hardly unexpected, and it is more surprising that multinodularity should be taken as reassurance against the likelihood of neoplasia in any dominant area of enlargement. Malignancy in association with chronic lymphocytic thyroiditis is a particular diagnostic pitfall. The hard consistency of some malignant lesions is similar to that of a dominant area of thyroiditis. In addition, it may be difficult cytologically to distinguish between thyroiditis and lymphoma and between thyroiditis and oxyphil cell follicular neoplasm.

Although dominant swellings should clearly be regarded with greater clinical suspicion than has been traditional, the discriminant power of investigations to predict the risk of neoplasia is in general disappointing, including fine needle aspiration cytology, now widely regarded as the preferred investigation. We find that the accuracy of aspiration cytology analysed prospectively is lower than generally believed.[8] The main source of error in this small series of dominant swellings was the inaccurate prediction of possible neoplasia in histologically benign swellings. We emphasise, however, that all patients with a possibly neoplastic cytological picture were operated on whereas 102 patients with non-neoplastic findings on repeated sampling were not. The true false positive rate was therefore likely to be considerably lower than might appear from this highly selected analysis. In addition, although eight of 24 neoplastic lesions were incorrectly predicted as non-neoplastic, these were histologically benign follicular adenomas, and all eight carcinomas (and one of three occult carcinomas) were correctly predicted as either malignant or possibly neoplastic.

Clearly dominant thyroid swellings cannot simply be dismissed as part and parcel of chronic lymphocytic thyroiditis or multinodular goitre, but it is not possible on the basis of this study to give clear guidelines on which should be removed. There are other factors, outlined above, apart from cytology, which influence the decision. Despite its apparent limitations, however, routine aspiration cytology has alerted us to the risks of neoplasia and malignancy in dominant swellings and, although cytological appearances influenced the decision to remove roughly four non-neoplastic dominant swellings annually, we still consider it the most valuable and only appropriate investigation.

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Reported social alcohol consumption during pregnancy and infants' development at 18 months

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Abstract

***Objective*—To determine the relation between mothers' self reported drinking habits before, during, and after pregnancy and infants' mental and motor development at 18 months of age.**

***Design*—Follow up study of all singleton live births born to primigravidas living in Dundee and booked into antenatal clinics from 1 May 1985 to 30 April 1986.**

***Setting*—District of Dundee.**

***Subjects*—846 children aged 18 months, of whom 592 attended for assessment.**

***Main outcome measures*—Scores on Bayley scales of infant mental and motor development.**

***Results*—For full term children, maternal alcohol consumption was not significantly related to any adverse effect on the children's mental or motor development measures at age 18 months. After confounding factors had been controlled for, alcohol consumption before pregnancy and after pregnancy was significantly related to better motor performance and mental performance.**

***Conclusion*—Pregnant women probably need not abstain from alcohol altogether as no detectable adverse relation was found between the child's mental and physical development and the mother's weekly consumption at levels in excess of 100 g absolute alcohol. However, to allow for a margin of safety and taking into account the findings of an earlier phase of this study on the immediate effects on the newborn, it is recommended that pregnant women should drink no more than eight units of alcohol a week, the equivalent of about one drink a day.**

Introduction

The serious effects on the offspring of excessive maternal alcohol consumption during pregnancy have been known for over 15 years. In 1973 Jones and Smith developed the term fetal alcohol syndrome to describe a cluster of signs including abnormal facial features, central nervous system dysfunction, and growth deficiency.[1] Follow up studies of patients with fetal alcohol syndrome have indicated that these signs tend to persist into childhood.[2-4]

The question then arose whether more moderate levels of maternal alcohol consumption during pregnancy could have smaller but nevertheless disadvantageous effects on child development. Some studies have shown adverse effects of mothers' moderate drinking on infants' mental development,[5,6] motor development,[5,7] behaviour,[8-10] and size,[11,12] but others have found no detectable adverse effect on moderate drinking on the development of the child.[13-15]

The main aim of the present study was to determine the nature of the relation between maternal alcohol consumption before, during, and after pregnancy and infant mental and motor development at 18 months, taking into account the possible con-

founding effects of cigarette smoking, social class, and other variables.

