of the studies have used prospective data.

We conducted a follow up study among couples who were trying to conceive for the first time, with repeated measurements of alcohol intake over six menstrual cycles, to examine the hypothesis that alcohol consumption decreases fecundability and to determine the threshold, if any.

Subjects and methods

Study population

From 1992 to 1995 a total of 430 couples were recruited after a nationwide mailing of personal letters to 52 255 trade union members (metalworkers, office workers, nurses, and day care workers) who were 20-35 years old, lived with a partner, and had no children. Couples without previous reproductive experience who intended to discontinue contraception to become pregnant were eligible for enrolment. The exact number of eligible couples in the source population of 52 255 people was unknown. Under the assumption that 75% of pregnancies in Denmark are planned, an average participation rate of 16% was estimated by using data from union, age, parity, and calendar specific birth rates obtained from the Danish civil registration system. A detailed description of the study cohort is provided elsewhere.²¹

Enrolment and follow up

The couples were enrolled into the study when they discontinued birth control and were followed for six menstrual cycles or until a clinically recognised pregnancy. The couples were enrolled at two centres in Denmark: the department of occupational medicine in Aarhus (west centre) and the department of growth and reproduction in Copenhagen (east centre). At enrolment both partners filled in a questionnaire on demographic, medical, reproductive, occupational, and lifestyle factors and the men provided a semen sample. During follow up the women recorded vaginal bleeding and sexual intercourse daily, and one additional semen sample was collected during the menstrual period of each cycle. Finally, couples completed a monthly questionnaire on changes in occupational exposures and lifestyle factors.

The couples were asked to report on smoking and intake of alcohol and caffeine as average daily or weekly consumption during the week before completion of the questionnaire. Smoking habits were reported as the average number of cigarettes, cigars, or pipes smoked a day. The key question on intake of alcohol intake was: "How much did you consume of the following beverages during the last week: bottles of

beer (0.33 l), glasses of wine and spirits (about 12 g alcohol in each)." The total weekly alcohol intake (number of drinks) was calculated by summing the intake of beer, wine, and spirits. Intake of coffee, tea, and beverages containing chocolate was measured as the average number of cups a day, and consumption of cola drinks was measured as the average weekly number of bottles [0.25 l] consumed to estimate each person's daily caffeine intake.²² If the information on lifestyle factors was missing in a monthly questionnaire the person was assumed to have consumed the same amount of caffeine and alcohol or smoked the same number of cigarettes as during the previous month.

The participants were also asked: "Did your mother smoke when she was pregnant with you?" and to report whether this information was provided by their mother or not. Body mass index was calculated as weight divided by height squared (kg/m²). Reported diseases associated with fecundability (salpingitis, ovarian cysts, gonorrhoea, peritonitis, epididymitis, adult parotitis, testicular cancer, and cryptorchidism) were transformed into one variable (present or not present) for both men and women.

Women recorded sexual intercourse daily, but this information was missing for 336 cycles (available for 1325 cycles). If the information was missing in one cycle the frequency of sexual intercourse was assumed to be the same as during the previous months, but in 205 cycles (88 couples) no diary information on sexual intercourses was obtained because the women became pregnant in the first cycle before the diaries were handed out. Therefore, this information was not used, and we excluded cycles with no intercourse from day 11 to 20 in the cycle as no couples who refrained from intercourse in that period became pregnant (47 cycles).

The number of cycles to pregnancy or to the end of follow up were calculated from the day the couples discontinued contraception. Day 1 of the cycle was defined as the day of onset of menstrual bleeding. If the discontinuation was 10 days or more before the first day of the next menstrual bleeding or the expected day of the next menstrual bleeding (calculated from last menstrual bleeding and cycle length) the cycle was counted as the first. For other couples the first cycle was that after the first menstrual bleeding after discontinuation of contraception. Couples who dropped out of the study before the six follow up cycles were censored at the cycle in which they stopped participation (n=22). Data were available on 1661 cycles. Seven couples were excluded because of azoospermia. A total of 423 couples with 1596 cycles were included in the analyses.

