Alcohol Consumption during Pregnancy and the Risk of Preterm Delivery

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The authors evaluated the association between amount and type of alcohol consumed during pregnancy and the risk of preterm delivery and whether the relation differs among very (<32 completed weeks) and moderate (from 32 to <37 completed weeks) preterm delivery. The study is based on data of 40,892 pregnant women included in the first part of the Danish National Birth Cohort. The women completed a computer-assisted telephone interview between December 12, 1997, and December 31, 2000, and delivered a liveborn singleton. Of these women, 1,880 gave birth preterm. Compared with those who abstained during pregnancy, the relative risks for preterm delivery among women who consumed from four to less than seven drinks and seven or more drinks per week during pregnancy were 1.15 (95% confidence interval: 0.84, 1.57) and 1.77 (95% confidence interval: 0.94, 3.31), respectively. Below these intake levels of alcohol, no increased risk of preterm delivery was found. Among women who consumed seven or more drinks per week, the relative risk of very preterm delivery was 3.26 (95% confidence interval: 0.80, 13.24) compared with that of nondrinkers. There were no differences in the associations between type of beverage and preterm delivery.

alcohol drinking; alcoholic beverages; delivery, obstetric; labor, premature; pregnancy

Abbreviation: CI, confidence interval.

Alcohol in high doses is known to have a teratogenic effect. Whether a low intake of alcohol is teratogenic is not known, and it remains controversial whether there exists a safe level of drinking during pregnancy (1). Preterm birth is one of the main causes of neonatal mortality, neonatal morbidity, and functional impairments (2, 3). Previous studies on alcohol consumption during pregnancy and preterm delivery have revealed conflicting results. An increased risk has been reported even at an intake of less than two drinks per week in late pregnancy (4), while others report increased risk at intake levels around 10–14 drinks per week (5, 6). A J-shaped relation between alcohol consumption and risk of preterm delivery has been reported from two prospective studies (6, 7), but only one of these studies found a threshold for adverse effect at 10 drinks per week, while the other found no significant increased risk even at a weekly intake of 21 or more drinks of alcohol. Other studies have had too small a sample size or used too broad exposure categories to find any association between alcohol consumption and preterm delivery (8, 9). Possible explanations for the lack of agreement between studies include low statistical power and inadequate or biased information on maternal alcohol consumption.

If a low consumption of alcohol has an impact on the risk of preterm delivery, it has public health importance, since a low level of alcohol consumption during pregnancy is widespread in many countries. It is also of importance to evaluate if alcohol consumption is related to the degree of preterm delivery, since very preterm deliveries (those occurring before 32 weeks) account for the majority of early neonatal deaths (10). We further find it of interest to investigate the differences in associations between type of alcohol and...
preterm delivery. A difference would indicate that the ethanol part of alcohol is not the only exposure of interest. Other substances in beer, wine, or spirits may be involved in the causal pathway to preterm delivery.

The aims of this study are therefore to examine the association between the amount and type of alcohol consumption and the risk of preterm delivery (before 37 weeks), moderate preterm delivery (32 to before 37 weeks), and very preterm delivery (before 32 weeks).

MATERIALS AND METHODS

Study design and population

The study was carried out within the Danish National Birth Cohort, which is an ongoing nationwide study of pregnant women and their offspring. The pregnant women received written information about the cohort at the first antenatal visit to the general practitioner in gestational weeks 6–10 and were included when an informed consent form was registered. About half of all general practitioners in Denmark participated in the study, and it is estimated that around 60 percent of all women invited chose to participate. Approximately 35 percent of all pregnant women in Denmark are recruited into the cohort. Besides being pregnant, the criteria for inclusion in the cohort were as follows: 1) a permanent address in Denmark, 2) intention to carry the pregnancy to term, and 3) the woman spoke Danish well enough to participate in four telephone interviews during pregnancy and early motherhood. Participants contribute with information on exposures during the pregnancy by means of computer-assisted telephone interviews and blood samples. The first pregnancy interview is scheduled to take place between 12 and 16 weeks of gestation (11).

In the present study, we used data from 41,847 pregnant women who had given their first pregnancy telephone interview within the time period from December 12, 1997, to December 31, 2000, and whose pregnancy resulted in live-born singletons. A total of 955 pregnancies were excluded from the analysis for the following reasons: missing or invalid information on gestational age at delivery (n = 60), missing data on alcohol consumption during or before pregnancy (n = 249), or missing data on the covariates included in multivariate models (n = 82). Women who participated with more than one pregnancy (n = 558) were included only for their first pregnancy, fulfilling the above-mentioned inclusion criteria. Women who were interviewed later than 37 weeks of gestation were excluded (n = 6), since they were not at risk of preterm delivery. Altogether, 40,892 (97.7 percent) women were eligible for analyses.