Methods

This survey was a follow up of the cohort investigated in an earlier study.[16] The sample consisted of the children born to 846 primigravidas living in Dundee and booked into antenatal clinics between 1 May 1985 and 30 April 1986. The study was population based in a relatively stable community. The mothers were invited to bring their children to Ninewells Hospital for assessment when the children were 18 months old. Up to three requests to participate were sent by post, and telephone contact was made when possible. Home visits were made to a subsample of those who did not respond to these approaches. The subsample included all non-responders who had consumed 100 g or more of absolute alcohol a week in early pregnancy, but the two fieldworkers making the home visits were not aware of the women's drinking status. This stratification was maintained in the analysis by treating the group consuming $\geq$100 g a week separately. Because of the age dependence of the Bayley test we could assess each child only within two weeks of the date when the child became 18 months old. Non-responders could thus be followed up for only a limited period, with a consequent effect on the overall response rate.

Measurements made during pregnancy and details about the pregnancy and its outcome were obtained from data collected during the first part of the study.[16] Information on quality, frequency, and variability of maternal alcohol consumption, cigarette smoking, and socioeconomic factors after pregnancy was obtained by questionnaire administered by a trained interviewer using the same structure as for the questionnaire administered during pregnancy. Data on maternal alcohol consumption were converted to an average amount of absolute alcohol in grams consumed weekly according to the method used in the first part of the study. One unit—one glass of wine, a half-pint of beer, or one standard measure of spirits—is equivalent to approximately 10 g absolute alcohol.

All the children were assessed by a trained psychologist (FF) who was blind to knowledge of maternal drinking. Children's mental development and motor development were assessed by using the Bayley scales of infant development.[17] The scores achieved on the mental and motor scales gave a mental development index and a psychomotor development index for each child, which were adjusted for the child's age by using standard tables. The reliability of the Bayley measurements in our hands has been reported elsewhere, based on tester-observer and test-retest data.[18,19] Tester-observer reliability was studied in 20 randomly selected infants who were tested by the psychologist under the observation of a principal clinical psychologist, who also scored the test. Test-retest reliability was studied in another 20 randomly selected infants who were retested by the psychologist one week after she administered the first test. The mean (SD) differences between paired observations of mental development index and psychomotor development index for tester-observer and test-retest reliability were, for the mental development index, 1·55 (7·2) units between tester and observer and −2·15 (11·6) units between test and retest; for the psychomotor development index the differences were −2·05 (8·9) units between tester and observer and −0·65 (7·3) units between test and retest.

Ethical approval of the study was obtained from the Tayside Health Board's Dundee Committee on Medical Ethics.

TABLE I—*Sample size and response*

	N
Singleton live births	846
Lost to follow up	254
Owing to time of starting follow up*	18
Letters returned	69
Moved away	9
Infant deaths	4
No response or defaulters	147
Refusals	7
Total	592

*Eligible to take part during the first four months of the follow up period but not seen for economic reasons.

TABLE II—*Categories of alcohol consumption in early pregnancy*

	Alcohol consumption in early pregnancy (g absolute alcohol/week)					
	Nil	1-49	50-99	100-119	≥120	Total
Responders	257	281	37	5	12	592
Non-responders	115	107	13	1	0	236
Totals	372	388	50	6	12	828

STATISTICAL METHODS

The sample size available for this project was already fixed by the number of mothers participating in the first part of the study. The relations of greatest interest were those between the developmental quotient of the infant measured by the Bayley scales and maternal alcohol consumption before and during pregnancy. To detect a true correlation of 0·1 at an α of 0·05 (type I error) and a β of 0·2 (type II error) a sample size of 782 would be required. Coefficients of biological significance were thought likely to be rather larger than this, so the sample size was considered more than adequate for the aims of the study.

Multiple regression methods were used to examine the relation between maternal alcohol consumption and infant mental and motor development while controlling for potentially confounding factors: maternal cigarette consumption, age, and social class and the child's sex, birth weight, and gestational age. As in the first part of the study,[16] maternal alcohol consumption was coded into indicator variables corresponding to levels of weekly alcohol consumption. The use of indicator variables avoided the necessity of assuming any particular underlying relation between consumption and outcome, which would have been necessary if the variable had been used in its continuous form. The levels used were 1-49 g (mild), 50-99 g (moderate), and $\geq$100 g (heavy). All three variables were coded 0 if the mother did not consume alcohol. Further grouping above 100 g was not used owing to the small numbers of women consuming these quantities of alcohol. Cigarette consumption was divided into four groups: non-smokers and 1-9, 10-19, and $\geq$20 cigarettes a day, represented by three indicator variables. All three variables were coded 0 if the mother was a non-smoker. Social class was coded into seven indicator variables corresponding to social classes II, III non-manual, III manual, IV, V, the unemployed, and armed forces or students or single or unclassified. The code was 0 for all variables if the mother was in social class I. Parity was not included as a variable because all mothers were primigravidas. The data were analysed by multiple regression in which the choice of the independent variables was made by the user.