Statistical analyses

Alcohol intake was categorised before the analyses into five levels; 0, 1-5, 6-10, 11-15, and > 15 drinks a week and was also entered as a continuous variable. Furthermore, we computed the mean alcohol intake for all reported cycles. We also compared couples with a weekly alcohol intake of over five drinks in the entire follow up period with couples with a lower weekly intake in all cycles (this was performed for men and women separately). No significant interaction between alcohol intake and caffeine or smoking was found. Accordingly no interaction terms were entered in the

multiple logistic regression analyses, but smoking and caffeine intake were entered as confounders.

The time to pregnancy by level of alcohol intake was analysed by survival analysis techniques, which are equivalent to logistic regression on the total number of observed cycles with the outcome "pregnant/not pregnant." Fecundability denotes the probability of obtaining a clinically recognised pregnancy in a menstrual cycle among couples not pregnant in the previous cycles. The fecundability odds ratio measures the odds of conception among exposed couples divided by the odds among those not exposed. Other variables mentioned above were excluded stepwise and if the point estimate of the association between alcohol intake and fecundability changed by less than 10% after exclusion, the variable was removed from the final model. Those variables which did not affect point estimates by 10% or more were also not significant at the 5% level.

Potential confounders were examined in bivariate analyses by comparing couples who became pregnant within six cycles with couples who did not. The following variables were related to becoming pregnant during follow up: the woman's age, smoking in either partner or smoking exposure in utero, diseases in the reproductive system of either partner, sperm concentration (categorised as <10, 10-19, 20-49, and >49 million/ml), duration of menstrual cycle, use of oral contraceptives as last method of birth control, and the woman's body mass index. Variables not associated with fecundability were centre of enrolment, age at menarche, the man's body mass index, the man's age, and caffeine intake of both partners.

The square root transformed continuous alcohol intake was entered into the multivariate model. Furthermore, dummy variables were created for each source of alcohol intake. Also, men and women who reported alcohol intake from only beer, only wine, or from other sources were included in all analyses to determine the independent effect of each. Fecundability odds ratios are presented with 95% confidence intervals.

Results

In the first cycle 120 (28%) women reported no weekly alcohol intake, and 73 (17%) had no alcohol intake during all cycles. The mean weekly alcohol intake among women was four drinks. Among men, 42 (10%) reported no alcohol intake during the week before enrolment; overall, the mean weekly intake was 9.5 drinks. The main source of alcohol intake for women was wine whereas the men more often drank beer. Eighty two (19%) women and 112 (27%) men drank spirits in the first cycle.

Table 1 shows the characteristics of women with and without a weekly alcohol intake during the first cycle. Alcohol intake was mainly associated with their own and their partners' smoking habits, caffeine consumption, and alcohol intake. Women with any alcohol intake were less likely to have used oral contraceptives before trying to get pregnant, had a lower body mass index, and were older.

Among women with a reported average weekly alcohol intake below five drinks, 179/280 (64%) conceived within six cycles compared with 75/136 (55%) women with a higher intake. Among the men the figures were 90/134 (67%) and 164/282 (58%), respectively.

Table 1 Characteristics of study population according to any alcohol intake in women. Data based on information provided in first questionnaire (n=430). Figures are numbers (percentage) of subjects

Characteristic	Alcohol intake in first cycle	
	No (n=120)	Yes (n=310)
Alcohol intake in first cycle (drinks/week)		
Woman: 0	120 (28)	0
1-5	0	193 (45)
6-10	0	74 (17)
11-15	0	28 (7)
>15	0	15 (3)
Man: 0	33 (27)	9 (3)
1-5	42 (35)	98 (32)
6-10	30 (25)	83 (27)
11-15	7 (6)	60 (19)
>15	8 (7)	60 (19)
Smoking		
Woman: No	87 (73)	216 (70)
Yes	33 (27)	94 (30)
Man: No	73 (61)	220 (71)
Yes	47 (39)	90 (29)
Mother smoked during pregnancy		
Woman: No	69 (63)	161 (57)
Yes	40 (37)	123 (43)
Man: No	73 (68)	161 (57)
Yes	35 (32)	119 (43)
Caffeine intake (mg/day)		
Woman: 0-299	71 (59)	164 (53)
300-699	39 (33)	120 (39)
>699	10 (8)	26 (8)
Man: 0-299	42 (35)	97 (31)
300-699	41 (34)	145 (47)
>699	37 (31)	68 (22)
Length of menstrual cycle (days)		
<25	1 (1)	6 (2)
25-35	88 (79)	243 (81)
>35	23 (20)	53 (17)
Sexual intercourse per cycle		
0	4 (5)	6 (2)
1-4	18 (21)	55 (21)
5-6	23 (26)	48 (19)
7-10	22 (25)	93 (37)
>10	20 (23)	53 (21)
Last method of birth control		
Oral contraception	47 (39)	99 (32)
Other	73 (61)	211 (68)
Woman's body mass index (kg/m²)		
10-19	29 (24)	56 (18)
20-24	58 (48)	192 (63)
>25	33 (28)	59 (19)
Age (years)		
Woman: 18-24	57 (48)	97 (31)
25-29	58 (48)	185 (60)
>29	5 (4)	27 (9)
Man: 18-24	23 (19)	40 (13)
25-29	72 (60)	185 (60)
>29	25 (21)	84 (27)
Diseases in reproductive system		
Woman: No	108 (90)	282 (91)
Yes	12 (10)	28 (9)
Man: No	109 (91)	275 (89)
Yes	11 (9)	35 (11)
Centre		
West	61 (50)	170 (55)
East	59 (50)	140 (45)
Union of recruitment		
Metal workers	66 (55)	17 (41)
Nurses	21 (17)	127 (23)
Clerks	31 (26)	73 (30)
Day care workers	2 (2)	93 (6)