Exposures measurement

All women were asked to report their average weekly intake of beer, wine, and spirits during their pregnancy. The question was as follows: “How many ordinary beers do you drink per week?” The same question was asked for “glasses of wine” and “glasses of spirits.” We assumed that the alcohol content per drink was roughly equal for the three types of drinks; one bottle of beer contains 11.6 g of alcohol, and 12 g of alcohol are equal to one-sixth bottle of wine or 40 ml of spirits, which are approximate averages for one serving in Denmark. The total weekly alcohol consumption was calculated by adding the intakes of beer, wine, and spirits. Women who reported some intake of beer, wine, and/or spirits but less than one drink per week are assigned a numeric value of 0.5 drink. Alcohol consumption during pregnancy is categorized into nondrinkers, one-half drink per week, 1–1.5 drinks per week, 2–3.5 drinks per week, 4–6.5 drinks per week, and seven or more drinks per week. For the subsequent analysis of an association between type of alcohol and preterm delivery, we categorized the women into preference for type of alcohol. Preference for one type of alcohol was defined as beer, wine, or spirits if the intake of this type exceeded 50 percent of the woman’s total alcohol intake. Women who drank alcohol but did not have a preferred alcoholic beverage were classified as mixed drinkers. Women who abstained from drinking during pregnancy were classified in a separate category of nondrinkers.

Measurement of potential confounders

Information on the main part of potential confounders was obtained by self-reports in the telephone-based interview. Information on diabetes status was obtained from the National Discharge Register. The following known or suspected determinants of preterm delivery were assumed to potentially confound the analyses: number of spontaneous abortions (n = 0, 1, ≥2), prior preterm delivery (nulliparous, no, yes), type I diabetes (no, yes), hypertension (present, present only during pregnancy, no hypertension), bleeding episodes during pregnancy (yes or no), occupational status in the household defined as the highest attained occupational status of the woman or partner (higher-grade professionals, lower-grade professionals, skilled workers, unskilled workers, students, economically inactive, unclassifiable), maternal age (<20, 20–24, 25–29, 30–34, ≥35 years), parity (n = 0, 1, ≥2 births), maternal height (<160, 160–164, 165–169, 170–174, ≥175 cm), prepregnancy weight (<50, 50–59, 60–69, 70–79, ≥80 kg), gender of the infant (male, female), coffee consumption (0, 1–5, ≥6 cups per day; 1 cup = approximately 239 ml, depending on cup size and coffee strength), and smoking habits. Smoking habits were reported as the number of cigarettes (1 g), small cigars (3 g), cigars (5 g), or pipes (3 g) smoked a day, which were categorized into nonsmoking, stopped during pregnancy, 1–10 g, and ≥11 g per day.

Outcome measurement

The outcome measure of interest was gestational age at delivery based on information from the National Discharge Register, which comprises information on all deliveries in Denmark. Gestational age in the National Discharge Register is recorded in terms of completed weeks and days. National guidelines regarding the assessment of gestational age are as follows: either gestational age estimated from the first day of the last menstrual period (preconditioned, a regular bleeding pattern during the last 6 months, and no use of oral contraceptives during the last 3 months before pregnancy) or estimation from ultrasound examination before 24 weeks of gestation.
(12). Preterm delivery was defined as a gestational age of less than 37 weeks (259 days) of gestation and subdivided into degree of preterm: moderate preterm (32 to before 37 weeks) and very preterm delivery (before 32 weeks).

Statistical analyses

The relative risks of preterm delivery according to the amount of alcohol consumed and the preference for type of alcohol during pregnancy were estimated using the Cox regression model. Since the time of interview during pregnancy and the risk of preterm delivery vary during gestation, careful adjustment for gestational age was needed. Therefore, gestational age in days was used as an underlying time variable. We used the model with delayed entry, so women entered the cohort on the day of interview, and follow-up ended at delivery or after 258 days (36 weeks and 6 days) of gestation, whichever came first. Deliveries occurring after 258 days were censored at that time.

We conducted two sets of analyses: one estimating the relative risk estimates of preterm delivery according to total alcohol intake without considering type of beverage, and another estimating the relative risks of preterm delivery according to preference for type of alcohol adjusting for the total consumption. The reference group in the analyses of total alcohol consumption was nondrinkers. The reference group in the analyses of type of alcohol was women who preferred wine and had a total alcohol consumption of 1–1.5 drink(s) per week. Since the risk of repeating a preterm birth is high and since a previous preterm birth or other recognized reproductive problems might lead to reduced alcohol consumption, we furthermore analyzed data for nulliparous women only.