Results

RESPONSE

Table I shows the details of the follow up response rate (70%). Table II shows the distribution of alcohol consumption during early pregnancy in responders and non-responders. There was no differential drop out among those abstaining or drinking up to 99 g absolute alcohol a week. Almost all those drinking

more than this were included among the responders because of the method of sampling.

Proportionally more non-responders were classified as unemployed and in the composite group of armed forces or students or single or unclassified than responders ($p<0.0001$ by partitioning of χ^2). There was no difference for the other classes ($p=0.5$).

ALCOHOL AND CIGARETTE CONSUMPTION

Table III shows maternal alcohol and cigarette consumption before, during, and after pregnancy. Levels of drinking and smoking tended to decrease during pregnancy and then increase after pregnancy but remain at a lower level than before pregnancy. The proportional changes in drinking were much greater than for smoking.

RELATION OF THE DEVELOPMENT INDICES TO OTHER VARIABLES

The mental development index was positively related to mother's social class and age and to the child's sex (the girls' mean index was 6·4 units higher than the boys', 95% confidence interval 3·52 to 9·3), gestational age, and birth weight. The mean value of the index was lower for children whose mothers smoked 10-19 cigarettes a day than for those whose mothers smoked less (mean difference −6·0 units, −10·2 to −1·8), but the children of mothers who smoked ≥20 cigarettes a day had an intermediate score (−3·2 units, −10·7 to 4·33). The psychomotor development index was positively related to gestational age and birth weight but not to the child's sex (the girls' mean index was 1·2 units higher than the boys' −0·3 to 2·7), or mother's age, social class, or cigarette smoking (although the same pattern existed for cigarette smoking as with the mental development index).

TABLE III—*Alcohol and cigarette consumption of mothers before, during, and after pregnancy. Figures are numbers (percentages)*

	Before pregnancy (n=592)	Early pregnancy (n=592)	Late pregnancy (n=575)	After pregnancy (n=592)
Weekly alcohol consumption:				
0	42 (7)	257 (43)	360 (63)	97 (16)
1-49 g	284 (48)	281 (48)	202 (35)	341 (58)
50-99 g	147 (25)	37 (6)	9 (2)	105 (18)
≥100 g	119 (20)	17 (3)	4 (1)	49 (8)
Daily cigarette consumption:				
0	295 (50)	359 (61)	359 (62)	323 (55)
1-9	39 (7)	119 (20)	106 (18)	65 (11)
10-19	130 (22)	90 (15)	81 (14)	131 (22)
≥20	128 (22)	24 (4)	29 (5)	73 (12)

TABLE IV—*Mental development index score related to social class and alcohol consumption (g absolute alcohol/week) during early pregnancy*

	Alcohol consumption									
	Abstainers		1-49		50-99		≥100		Total	
Husband's social class	Mean score	No	Mean score	No	Mean score	No	Mean score	No	Mean score	No
I	110	11	116	16					113	27
II	107	34	112	32	109	5	132	1	110	72
III Non-manual	110	28	112	34	105	2	94	3	110	67
III Manual	108	62	106	74	106	7	99	3	106	146
IV	110	24	104	46	90	3	111	1	105	74
V	104	13	99	18	116	3	104	3	103	37
Unemployed	100	59	105	36	101	8	100	4	102	107
Unclassified	95	26	100	25	105	9	85	2	98	62
Total	105	257	107	281	105	37	100	17	106	592

TABLE V—*Psychomotor development index score related to social class and alcohol consumption (g absolute alcohol/week) during early pregnancy*

	Alcohol consumption									
	Abstainers		1-49		50-99		≥100		Total	
Husband's social class	Mean score	No	Mean score	No	Mean score	No	Mean score	No	Mean score	No
I	103	11	104	16					104	27
II	101	34	101	32	105	5	107	1	102	72
III Non-manual	102	28	102	34	100	2	97	3	102	67
III Manual	102	62	102	74	101	7	102	3	102	146
IV	102	24	104	46	104	3	113	1	103	74
V	100	13	100	18	98	3	112	3	101	37
Unemployed	102	59	102	36	97	8	98	4	102	107
Unclassified	98	26	102	25	102	9	91	2	100	62
Total	101	257	102	281	101	37	101	17	102	592