Table 2 Fecundability odds ratios (95% confidence intervals) according to alcohol intake and sex (logistic regression analysis performed for each sex separately)

Alcohol intake (drinks/ week)	No of cycles	Odds ratio	Adjusted* odds ratio
Women			
0	388	1	1
1-5	771	0.74 (0.54 to 1.01)	0.61 (0.40 to 0.93)
6-10	283	0.73 (0.48 to 1.10)	0.55 (0.36 to 0.85)
11-15	102	0.50 (0.28 to 0.98)	0.34 (0.22 to 0.52)
>15	52	0.66 (0.28 to 1.51)	0.34 (0.11 to 1.07)
Men			
0	151	1.09 (0.68 to 1.76)	0.91 (0.51 to 1.62)
1-5	519	1	1
6-10	390	1.09 (0.77 to 1.54)	1.02 (0.68 to 1.51)
11-15	229	0.76 (0.48 to 1.19)	0.76 (0.46 to 1.26)
>15	307	0.82 (0.55 to 1.23)	0.83 (0.53 to 1.30)

*Adjustments for women were cycle number, smoking in either partner and smoking exposure in utero, centre of enrolment, diseases in female reproductive organs, women's body mass index, use of oral contraception before conception attempt, sperm concentration, and duration of menstrual cycle categorised in table 1 and entered as dummy variables equal to number of categories minus 1. Adjustments for men were cycle number, smoking in either partner and smoking exposure in utero, centre of enrolment, diseases in female reproductive organs, women's alcohol intake and body mass index, use of oral contraception before conception attempt, and duration of menstrual cycle categorised in table 1 and entered as dummy variables equal to number of categories minus 1.

Table 3 Adjusted fecundability odds ratios* (95% confidence interval) according to alcohol intake from three different sources (spirits, wine, and beer) categorised as 1-5 and >5 drinks a week and entered simultaneously in logistic regression analysis (performed for both sexes separately). Reference groups are men and women with no alcohol intake

No of alcohol drinks per week	Women	Men
Spirits:		
1-5	0.95 (0.61 to 1.50)	1.37 (0.95 to 1.98)
>5	0.67 (0.18 to 2.46)	0.95 (0.41 to 2.22)
Wine:		
1-5	0.61 (0.42 to 0.90)	1.11 (0.78 to 1.59)
>5	0.60 (0.33 to 1.10)	0.70 (0.41 to 1.21)
Beer:		
1-5	0.83 (0.57 to 1.23)	0.83 (0.53 to 1.32)
>5	0.61 (0.24 to 1.56)	0.75 (0.45 to 1.25)

*See footnote to table 2.