Subsequently, we estimated the influence of alcohol on very and moderate preterm delivery, respectively, by including an interaction between alcohol and a variable indicating the degree of preterm delivery. This procedure corresponds to making separate analyses of very and moderate preterm delivery, except that common estimates of the influences of each of the covariates other than alcohol are obtained.

The change-in-estimate method was used to assess which of the potential confounders actually did confound the analyses (13). Variables that were equally distributed according to consumption levels of the amount and type of alcohol and that were not evident from the literature to be associated with alcohol consumption were removed one by one from the full model, if they did not change the estimates between alcohol and preterm birth by more than 5 percent.

RESULTS

The mean gestational age at delivery was 279 days (range, 158–315 days), and the overall proportion of preterm delivery was 4.6 percent (1,880/40,892) and of the preterm deliveries the proportion of very preterm delivery was 12 percent (217/1,880). Fifty-five percent of the women reported that they abstained from alcohol consumption in their first trimester. Women who had a high alcohol intake during pregnancy were more often above 35 years of age, smokers, and coffee consumers and less often nulliparous than were women who reported abstaining from alcohol (table 1). Among women who consumed any amount of alcohol, most (70.9 percent) preferred wine. Less than 1 percent of the drinking women preferred spirits, while 11.5 percent of the drinking women preferred beer. Women who preferred wine were more often nonsmokers and from higher-grade professional households than were women who preferred beer or spirits. Women who preferred beer were more often above 35 years of age and more often coffee consumers than were women who preferred wine or spirits. The few women who preferred spirits were less often above 35 years of age and more often nulliparous, and they had a lower mean alcohol consumption than did women who preferred beer or spirits (table 1).
Amount and type of alcohol and risk of preterm delivery

Alcohol consumption below four drinks per week was associated with risk estimates below unity. Women who had an intake between two and four drinks per week had a lower risk of preterm delivery, a relative risk of 0.80 (95 percent confidence interval (CI): 0.68, 0.96) compared with nondrinkers. Women who had alcohol consumption of between four and seven drinks per week had a relative risk of preterm delivery of 1.15 (95 percent CI: 0.84, 1.57) compared with nondrinkers. Likewise, women who had a consumption of seven or more drinks per week had a relative risk of 1.77 (95 percent CI: 0.94, 3.31) compared with nondrinkers (table 2). Adjustment for diabetes status, age, previous preterm delivery, parity, smoking, coffee consumption, and occupational status did not affect the results (table 2).

The estimates from the analysis restricted to nulliparous women only were in line with the estimates based on the entire population. However, the apparent protective effect of an alcohol consumption between two and four drinks per week in the analysis based on the entire population diminished and was no longer statistically significant, when the analysis is restricted to nulliparous women only (table 2). No significant interaction between alcohol consumption and parity was detectable.

In the analysis of preference of type of alcohol, no differences in risk were seen. All the estimates were close to 1.00. Only very few women preferred spirits, so the estimate for spirits is based on only 175 women. As seen from table 3,

### Table 2

<table>
<thead>
<tr>
<th>Alcohol (drinks/week)</th>
<th>Nulliparous women (n = 18,349)</th>
<th>All women (n = 40,892)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted RR</td>
<td>Adjusted† RR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RR 95% CI</td>
</tr>
<tr>
<td>Nondrinkers§</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>0.5</td>
<td>0.98</td>
<td>0.97 0.82, 1.15</td>
</tr>
<tr>
<td>1–1.5</td>
<td>0.95</td>
<td>0.94 0.79, 1.12</td>
</tr>
<tr>
<td>2–3.5</td>
<td>0.95</td>
<td>0.94 0.75, 1.18</td>
</tr>
<tr>
<td>4–6.5</td>
<td>1.44</td>
<td>1.41 0.92, 2.19</td>
</tr>
<tr>
<td>≥7</td>
<td>3.09</td>
<td>2.91 1.29, 6.55</td>
</tr>
</tbody>
</table>

* RR, relative risk; CI, confidence interval.
† Adjusted for type 1 diabetes, age, smoking during pregnancy, coffee consumption during pregnancy, and occupational status in the household.
‡ Adjusted for type 1 diabetes, age, previous preterm delivery, smoking during pregnancy, coffee consumption during pregnancy, occupational status in the household, and parity.
§ Reference group.