TABLE VI—*Regression coefficients (95% confidence intervals) for mental development index and psychomotor development index on alcohol consumption after controlling for confounding variables*

Weekly consumption of absolute alcohol	Mental development index	Psychomotor development index
Before pregnancy:		
1-49 g (n=252)	4·48 (−1·3 to 10·3)	3·65 (0·6 to 6·7)
50-99 g (n=129)	5·96 (−0·2 to 12·1)	3·54 (0·3 to 6·7)
≥100 g (n=108)	6·45 (0·1 to 12·8)	5·08 (1·8 to 8·4)
During early pregnancy:		
1-49 g (n=277)	0·80 (−2·2 to 3·8)	0·44 (−1·2 to 2·0)
50-99 g (n=37)	1·57 (−4·7 to 7·8)	−0·21 (−3·5 to 3·1)
≥100 g (n=17)	−2·00 (−10·8 to 6·8)	1·70 (−2·9 to 6·3)
When child aged 18 months:		
1-49 g (n=339)	4·85 (0·8 to 8·9)	2·59 (0·5 to 4·7)
50-99 g (n=104)	7·54 (2·6 to 12·5)	2·33 (−0·3 to 4·9)
≥100 g (n=49)	6·57 (0·5 to 12·7)	2·83 (−0·4 to 6·0)

THE INDICES, ALCOHOL CONSUMPTION, AND SOCIAL CLASS

The mental development index was strongly related to social class but not to alcohol consumption (table IV). Although all women in social class I drank before and after pregnancy, they reported very little drinking during pregnancy. On the other hand, those in social class V, the unemployed, and the unclassified tended to drink 50-99 g absolute alcohol a week more often than the other classes. The mental development index clearly decreased with social class whereas there was no consistent reduction in the index with increasing alcohol consumption.

Table V shows the mean psychomotor development index in the same format. There is little relation between the index and social class and none with alcohol consumption.

REGRESSION ANALYSIS

The data in tables IV and V do not take into account the possible effects of confounding variables other than social class. The data were therefore analysed by regression analysis to allow for the variables described in the methods section that might have affected the relation between infant development and alcohol consumption. Table VI shows the results of the analysis of both development indices on the levels of alcohol consumption before pregnancy, during early pregnancy, and after pregnancy. Each coefficient indicates the difference between the mean index for the children in the relevant alcohol consumption group compared with that for children of abstainers. For example, in the analysis of alcohol consumption during pregnancy the mean mental development index of the children of mothers drinking 1-49 g absolute alcohol a week was 0·8 units greater than that of the children of abstainers after all the potential confounders had been allowed for. The comparable unadjusted differences for the mental development index can be obtained from the totals in table IV by subtracting the mean for any drinking group from that for the children of abstainers. The regression coefficients for the confounding variables have been omitted for clarity.

The mean mental and psychomotor development indices of children of mothers who drank alcohol before pregnancy at all levels were higher than those of the children of abstainers. For the psychomotor development index the difference was statistically significant at all three levels of consumption. The relation between alcohol consumption in early pregnancy and either index was not significant, and nor

was that between alcohol consumption during late pregnancy and the two indices, with or without control for confounding factors (not shown). The findings for alcohol consumption 18 months after delivery were similar to those for alcohol consumption before pregnancy. In these analyses cigarette smoking was of no importance as a predictor of either index; in the case of the mental development index this was due to the strong association between smoking and social class.

In a second set of analyses the confounding variables were reduced to only those that affected the relation between alcohol consumption and the indices. This had no effect on the precision of the alcohol coefficients and altered the coefficients only slightly from those in the table. The analyses were then restricted to full term infants (≥37 weeks, n=559) and to full term infants who had not been admitted to the special care baby unit (n=535). None of these reanalyses led to a change in interpretation of the results. Furthermore, there was no evidence of an adverse relation between child development and any one of the three major groups of beverage (beer, wine, and spirits).

Discussion

It is conventional to advise pregnant women not to smoke, not to drink alcohol, and not to take any drugs unless absolutely necessary. Many women admit to intense feelings of guilt when they transgress their doctor's advice, but social circumstances often compel them to do so. Although the evidence against smoking is consistent and persuasive, the evidence against social drinking is not.