Table 2 shows the unadjusted and adjusted odds ratios among men and women with different alcohol intake. The odds ratio decreased with increasing alcohol intake among women from 0.61 (95% confidence interval 0.40 to 0.93) among women consuming 1-5 drinks a week to 0.34 (0.22 to 0.52) among women who consumed more than 10 drinks a week ($P=0.03$ for trend). This association was adjusted for cycle number, smoking in either partner or smoking exposure in utero, centre of enrolment, diseases in female reproductive organs, use of oral contraception before conception attempt, woman's body mass index, sperm concentration, and the duration of menstrual cycle. We excluded the duration of the menstrual cycle as this could be part of a causal pathway, but it did not change the reported associations. Among the men no possible dose-response association was seen after control for the above confounders, excluding semen quality (as this could mediate the effect) but including the woman's

alcohol intake (yes/no) ($P=0.3$ for trend). An association with fecundability was also found among men and women with a mean weekly alcohol intake above five drinks and among couples with a high alcohol intake (above five drinks a week) during the entire follow up period. A square root transformation on alcohol intake was entered in the multiple regression analysis with the four alcohol categories, but it did not improve the fit of the model significantly.

Additional analyses were conducted to determine whether the results were due to any specific type of alcohol or whether they were consistent among drinkers of spirits, beer, and wine (table 3). The analyses did not improve the fit of the model containing the variables for total alcohol intake. Analyses were also carried out separately for women who reported drinking only wine (375 cycles) and among men drinking only beer (352 cycles). All of these models showed association with fecundability to the same extent as the total alcohol consumption.

Discussion

Alcohol intake in women but not in men was associated with reduced fecundability. The reduction was independent of the sources of alcohol (spirits, wine, or beer). We obtained detailed and repeated information on the alcohol intake from three different sources. The alcohol intake was reported during each cycle before any knowledge about occurrence of pregnancy in that specific cycle. Information on alcohol intake in each cycle was recorded as the intake during the week before completion of the questionnaire, which was filled in on day 21 of the cycle. Thus, the effect on fecundability was confined to alcohol intake on days 14-21 in the cycle. As we obtained only the weekly intake we cannot determine if the decrease in fecundability was due to a constant use or a high intake during this week. The mean alcohol intake on days 14-21 during the entire follow up was calculated and results revealed similar associations with fecundability.

Alcohol intake is probably underreported, but the misclassification is most likely independent of cycle outcome. If the magnitude of underreporting was similar for all levels of exposure the trend analyses would be correct but the risk overestimated at the reported values. If the couples with high alcohol intake are more likely to underreport their intake than the couples with low intake, however, this would bias the risk towards high values.

We collected repeated information from both men and women on various potential confounding factors which have been only partly adjusted for in previous studies. Despite extensive adjustment for several potential confounders, residual confounding may still be present. In some studies alcohol intake has been associated with social class²³ and other lifestyle factors including diet,^{24, 25} for which we obtained no information. Wine is more often consumed by people in the higher social classes in Denmark, whereas beer drinking is more common in the lower social classes.²³ That fecundability decreased similarly with increasing alcohol intake among consumers of wine, spirits, and beer indicates that our findings were not due to confounding by social class.

Frequency of sexual intercourse was not analysed as a confounder as diary information on this was missing among couples who became pregnant in the first cycle. A higher proportion of women with alcohol intake in the first cycle had intercourse more than six times per cycle than women who had no alcohol intake in the first cycle (see table 1), which would yield an underestimation of the effect of alcohol when frequency of intercourse was not adjusted for. We repeated the analyses without excluding the cycles in which intercourse between day 11 and day 20 was not reported and including sexual intercourses in categories (as in table 1). This failed to change the association between women's alcohol intake and fecundability, although the estimates were no longer significant because of the smaller sample size (odds ratio 0.47 (0.13 to 1.69) in women consuming > 15 units a week).

Possible bias

The rate of pregnancies per cycle and the proportion of women who became pregnant during six cycles with unprotected intercourse (65%) was slightly lower in this study than in some of the previously published follow up studies.^{14 26} Study designs and methods differed, however, and the populations are not necessarily comparable. Recruitment bias may explain the low pregnancy rate in six cycles if couples with suspected fertility problems are included more often. To avoid this source of bias, couples should be unaware of their reproductive capacity and have used contraception before the study, but couples using less reliable methods of contraception for a longer time might suspect fertility problems. Bias in relation to the reported associations between fecundability and alcohol intake is likely only if infertile couples with high alcohol intake were oversampled. This is unlikely as alcohol intake is not an established risk factor for infertility.