### Table 3

<table>
<thead>
<tr>
<th>Preference for type of alcohol</th>
<th>Nulliparous women (n = 18,349)</th>
<th>All women (n = 40,892)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Unadjusted RR</td>
<td>Adjusted† RR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RR 95% CI</td>
</tr>
<tr>
<td>Nondrinkers§</td>
<td>1.10</td>
<td>1.10 0.91, 1.33</td>
</tr>
<tr>
<td>Wine§</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Beer</td>
<td>1.13</td>
<td>1.06 0.78, 1.43</td>
</tr>
<tr>
<td>Spirits</td>
<td>1.15</td>
<td>1.09 0.48, 2.45</td>
</tr>
<tr>
<td>Mixed</td>
<td>1.13</td>
<td>1.10 0.84, 1.44</td>
</tr>
</tbody>
</table>

* RR, relative risk; CI, Confidence interval.
† Adjusted for type 1 diabetes, age, smoking during pregnancy, coffee consumption during pregnancy, occupational status in the household, and total alcohol consumption during pregnancy.
‡ Adjusted for type 1 diabetes, age, previous preterm delivery, smoking during pregnancy, coffee consumption during pregnancy, occupational status in the household, parity, and total alcohol consumption during pregnancy.
§ Reference group.
Amount of alcohol and risk of very and moderate preterm delivery

An alcohol intake of between four and less than seven and of seven or more drinks per week was associated with a relative risk for very preterm delivery of 1.53 (95 percent CI: 0.67, 3.49) and 3.26 (95 percent CI: 0.80, 13.24), respectively, compared with that of nondrinkers (table 4). In general, the relative risks, but not risk difference, for very preterm delivery were higher than the relative risks for moderate preterm delivery. Adjustment for diabetes status, age, previous preterm delivery, parity, smoking, coffee consumption, and occupational status did not affect the results (table 4). In addition, our results show that the risk of preterm delivery increases at even lower levels of alcohol consumption. This is in agreement with the findings by Shiono et al. (14), who reported an increased risk at an intake level of one or more drinks per day in a large prospective study. Lundsberg et al. (4) reported an increased risk of preterm delivery at an intake level equivalent to less than two drinks per week in late pregnancy; however, their study showed no association with drinking early in pregnancy. However, other studies have not found any association between alcohol consumption and preterm delivery (8, 9). Our findings of higher relative risk estimates for very preterm than moderate preterm delivery corroborate two smaller studies subdividing preterm delivery. Both of these studies categorized alcohol consumption into only drinkers and nondrinkers (15, 16). Shiono et al. (14) also investigated the association between alcohol consumption and very preterm delivery, defined as birth before 33 weeks. In this study, preterm delivery was not subdivided into very and moderate preterm delivery but was defined as very preterm (before 33 weeks) or preterm (before 37 weeks). The relative risk estimates being even higher for very preterm delivery.

DISCUSSION

This study on birth outcomes of more than 40,000 pregnancies showed that an alcohol consumption of seven or more drinks per week during pregnancy was associated with a slightly increased risk of preterm delivery. We found no increased risk of preterm delivery among women with alcohol consumption less than four drinks per week. There was no obvious difference in the effects of intakes of beer, wine, or spirits on preterm delivery. Examining the influence of alcohol on risk of very preterm and moderate preterm delivery revealed results similar to those for preterm delivery, the risk estimates being even higher for very preterm delivery.

<table>
<thead>
<tr>
<th>Alcohol (drinks/week)</th>
<th>Before 32 weeks</th>
<th>From 32 to before 37 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted RR†</td>
<td>Adjusted† RR 95% CI</td>
</tr>
<tr>
<td></td>
<td>Adjusted† RR 95% CI</td>
<td></td>
</tr>
<tr>
<td>Nondrinkers‡</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>0.5</td>
<td>0.89</td>
<td>0.91</td>
</tr>
<tr>
<td>1–1.5</td>
<td>1.17</td>
<td>1.24</td>
</tr>
<tr>
<td>2–3.5</td>
<td>1.02</td>
<td>1.06</td>
</tr>
<tr>
<td>4–6.5</td>
<td>1.52</td>
<td>1.53</td>
</tr>
<tr>
<td>≥7</td>
<td>3.32</td>
<td>3.26</td>
</tr>
</tbody>
</table>

* RR, relative risk; CI, confidence interval.
† Adjusted for type 1 diabetes, age, previous preterm delivery, parity, smoking during pregnancy, and coffee consumption during pregnancy, and occupational status in the household.
‡ Reference group.
risk for very preterm delivery is lower than what we found in this study. We are aware of only two smaller studies having investigated the association between type of beverage and preterm delivery (4, 17). Our findings of no obvious differences in associations between the type of beverage and preterm delivery are in accordance with their results. Possible explanations for the lack of agreement across studies investigating the association between alcohol consumption and preterm delivery include unequal characterization and timing of alcohol consumption, low statistical power for addressing small effects, differences in methods of obtaining the measure of exposure, and differences in adjustments of the confounding variables.

