Alcohol Consumption at the Time of Conception and Spontaneous Abortion

Tine Brink Henriksen¹, Niels Henrik Hjollund², Tina Kold Jensen³, Jens Peter Bonde², Anna-Maria Andersson³, Henrik Kolstad², Erik Ernst⁴, Aleksander Giwercman³, Niels Erik Skakkebæk³, and Jørn Olsen⁵

¹ Perinatal Epidemiological Research Unit, Department of Obstetrics and Gynaecology, Aarhus University Hospital, Aarhus, Denmark.
² Department of Occupational Medicine, Aarhus University Hospital, Aarhus, Denmark.
³ Department of Growth and Reproduction, the National Hospital, Copenhagen, Denmark.
⁴ Reproductive Toxicology Unit, Institute of Anatomy, University of Aarhus, Aarhus, Denmark.
⁵ The Danish Epidemiology Science Center, University of Aarhus, Aarhus, Denmark.

Received for publication August 20, 2002; accepted for publication April 2, 2004.

The authors studied the association between female and male alcohol intakes at the time of conception and the risk of spontaneous abortion, including early pregnancy loss detected by urinary human chorionic gonadotropin. After a nationwide mailing to about 50,000 members of four trade unions in Denmark in 1992–1994, 430 couples without previous pregnancy attempts were enrolled when birth control was discontinued, and they were followed until a clinically recognized pregnancy or for six menstrual cycles. Alcohol intake and potential confounding factors were reported in monthly questionnaires. Women collected morning urine for 10 days from the first day of vaginal bleeding in each cycle. The authors detected 186 pregnancies: 131 resulted in childbirth, and 55 resulted in spontaneous abortion (34 detected by urinary human chorionic gonadotropin). Depending on the intake in the cycle of conception and the adjustment factors, female alcohol intake was associated with 2–3 times the adjusted risk of spontaneous abortion compared with no intake, and male alcohol intake was associated with 2–5 times the adjusted risk. Only the adjusted relative risks for 10 or more drinks/week compared with no intake were statistically significant. Both male and female alcohol intakes during the week of conception increased the risk of early pregnancy loss.

Alcohol administered in high doses to males and females around the time of conception or during early pregnancy increases the frequency of embryonal resorption, chromosomal abnormalities in the offspring, and fetal deaths in some animals (1–3). In humans, the association between alcohol consumption and clinically recognized or self-reported spontaneous abortion is less clear (4–13). Women with a very high alcohol intake have been shown to be at increased risk of preterm delivery and stillbirth, and a high intake during pregnancy may be teratogenic for some (14).

Early biochemically detected embryonal losses may account for as many as 40–70 percent of all pregnancy losses (15–18). Thus, studies of clinically recognized abortions may fail to reveal even very high risks if the exposure shifts the associated spontaneous abortions toward clinically undetectable abortions.

There are few studies on male alcohol intake and spontaneous abortions, and the published studies show no association (5, 12, 19). Alcohol consumption has been shown to be associated with aneuploidy in sperm cells (20), and spontaneously aborted embryos are frequently chromosomally abnormal (21). Alcohol is present in semen relatively shortly after ingestion, and it may also interfere directly with conception and thereby implantation (22). Thus, male alcohol intake may affect risk of early losses.

Abbreviation: hCG, human chorionic gonadotropin.

Correspondence to Dr. Tine Brink Henriksen, Perinatal Epidemiological Research Unit, Aarhus University Hospital, Skejby, DK-8200 Aarhus, Denmark (e-mail: tbh@dialnet.dk).
By follow-up of couples that attempted to conceive for the first time, we set out to study the association between female and male alcohol intakes and the risk of spontaneous abortion. We included early pregnancy loss, detected by measurement of human chorionic gonadotropin (hCG) in urine.

**MATERIALS AND METHODS**

**Population**

From 1992 to 1994, a total of 430 couples were enrolled at two centers (Copenhagen and Aarhus, Denmark) after a nationwide mailing of personal letters to more than 50,000 members of four trade unions. We sent letters to union members who were 20–35 years of age (index person) and lived with a partner of the opposite sex. Couples without any knowledge about their reproductive capacity, such as previous pregnancies or attempts to become pregnant, who planned to stop contraception to conceive were invited to participate. They were enrolled when birth control was discontinued and followed until a clinically recognized pregnancy or for six menstrual cycles if no pregnancy occurred. A crude estimate of the participation rate, based on an estimation of the eligible population, has been calculated as 16 percent (23).