The exclusion of couples with unplanned pregnancies may cause selection bias, and the magnitude of this bias cannot be ruled out as only couples planning a pregnancy were invited to take part in the study. If alcohol intake is associated with irregular use of birth control, or the use of less effective methods, the fecundability of alcohol consumers will be underestimated. Also, the repetitive measurement of alcohol intake during follow up may change the intake. The alcohol intake was, however, relatively constant across cycles.

Effect of alcohol on women's fertility

The observed reduction of female fecundability even among women with a low alcohol intake (five drinks a week) was unexpected and has not previously been reported.¹⁶⁻²⁰ The observation that higher alcohol intake is associated with reduced fecundability is supported by previous studies.^{17 18} The biological evidence for a detrimental effect of alcohol on female fecundability^{1-3 27} may indicate an effect of a moderate intake at critical time periods around the time of conception. We obtained information on alcohol intake around ovulation but most other studies have relied on more general exposure data, such as average alcohol intake before conception, that was obtained only once during follow up or retrospectively (with recall of up to several years). This is more likely to lead to misclassification and underreporting of exposure. One study among women receiving artificial donor insemination

Key messages

- As alcohol consumption is widespread and increasing in many countries, even a minor effect on fertility is of public health interest
- Some studies have found that women with high alcohol intake take longer to become pregnant, but none have found that moderate intake has an effect
- The probability of conception in a menstrual cycle decreased with increasing alcohol intake in women, even among those drinking five or fewer drinks a week
- Women who are trying to conceive should be encouraged to avoid intake of alcohol

reported slightly higher fecundability in women consuming 1-10 glasses of alcoholic beverage the week before insemination than in women with no alcohol intake.¹⁹ The women were not asked about changes in alcohol intake over the study period, and a quarter of the women who became pregnant reported a different alcohol intake after the study period than during it.

Two studies found no effect even of high weekly alcohol intake (more than 12 drinks) on fecundability.^{16 28} In one study the mean time from exposure to questioning was almost 10 years, and recall bias probably explains the negative findings.²⁸ The other study included only a few women from one occupational group, and 60% had tried to conceive before enrolment in the study.¹⁶ Two other studies found no association between alcohol intake and fecundability at low exposures, but a detrimental effect was found among women who consumed more than eight drinks a week.^{17 18} Data were obtained retrospectively during pregnancy, which may have affected the results.

Several retrospective studies have found no significant unadjusted effect of alcohol intake in women,^{14 29 30} and some studies that have included alcohol intake as a confounder in the multivariate analysis of other risk factors have found no independent effect.^{12 20 31 32} Several case-control studies have found that infertile women who seek medical care have a significantly higher alcohol intake than women who become pregnant naturally.^{6 8 33} These studies are vulnerable to selection bias, however, as only half of all couples with infertility problems seek medical care.^{34 35} Also, the couples with problems may have to remember their intake further back in time than those without problems (controls), which may cause bias, and couples with problems may have changed their drinking habits because of their infertility. One study included no information on when alcohol exposure was assessed, and exposure was measured as no use or frequent use.⁸ The quality of our data on alcohol exposure may thus be better than other published studies with respect to accuracy and time specificity, and that may explain our findings of decreased fecundability even at low alcohol exposures.

No effect of men's alcohol intake on fecundability was observed, which is consistent with other studies.^{16 18 28} Only a few studies have evaluated the effect of alcohol intake on semen quality and no association has been found.³⁶⁻³⁹

We found an association between women's alcohol intake and decreased fecundability even among women who had five or fewer drinks a week, which would indicate that fecundability is reduced in a high proportion of women because of alcohol intake. This finding needs further corroboration, but it seems reasonable to encourage women to reduce their intake of alcohol or not to drink at all when they are trying to become pregnant.

We are indebted to several trade union officials for support, and we thank technicians from the laboratories for performing the semen analyses.

Contributors: The study was designed and piloted by JPB, JO, NHH, HK, TBH, and EE. TKJ, AG, and NES contributed to recruitment of participants and execution of the study. EE and AG were responsible for laboratory analyses. NHH coordinated data collection and documentation and TKJ was project manager at the east centre. TKJ and TS did the statistical analyses and TKJ drafted the paper. All authors took part in further analyses, interpretation of the data, and writing of the final paper. JPB, JO, and NES are the guarantors.