This study was based on a large population with almost complete follow-up. The number of women with missing information on alcohol consumption and covariates was low, because of the use of computer-assisted telephone interviews in data collection. This study is the largest so far regarding alcohol consumption and preterm delivery, and it is one of the few investigating the risk of very preterm delivery according to different consumption levels of alcohol. Although this study included a large number of participants, few events hampered the analysis of an association between alcohol consumption and very preterm delivery.

A possible limitation of this study is the participation rate of only 60 percent of those women invited to the Danish National Birth Cohort. In order to introduce bias, the decision to participate should be selective regarding both the alcohol consumption and the risk of preterm delivery. It is unlikely that the risk of preterm delivery could play a role since women did not report this information. It is unlikely that the decision to participate is especially influenced by alcohol consumption, since the Danish National Birth Cohort is not directly aimed at examining health consequences of alcohol intake. We therefore find it unlikely that the small percentage of participants biased the results considerably.

All studies on alcohol consumption in humans, including this study, rely on self-reported data, which are susceptible to information bias, almost certainly in the form of underreporting. However, a methodological study showed that, in the absence of overreporting, even considerable underreporting seems to have little impact on the association between exposure and outcome, especially when the number of nonexposed is large (18). For these data, the interviewer effect (arising from variations in interviewers’ health beliefs and personal habits) was found to be negligible in this methodological study (19). Information on alcohol intake during pregnancy was obtained prospectively, so that differential recall bias is thus unlikely. Information on alcohol intake during pregnancy was obtained only once in the first half of pregnancy, and the reported value was used as an indicator for the general level of exposure during pregnancy. This may imply misclassification for women who change their alcohol habits during pregnancy, which would, if anything, affect the results toward the null value. The exposure measure is not time specific, because the range in time of interviewing varied; however, it is not known how the timing of alcohol might play a role in the induction of preterm delivery. The use of average measures of alcohol exposure masks variations in the drinking pattern, and it is possible that periodic high alcohol intakes (binge episode) have a different effect on the fetus than an alcohol intake that does not reach the same blood alcohol levels. There may be different explanations for the apparent protective effect of alcohol consumption of between two and four drinks per week. First, it may be due to a healthy drinker effect, for example, that healthy women generally tend to drink more than women with recognized reproductive problems. The lack of a protective effect in the analysis restricted to nulliparous women supports this explanation. Second, the reference group of nondrinkers consists of two distinct groups of women: women who decrease alcohol intake during pregnancy and women who abstain both prior to and during pregnancy. In accordance with the results from Passaro et al. (20), the results from our study found that women who abstained from alcohol prior to pregnancy had a higher risk of preterm delivery compared with women drinking some amounts of alcohol (data not shown). In addition, the group of women who abstained from alcohol prior to and during pregnancy had the highest risk of preterm delivery (data not shown).

The gestational age at delivery was obtained through register linkage, and most of these measures are based upon ultrasound examinations. The use of gestational age determined from the first day of the last menstrual period as the only source of calculation of gestational age tends to overestimate the gestational age for those with long menstrual cycles, thereby underestimating the proportion of preterm delivery (21). The proportion of preterm delivery in this study is lower than those in many other studies, but it is comparable with the proportion of preterm delivery in Denmark (22).

The suggested pathophysiologic mechanism for alcohol to induce preterm delivery is related to an increase in the production of prostaglandins in relation to alcohol intake. Increased secretion of prostaglandins has been found in alcoholic mothers and their offspring (23). Alcohol has, on the other hand, been used clinically to avoid premature labor in the late 1960s and during the 1970s. This alleged tocolytic effect of alcohol has, however, not been supported by double-blinded clinical trials (24).

No difference in the associations between types of alcohol and preterm delivery implies that ethanol probably is accountable in the causal pathway between alcohol consumption and preterm delivery.

In conclusion, alcohol consumption below four drinks per week does not increase the risk of preterm delivery, while a daily alcohol intake during pregnancy seems to increase the risk of preterm delivery. The alcohol-related risk of preterm delivery is independent of type of alcohol consumed.

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