At enrollment, both partners completed a questionnaire on demographic, medical, reproductive, occupational, and lifestyle factors. Moreover, a monthly questionnaire on lifestyle factors completed 14–21 days from the last menstrual

**TABLE 1.** Male and female characteristics, lifestyle factors, and spontaneous abortion in 186 pregnancies presented as frequencies and relative risks with 95% confidence intervals, Denmark, 1992–1994

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of pregnancies</th>
<th>No. of abortions</th>
<th>Row %</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Center</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copenhagen</td>
<td>96</td>
<td>28</td>
<td>29</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Aarhus</td>
<td>90</td>
<td>27</td>
<td>30</td>
<td>1.0</td>
<td>0.6, 1.5</td>
</tr>
<tr>
<td><strong>Female characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;27</td>
<td>146</td>
<td>37</td>
<td>25</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>≥28†</td>
<td>40</td>
<td>18</td>
<td>45</td>
<td>1.7</td>
<td>1.1, 2.5</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤19</td>
<td>40</td>
<td>14</td>
<td>35</td>
<td>1.2</td>
<td>0.7, 2.0</td>
</tr>
<tr>
<td>20–24</td>
<td>114</td>
<td>33</td>
<td>29</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>≥25</td>
<td>32</td>
<td>8</td>
<td>25</td>
<td>0.8</td>
<td>0.4, 1.7</td>
</tr>
<tr>
<td>Average menstrual cycle length (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤32</td>
<td>144</td>
<td>37</td>
<td>26</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>≥33†</td>
<td>42</td>
<td>18</td>
<td>43</td>
<td>1.7</td>
<td>1.0, 2.5</td>
</tr>
<tr>
<td>Reproductive illness‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>174</td>
<td>50</td>
<td>29</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12</td>
<td>5</td>
<td>42</td>
<td>1.4</td>
<td>0.7, 3.3</td>
</tr>
<tr>
<td>Alcohol intake (drinks/week)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>46</td>
<td>7</td>
<td>15</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>81</td>
<td>26</td>
<td>32</td>
<td>2.1</td>
<td>1.0, 4.3</td>
</tr>
<tr>
<td>5–9</td>
<td>34</td>
<td>12</td>
<td>35</td>
<td>2.3</td>
<td>1.0, 5.1</td>
</tr>
<tr>
<td>≥10</td>
<td>25</td>
<td>10</td>
<td>40</td>
<td>2.6</td>
<td>1.2, 5.9</td>
</tr>
<tr>
<td>Smoking§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>146</td>
<td>47</td>
<td>32</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>40</td>
<td>8</td>
<td>20</td>
<td>0.6</td>
<td>0.3, 1.1</td>
</tr>
<tr>
<td>Caffeine intake (mg/day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–149</td>
<td>54</td>
<td>7</td>
<td>13</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>150–299</td>
<td>52</td>
<td>17</td>
<td>33</td>
<td>2.5</td>
<td>1.2, 5.3</td>
</tr>
<tr>
<td>≥300</td>
<td>80</td>
<td>31</td>
<td>39</td>
<td>3.0</td>
<td>1.5, 5.8</td>
</tr>
</tbody>
</table>

Table continues
bleeding was collected during follow-up. The women furthermore recorded vaginal bleeding and sexual intercourse in a diary. The time of questionnaire completion was estimated by the dates of returning questionnaires.

Alcohol intake was reported as the average number of drinks (glasses of wine, spirits, and bottles of beer of 0.33 liter, each corresponding to 12 g of alcohol) during the week before completion of the questionnaire. Wine and beer drinking were analyzed as separate exposures and subsequently combined into a compound measure together with spirits. Alcohol intake was categorized a priori into four categories (0, 1–4, 5–9, and ≥10 drinks/week).

The variables listed in table 1 were considered as potential confounders or modifiers. Caffeine intake was calculated from the reported daily consumption of coffee, tea, cola, and chocolate bars (24). Furthermore, the type of contraception last used, education, and hours at work were considered.

Each woman collected the first morning urine specimen for 10 consecutive days from the first day of each vaginal bleeding episode. All urine samples from the first day of the vaginal bleeding period were analyzed for the content of intact hCG by an immunofluorometric assay (DELFIA, Wallace, Finland). If the hCG level was above 0.8 IU/liter, the following seven samples were analyzed as well (23). Early pregnancy loss was considered present if one of the hCG values was above 1 IU/liter, followed by a decline (23).