Funding: This study was supported by a grant from Aarhus University Research Foundation (J nr 1994-7430-1) with additional support from the Danish Medical Research Council (J nr 12-2042-1) and the Danish Medical Health Insurance Foundation (J nr 11/236-93 and J nr 11/243-91).

Conflict of interest: None.

- Sharma SC, Chaudhury RR. Studies on mating. II. The effect of ethanol on sperm transport and ovulation in successfully mated rabbits. *Indian J Med Res* 1970;58:501.
- Gavaler JS, Van Thiel DH, Lester R. Ethanol: a gonadal toxin in the mature rat of both sexes. *Alcohol Clin Res* 1980;4:271-6.
- Mello NK, Bree MP, Mendelson JH, Ellingboe J, King NW, Sehgal P. Alcohol self-administration disrupts reproductive function in female macaque monkeys. *Science* 1983;221:677-9.
- Välimäki M, Laitinen K, Tiitinen A, Steman U-H, Ylöstalo P. Gonadal function and morphology in non-cirrhotic female alcoholics: a controlled study with hormone measurements and ultrasonography. *Acta Obstet Gynecol Scand* 1995;74:462-6.
- Becker U. The influence of ethanol and liver disease on sex hormones and hepatic oestrogen receptors in women. *Dan Med Bull* 1993;40:447-59.
- Wilsnack SC, Klassen AD, Wilsnack RW. Drinking and reproductive dysfunction among women in a 1981 national survey. *Alcohol Clin Exp Res* 1984;8:451-8.
- Becker U, Tennesen H, Kaas-Claesson N, Gluud C. Menstrual disturbances and infertility in chronic alcoholic women. *Drug Alcohol Depend* 1989;24:75-82.
- Bahamondes L, Vera S, Bueno JGR, Pimental E, Hardy E, Ramos M. Identification of main factors for tubal infertility. *Fertil Steril* 1994;61:478-82.
- Harlap S, Shiono PH. Alcohol, smoking, and incidence of spontaneous abortions in the first and second trimester. *Lancet* 1980;ii:173-6.
- Hadi HA, Hill JA, Castillo RA. Alcohol and reproductive function: a review. *Obstet Gynecol Surv* 1987;42:69-74.
- Howe G, Westhoff C, Vessey M, Yeates D. Effects of age, cigarette smoking, and other factors on fertility: findings in a large prospective study. *BMJ* 1985;290:1697-700.
- Baird DD, Wilcox AJ. Cigarette smoking associated with delayed conception. *JAMA* 1985;253:2979-83.
- Alderete E, Eskenazi B, Sholtz R. Effect of cigarette smoking and coffee drinking on time to conception. *Epidemiology* 1995;6:403-8.
- Wilcox A, Weinberg CR, Baird DD. Caffeinated beverages and decreased fertility. *Lancet* 1988;ii:1453-5.
- Olsen J. Cigarette smoking, tea and coffee drinking, and subfecundity. *Am J Epidemiol* 1991;133:734-9.
- Florack EIM, Zielhuis GA, Rolland R. Cigarette smoking, alcohol consumption, and caffeine intake and fecundability. *Prev Med* 1994;23:175-80.
- Olsen J, Rachoottin P, Schiedt AV, Damsbo N. Tobacco use, alcohol consumption and infertility. *Int J Epidemiol* 1982;12:179-84.
- Olsen J, Bolumar F, Boldsen J, Bisanti L, the European Study Group of Infertility and Subfecundity. Does moderate alcohol intake reduce fecundability? A European multicenter study on infertility and subfecundity. *Alcohol Clin Exp Res* 1997;21:206-12.
- Zaadstra BM, Habbema JDF, Looman CWN, Karbaat J, Velde ER. Moderate drinking: no impact on female fecundity. *Fertil Steril* 1994;62:948-54.
- Joesoef MR, Beral V, Aral SO, Rolfs RT, Cramer DW. Fertility and use of cigarettes, alcohol, marijuana, and cocaine. *Am J Epidemiol* 1993;3:592-4.
- Bonde JP, Hjøllund NHI, Jensen TK, Ernst E, Kolstad H, Henriksen TE, et al. A follow-up study of environmental and biologic determinants of fertility among 430 Danish first-pregnancy planners: design and methods. *Reprod Toxicol* 1998;12:19-27.
- Bunker ML, McWilliams M. Caffeine content of common beverages. *J Am Diet Assoc* 1979;74:28-32.
- Grenbaek M, Deis A, Sorensen TI, Becker U, Schnohr P, Jensen G. Mortality associated with moderate intakes of wine, beer, or spirits. *BMJ* 1995;310:1165-9.
