Correspondence

Alcohol consumption in pregnancy

Sir,

We would like to draw attention to the following points in the paper by Davis, Partridge, and Storrs in which they conclude that 'there is no safe level of alcohol consumption in pregnancy'. In this paper 973 women were followed up after filling in questionnaires on alcohol consumption in the antenatal period. Of 479 births to women who claimed to drink no alcohol, there were 11 abortions, 5 perinatal deaths, and no infants with major malformations. Of the 494 infants born to women who drank at least some alcohol, there were 11 abortions, 7 perinatal deaths, and 6 infants with major malformations. Thus, although there was no association with mortality, there was said to be significant association at the 1% level with major malformations. In fact the difference in incidence between drinkers and non-drinkers is only just significant at the 5% level with Yates's continuity correction applied ($\chi^2 = 4.04, P = 0.044$). A 2 tailed exact test leads to a similar result ($P = 0.034$).

In fact, the 6 cases of malformation all occurred among the 359 pregnancies of mothers with low average daily intakes of alcohol (1–10 ml), and it may be that the authors have tested this group against all others. It is not clear whether all 8 groups were used, but if so then the large number of very small expected frequencies would invalidate the use of the $\chi^2$ test. It is, in addition, statistically frowned on to examine the data and then decide which groups to test against the others. In this particular case it is illogical as well as unsound to take the moderate drinkers in isolation. Thus, both the marginal significance of this single result and the observation that it is due to the low abnormality rate for the non-drinkers, rather than a high rate for the drinkers compared with the area population, leads to doubt concerning the general conclusion.

In addition, the authors analysed data on the birthweights and head circumferences of all infants, according to the gestational age at delivery. There were no significant differences between the mean birthweights or mean head circumferences at each gestational age between the infants of all drinkers and those of non-drinkers. The authors, however, stated that infants of mothers drinking over 20 ml of alcohol per day did have smaller head circumferences.

This general conclusion was reached on the basis of 3 selected subgroups. At gestational ages 35, 38, and 39 weeks the average head circumference of children of heavy drinkers was claimed to be significantly smaller (presumably relative to non-drinkers). No such differences were found for this outcome at any other gestational age. In addition, the results of the $t$-test were based on samples of only 1, 4, and 5 cases respectively. They are unlikely to be representative of the relevant populations.

In summary, while the few positive results are open to doubt, most of the comparisons made between the drinking groups give no evidence to reject the null hypothesis (of no drinking effect). Most of the defects in this study were based on the dubious method of searching for significant effects among small subgroups. The basic design of the study, however, is admirable, and a repeat of the survey with larger numbers should help to clarify the problem of whether moderate drinking has a harmful effect on the fetus.

Reference


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Sir,

We would like to suggest that the methods and results of the study by Davis et al are subject to several important methodological and statistical flaws.

(1) Of 1120 initial invitations to participate there was a combined non-response and unknown outcome rate of 13·1%. There is no mention of any attempt to check whether non-respondents and those lost to follow up differ in any important way from the achieved sample with respect to certain standard criteria such as age, parity, social class, and smoking behaviour (presumably this information would have been available from antenatal records). Clearly, bias in response or outcome follow up (such as heavier drinking among non-respondents or higher rates of fetal loss among those lost to follow up) may have seriously compromised the results of the study.

(2) No standardisation is made in the results for the variability in gestational age at recruitment to the study, despite suggestions in the published reports that the effects of alcohol on the fetus may vary during pregnancy.

(3) The authors obtain a significant result for the difference between the proportion of congenital abnormalities among babies of non-drinkers in their sample and the population of South Warwickshire. However, the proportions (%) of congenital abnormalities among the groups are actually as follows:

<table>
<thead>
<tr>
<th>Sample</th>
<th>South Warwickshire</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-drinkers</td>
<td>Drinkers</td>
</tr>
<tr>
<td>0·0</td>
<td>1·23</td>
</tr>
<tr>
<td>0·62</td>
<td>1·64</td>
</tr>
</tbody>
</table>

It can be seen that the proportion among the study population is in fact less than half that for South Warwickshire (0·62% as opposed to 1·64%, $P<0·01$). The obvious...
conclusion is that the sample population is not representative of the population of South Warwickshire, from which it has been drawn. The 2 populations should not, therefore, have been compared in the way the authors have chosen. Bias introduced by non-response and loss to follow up, as described in (1) may be responsible for the non-representative nature of the sample population.