Collection and analyses of urine samples on 10 consecutive days starting on the day of vaginal bleeding have previously been shown to be almost as efficient in the detection of early pregnancy losses when compared with analyses of daily urinary samples (25). Information on the outcome of clinically recognized pregnancies diagnosed during the six cycles of follow-up, including the date of pregnancy termination, was collected by questionnaires mailed in June 1996. By telephone interview of nonresponders, a response rate of 100 percent was obtained. Information on the date of termination of any pregnancy and pregnancy outcome was collected. Gestational duration was estimated from the recording of the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of pregnancies</th>
<th>No. of abortions</th>
<th>Row %</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤29</td>
<td>140</td>
<td>41</td>
<td>29</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>≥30†</td>
<td>46</td>
<td>14</td>
<td>30</td>
<td>1.0</td>
<td>0.6, 1.7</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤19</td>
<td>12</td>
<td>4</td>
<td>33</td>
<td>1.0</td>
<td>0.9, 1.1</td>
</tr>
<tr>
<td>20–24</td>
<td>111</td>
<td>37</td>
<td>33</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>≥25</td>
<td>63</td>
<td>14</td>
<td>22</td>
<td>0.7</td>
<td>0.4, 1.1</td>
</tr>
<tr>
<td>Reproductive illness‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>169</td>
<td>50</td>
<td>30</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17</td>
<td>5</td>
<td>29</td>
<td>1.0</td>
<td>0.9, 1.1</td>
</tr>
<tr>
<td>Alcohol intake (drinks/week)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>20</td>
<td>2</td>
<td>10</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>1–4†</td>
<td>51</td>
<td>14</td>
<td>28</td>
<td>2.7</td>
<td>0.8, 10.0</td>
</tr>
<tr>
<td>5–9</td>
<td>49</td>
<td>10</td>
<td>20</td>
<td>2.0</td>
<td>0.5, 8.0</td>
</tr>
<tr>
<td>≥10</td>
<td>66</td>
<td>29</td>
<td>44</td>
<td>4.4</td>
<td>1.5, 12.6*</td>
</tr>
<tr>
<td>Smoking§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>141</td>
<td>43</td>
<td>31</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>45</td>
<td>12</td>
<td>27</td>
<td>0.9</td>
<td>0.5, 1.5</td>
</tr>
<tr>
<td>Caffeine intake (mg/day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–149</td>
<td>33</td>
<td>5</td>
<td>15</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>150–299</td>
<td>34</td>
<td>12</td>
<td>35</td>
<td>2.3</td>
<td>1.0, 5.6</td>
</tr>
<tr>
<td>300–699</td>
<td>87</td>
<td>28</td>
<td>32</td>
<td>2.1</td>
<td>1.0, 4.7</td>
</tr>
<tr>
<td>≥700</td>
<td>32</td>
<td>10</td>
<td>31</td>
<td>2.1</td>
<td>0.8, 5.2</td>
</tr>
</tbody>
</table>

*p < 0.05.
† Upper quartile.
‡ If yes, one or more of the following were reported: salpingitis, ovarian cysts, gonorrhea, peritonitis, epididymitis, adult parotitis, testicular cancer, and/or cryptorchidims.
§ Most smokers smoked 10–19 cigarettes.
date of the menstrual bleeding in the woman’s diary and the
date of termination of pregnancy regardless of whether it
was hCG detected or self-reported (i.e., detected by
the woman’s general practitioner). Gestational age was es-

timated in completed weeks.

A total of 291 pregnancies were conceived. All cycles (n = 83 pregnancies) with no urinary sampling were excluded,
because they were unavailable for detection of a potential
early pregnancy loss. Only the woman’s first pregnancy
conceived during the study period was considered, leaving
186 pregnancies for our analyses. A spontaneous abortion
was defined as an involuntary loss within 28 weeks of the
last menstrual period.