- Colditz GA, Giovannucci E, Rimm EB, Stampfer MJ, Rosner B, Speizer F, et al. Alcohol intake in relation to diet and obesity in women and men. *Am J Clin Nutr* 1991;54:49-55.
- Williamson DE, Forman MR, Binkin NJ, Gentry EM, Remington PL, Trowbridge FL. Alcohol and body weight in United States adults. *Am J Public Health* 1987;77:1324-30.
- De Mouzon J, Spira A, Schwartz D. A prospective study of the relation between smoking and fertility. *Int J Epidemiol* 1988;17:378-84.
- Leach RE, Stachecki JJ, Armant DR. Development of in vitro fertilized mouse embryos exposed to ethanol during the preimplantation period: accelerated embryogenesis in subtoxic levels. *Teratology* 1993;47:57-64.
- Curtis KM, Savitz DA, Arbuckle TE. Effects of cigarette smoking, caffeine consumption, and alcohol intake on fecundability. *Am J Epidemiol* 1997;146:32-41.
- Stanton CK, Gray RH. Effects of caffeine consumption on delayed conception. *Am J Epidemiol* 1995;142:1322-9.
- Joffe M, Li Z. Male and female factors in fertility. *Am J Epidemiol* 1994;140:921-9.
- Ahlborg G, Axelsson G, Bodin L. Shiftwork, nitrous oxide exposure and subfertility among Swedish midwives. *Int J Epidemiol* 1996;25:783-90.
- Sallmén M, Lindbohm M-L, Kyrrönen P, Nykyri E, Anttila A, Taskinen H, et al. Reduced fertility among women exposed to organic solvents. *Am J Ind Med* 1995;27:699-713.
- Grodstein F, Goldman MB, Cramer DW. Infertility in women and moderate alcohol use. *Am J Public Health* 1994;84:1429-32.
- Olsen J, Küppers-Chinnow M, Spinelli A. Seeking medical help for subfecundity: a study based upon surveys in five European countries. *Fertil Steril* 1996;66:95-100.
- Schmidt L, Münster K, Helm P. Infertility and the seeking of infertility treatment in a representative population. *Br J Obstet Gynaecol* 1995;102:978-84.
- Dunphy BC, Barratt CLR, Cooke ID. Male alcohol consumption and fecundity in couples attending an infertility clinic. *Andrologia* 1991;23:219-21.
- Goverde HJM, Dekker HS, Janssen HJG, Bastiaans BA, Rolland R, Zielhuis GA. Semen quality and frequency of smoking and alcohol consumption—an explorative study. *Int J Fertil* 1995;40:135-8.
- Olderoid NB, Rui H, Purvis K. Lifestyles of men in barren couples and their relationships to sperm quality. *Int J Fertil* 1992;37:343-9.
- Parazzini F, Marchini M, Tozzi L, Mezzopane R, Fedele L. Risk factors for unexplained dyspermia in infertile men. A case-control study. *Arch Androl* 1993;31:105-13.

(Accepted 13 May 1998)

One hundred years ago Special correspondence: Paris

The question how to protect the public from lunatics is now as pressing as that of the prevention of hydrophobia once was. A police commissary is in a state of anxiety; he had taken measures to keep a whole family for a certain time confined to their house. Violent scenes had taken place in the house. The husband accused the wife of having lost her senses through hypnotism. The wife said her husband was mad. A few days ago a more than usually violent outbreak occurred. The husband escaped half naked, and appeared at the Commissary's office, exclaiming that his wife had tried to kill him. The Commissary went to the family dwelling; as soon as the door was half-opened,

a bullet whizzed past his ear without hitting him. Discretion being the better part of valour, he left the premises, and stationed two policemen outside the door to prevent the family from leaving the house. During two days relays of policemen succeeded each other, but no one passed the door. The family preferred making their escape through the window; the mother, two young children, a girl aged 15, and a boy aged 14 are now at large. The father is also wandering about, a probable danger to the public safety. A farmer has lately been shot by a mad neighbour; the murderer has not yet been arrested. (*BMJ* 1898;ii:115)