(4) A more appropriate comparison would have been to look at the within sample difference in congenital abnormalities among the babies of drinkers and non-drinkers. Fisher’s exact test (used in preference to $\chi^2$ where cell sizes are very small) yields an approximate 2 tailed probability of 0·03 that the difference between the proportion of congenital abnormalities among the babies of drinkers and non-drinkers in a sample of this size could be due to chance alone. Conventionally, this is accepted as a significant result. The assumptions underlying significance testing, however, require that the samples be randomly selected. Biases such as those referred to in (1) (and that we have some some reason to believe may apply to this study, see (3)) would render the results of these tests invalid.

(5) If the authors’ inference that the head circumferences of the babies of drinking mothers are smaller than those of non-drinking mothers is correct we would expect to see a consistent pattern of differences in mean values for drinkers and non-drinkers across gestational ages. In fact, of the 8 different gestational ages, 4 show a negative difference, 3 a positive difference, and in 1 instance the mean values shown on the graphical presentation are indistinguishable. Moreover, these differences are distributed randomly with respect to gestational age.

Since the raw data are not reported it is impossible to verify the stated P values, but it is remarkable that a significant result is found for the 1 case (that of 39 weeks gestational age) for which mean values are apparently identical. A significant result is also quoted for 35 weeks gestational age, yet the authors claim not to find the standard deviations for this group ‘meaningful’, due to small numbers. (Standard errors would anyway have been a more appropriate measure of the variability of mean values.) As to the remaining significant result (P<0·01 at 38 weeks gestational age), in a series of 8 comparisons there are odds of approximately 1 in 10 of finding 1 such result purely by chance. A more rigorous analysis of these data might have included an analysis of covariance, taking head circumference as the dependent variable, and controlling for the effect of gestational age.

Bearing these comments in mind, and given the small numbers, we are dismayed by the authors’ far reaching conclusion that ‘even moderate social drinking is associated with a risk of abnormal fetal outcome’. The study simply does not permit the conclusion that ‘there is a striking association’—or, indeed, any association—between alcohol consumption by pregnant women and major congenital abnormality or reduced head circumference in their babies.

References


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Dr Davis comments:

It is inevitable that in a study using a questionnaire to gather data there is a risk that the study group may not be representative of the population from which they are drawn. We agree that the incidence of major malformations in our total study group falls short of that expected in South Warwickshire. There are two main reasons for this. The incidence of malformations in South Warwickshire (1·64%) was taken from Office of Population Censuses and Surveys (OPCS) figures that we now find include minor as well as major malformations. In addition, the OPCS figures include malformations notified later and not only at birth.

There was only 1 severely malformed baby (anencephaly) born to the 120 mothers not responding to our questionnaire, giving an incidence of 0·83%. This compares closely with the 0·62% incidence (6 out of 961) in the whole of our study group, and with the 0·93% incidence when 3 extra malformed babies are included, as mentioned below. There is little evidence therefore that as far as malformations are concerned the relatively high non-response rate of 10·7% biased our results. We have not attempted to trace the 2·4% of cases lost to follow up.

We have not analysed the non-respondents to our questionnaire for age, parity, social class, and smoking behaviour. We can do this, but the results will not be available in time to be included in this letter. We would expect the self reported alcohol consumption to have been underestimated by respondents and bias resulting from this would increase rather than decrease the significance of our results. We agree that a within sample difference in congenital abnormalities between babies of drinkers and non-drinkers might have been an alternative method of analysis. It must be emphasised, however, that we compared the babies of all the drinking mothers (and not any of the 7 subgroups) against those of the non-drinking mothers. This is what we planned to do. The very small numbers of heavier drinkers would make interpretation of the results questionable if analysed separately.

We set out to record only those malformations apparent at birth. However, there are now known to have been 3 study babies with abnormalities diagnosed later. These were Hirschsprung’s disease, Treacher Collins syndrome, and congenital hypothyroidism. Maternal alcohol consumption was 1–10 ml/day in the first 2 of these and the third mother was a non-drinker. If these 3 extra babies are included a within sample analysis of abnormalities between drinkers and non-drinkers (8 and 1 cases respectively) shows $\chi^2 = 5·41$, $P = 0·019$, when Yates’s correction for continuity is applied in view of the