Statistics

In the analyses, the outcome was dichotomized: sponta-
eneous abortion versus delivery. Since early biochemically
detected pregnancy losses and clinically recognized abor-
tions may not have the same etiology, separate analyses of
each outcome were carried out before they were analyzed
together. Survival curves were computed by the Kaplan-
Meier method. Cox proportional hazards regression analyses
were carried out with gestational age in completed weeks as
the measure of time and abortion as the event of interest.
Potential confounding factors were included in the regres-
sion analyses coded as shown in table 1. All pregnancies that
continued beyond 28 completed weeks were right censored,
as the women were no longer at risk of an abortion. The
adjusted hazard ratios for abortion were present with 95
percent confidence intervals. Confounding factors were
selected for the final model by the change-in-estimate
method (26). Models were built for male and female alcohol
intakes separately. Menstrual cycle length, maternal age,
smoking, and caffeine intake were adjusted for in the final
model. The two exposures were also tested in the same
model with and without interaction terms. The level of statis-
tical significance is defined as a two-sided p value of less
than 5 percent.

RESULTS

Of the 186 pregnancies, 131 resulted in delivery of a child,
and 55 (30 percent) were spontaneously aborted. Of the
abortions, 34 were detected only by urinary hCG before or at
6 completed gestational weeks. The 21 clinically recognized
abortions occurred in the interval after 6 and by 15
completed gestational weeks.

A high intake of alcohol by women or their partners was
associated with a higher frequency of spontaneous abortions
than was a low intake (table 1). Women who experienced a
spontaneous abortion were older and had, on average, longer
menstrual cycles, a higher caffeine intake, and partners with
a higher caffeine intake than did women who gave birth
(table 1). No association was found between spontaneous
abortions and the partner’s smoking habits, partner’s age,
body mass index, and partner’s reproductive illnesses;
contraception last used; education for both man and woman;
or hours at work for both partners.

The crude associations between female and male alcohol
intakes and spontaneous abortion shown in figures 1 and 2
changed only slightly by adjustment for the confounders
listed in table 2. Female alcohol intake was associated with
a 2–3 times higher adjusted risk of spontaneous abortion
compared with no intake, and male intake was associated
with a 2–5 times increase in the adjusted risk. However, only
the relative risks for male and female intakes of 10 or more
drinks/week compared with no intake were statistically

FIGURE 1. Cumulated adjusted survival of 186 pregnancies by four
levels of female alcohol intake, Denmark, 1992–1994. Survival
adjusted for female age, caffeine intake, smoking, and menstrual cycle
length. Dashed line, 0 drinks/week; dashed line with dots, 1–4 drinks/
week; dots, 5–9 drinks/week; solid line, 10 or more drinks/week.

FIGURE 2. Cumulated adjusted survival of 186 pregnancies by four
levels of male alcohol intake, Denmark, 1992–1994. Survival adjusted
for female age, caffeine intake, smoking, and menstrual cycle length.
Dashed line, 0 drinks/week; dashed line with dots, 1–4 drinks/week;
dots, 5–9 drinks/week; solid line, 10 or more drinks/week.
significant. We found a high correlation between male and female alcohol intakes. Additional adjustment for male intake revealed a lower risk of spontaneous abortion associated with female alcohol intake, whereas the higher risk associated with a high male alcohol intake changed only slightly following adjustment for female intake (table 2).

We found no differences in risk of spontaneous abortion for different gestational ages. Thus, the association between male and female intakes of alcohol and spontaneous abortion was similar for abortions detected clinically and by hCG (data not shown).

Only a few of the participants had an intake of spirits in the study period, and the associated risk of spontaneous abortion with alcohol could not be ascribed to a particular source, such as wine or beer. However, the size of our study did not allow us to fully explore each source of alcohol separately.

Alcohol consumption varied throughout the study period. We used information on alcohol intake from the cycle of conception as the primary exposure. Alcohol intake reported at the study entry was not statistically significantly associated with spontaneous abortion.

**DISCUSSION**

Both male and female alcohol intakes in the cycle of conception were associated with a high risk of spontaneous abortion, even at low consumption levels, but no obvious dose-response pattern was seen. Only an intake of 10 or more drinks/week was statistically significantly associated with spontaneous abortion. The risk was increased for both very early biochemically detected and later clinically detected abortions. However, because of the small number of abortions, we were unable to fully explore risks according to gestational age at abortion.

Both partners reported their weekly alcohol intake in the cycle of conception on days 14–21 from the last menstrual bleeding. Thus, the outcome of the cycle was unknown, and differential misclassification of alcohol intake is therefore unlikely. Most previous studies report average weekly consumption, which may be too imprecise. Accordingly, we found no association when alcohol intake reported at the time of pregnancy planning was studied. Other studies suffer from both selection bias and recall bias (27). Alcohol intake during early pregnancy may also be influenced by fetal death prior to an abortion, which may eliminate nausea and increase intake. Thus, if alcohol intake during conception is the proper exposure, it may explain why our estimates differ from those of previous studies. However, several studies with collection of information on alcohol intake in early pregnancy prior to recognition of clinical abortions have similar findings (8, 28). If our findings are causal, the possibility that female exposure may partly be a surrogate measure of male exposure also exists. None of the studies with information on alcohol intake in early pregnancy has collected information on male alcohol intake.

Some previous studies have reported a dose-response-like association between the number of drinks consumed and the risk of clinically recognized abortion (29). We found no dose-response relations that could be due to random misclassification of a light and moderate alcohol intake, because the exact number of drinks may be difficult to remember unless it is zero. If we grouped the light and the moderate consumers, a dose-response-like pattern was seen. The lack of a dose-response relation could also be due to our relatively small sample size and the concomitant imprecision.

No previous studies have investigated the combined effects of male and female alcohol intakes. In our study, a high intake of alcohol in both partners around the time of conception failed to increase the risk beyond that associated with male and female intakes separately.

If even small amounts of alcohol affect the conceptus and its survival immediately after the implantation, this may explain the male effect since seminal fluid has an alcohol content similar to what is found in blood (22). However, the male effect of alcohol on very early pregnancy losses may also be due to chromosomal abnormalities in the sperm cells, which condition is likely to occur some months prior to the conception. Unfortunately, we had no information on detailed cycle-specific alcohol intake during the cycles prior to the couples’ entry into the study, and a high proportion of our pregnancies occurred in the first couple of cycles during the study period. However, if alcohol intake is stable over time, our data are appropriate.

We tested a number of potential confounders but found that only menstrual cycle length, female caffeine intake, smoking, and age changed the estimated risks. Only some of these factors have been considered before (4, 8–10, 12, 30). Even with careful collection of and adjustment for potential confounding factors, residual confounding cannot completely be ruled out.

Self-reported information on lifestyle factors, such as alcohol intake, may underestimate the true consumption. If underreporting was present, it is unlikely to be differential,
as the outcome of pregnancy in our study was unknown at the time of the reporting. Therefore, underreporting could indicate effects at biased low levels of intake or even obscure an association between alcohol intake and spontaneous abortion.

We emphasized that participants should have no prior knowledge about their fecundity, including no pregnancies or previous attempts to become pregnant. Thus, selection of couples with known problems related to fertility is unlikely, as is bias due to specific selection of subfertile couples with a very high or low alcohol intake. We also avoided enrollment of couples who may have changed their alcohol intake and other lifestyle factors because of previous pregnancy experience or because of a loss in the beginning of the study period by including only first pregnancies. Furthermore, 100 percent follow-up was obtained.

Our sample is not a representative sample of the population (23). However, it is unlikely that this will bias our estimates of the association between alcohol intake and spontaneous abortion. We have previously shown that women in this study with a moderate or high alcohol intake have an increased waiting time to pregnancy (31). However, our estimated risk of spontaneous abortion associated with female alcohol consumption would only partly explain the decreased fecundability. This suggests that the effects of alcohol on female fecundability are mediated through different mechanisms, and early pregnancy loss is only one of those. Our analyses of time to pregnancy, however, did not indicate an increased risk of spontaneous abortion associated with male alcohol intake. Thus, time to clinically recognized pregnancy is a rather insensitive measure of the risk of early pregnancy loss.

In conclusion, we found that both male and female alcohol intakes during the week of conception increased the risk of spontaneous abortion, including biochemically detected pregnancy loss.

ACKNOWLEDGMENTS

The study was supported by the Aarhus University Research Foundation (grant 1994-7430-1), the Danish Medical Research Council (grant 12-2042-1), and the Danish Medical Health Insurance Foundation (grants 11/236-93 and 11/243-91). The activities of the Danish Epidemiology Science Centre are financed by a grant from the Danish National Research Foundation.

The authors thank Dr. Allen J. Wilcox for fruitful discussions during the design of the study and Dr. Ulrik Kesmodel for valuable comments on a previous version of the manuscript.

REFERENCES


Am J Epidemiol 2004;160:661–667