STUDIES OF IMMEDIATE OUTCOME OF PREGNANCY

Review of the literature suggests that effects of alcohol in humans are not seen at low levels of consumption.[20] Studies of the immediate outcome of pregnancy tend to show consistent correlations only with consumption at levels above about 120 g absolute alcohol a week. These effects consist of reduced birth weight, gestational age, length, head circumference, and placental weight; increased frequency of spontaneous abortion, stillbirths, and congenital malformations; and a variety of other characteristics including lower Apgar scores, low sucking pressure, and adverse neonatal neurobehavioural characteristics. The evidence for an effect on any of these factors at lower consumption levels is sparse, inconsistent, and handicapped by the lack of precision in the measurement of intake.

STUDIES OF CHILD DEVELOPMENT

The much smaller number of reports on effects of maternal alcohol consumption in infants and young children support our own findings.[5 6 8-15 21 22] Streissguth and coworkers in Seattle have followed up about 500 children for whom they had information about maternal drinking habits during gestation.[5 8 9 11 21] Immediate adverse outcomes of pregnancy were related to a daily average alcohol consumption of above 200 g absolute alcohol a week in the month before recognition of pregnancy.[23] Adverse developmental outcomes, however, seem to be related to much higher alcohol consumption. At the age of 8 months decreased mean values for the mental development index and psychomotor development index were found when mothers had consumed about 400 g absolute alcohol a week (2 ounces a day).[5] At later ages the mother's consumption of more than about 300 g a week (1·5 ounces a day) was related to a significant adverse effect on IQ at the age of 4 years[21] and on impairment of distraction and reaction times at 7 years.[9]

Other studies have suggested that effects on child development occur only when high levels of consumption persist throughout pregnancy. Larsson *et al* and Coles *et al* both used a study design in which heavy drinkers were divided between those who reduced or gave up drinking during pregnancy and those who did not and compared these with a group of abstainers.[13 15] The children of those mothers who had continued to drink more than 875 g or 350 g absolute alcohol a week were significantly less developed mentally and physically than the children in the other two groups. The children of mothers who had reduced their intake did not differ from those of abstainers, suggesting that a consumption of at least 350 g absolute alcohol a week throughout pregnancy is required to influence mental and physical development.

The Ottawa prenatal prospective study has presented somewhat conflicting results in three subsets of children of about the same age as our sample. Gusella and Fried, in an early report from the study, described the results of testing with the Bayley scale in 84 children whose average age was just over 1 year.[22] Average consumption during pregnancy was not significantly related to birth weight, but there was a significant though small negative correlation with children's mental development index. As only one woman drank more than an average of 300 g absolute alcohol a week the results suggest an "effect" of alcohol on mental development at substantially lower levels than had been found in other studies. In a more recent publication Fried and Watkinson found no relation between the indices and alcohol consumption at the age of 1 year, but the mental development index at 2 years was related to an intake of ≥170 g a week.[24]

The variation in the results of different investigations must be due in part to the inability to measure intake with any degree of accuracy, and in some studies it may be due to failure to draw representative samples. In addition, several studies have reported a relation between disadvantage for the infant, and the mother's drinking of beer, but not necessarily wine or spirits.[16 25-27] None of the cited studies has considered this possible source of confounding.

Published reports have not provided a clear cut answer about the long term effects of maternal alcohol consumption. The work on the immediate outcome of pregnancy seems to indicate a threshold at about 120 g absolute alcohol a week. The most careful and epidemiologically respectable work on child development after the neonatal period has been done by Streissguth and colleagues. Their results suggest a threshold value of about 300 g a week.

Our own results are in keeping with these postulated thresholds in that we found no adverse effect on development in a sample of children of whose mothers only two drank over 300 g absolute alcohol a week. It is possible that the limitations of the epidemiological method have precluded the identification of real relations. A general problem in all the follow up studies has been to maintain high response rates. In the Seattle study the cohort of 500 children had repeatedly to be topped up with new recruits from the main sample at each follow up. In the Ottawa study the original sample was 700, but follow up occurred on widely differing numbers of children. Our follow up rate of 70% of a population based sample (rather than one obtained from an unknown base) compares favourably with that in other studies. Although some potential biases were identified, there seemed to be no bias with respect to alcohol consumption except that imposed by the sampling procedure and accounted for in the analysis. Reliability of the Bayley test is not high at an individual level, but at the group level the differences for test-retest and tester-observer results were small and not significant. As a single trained person did all the examinations it is unlikely that we could have reduced the variability any further.

RECOMMENDATION

Keeping in mind the limitations of the methods, we believe that long term effects in humans are very likely to occur at levels of maternal alcohol consumption during pregnancy of 300 g or more of absolute alcohol a week. Below this level the evidence is conflicting and open to methodological objections. We continue to support the recommendation from our results of immediate outcome of pregnancy that, allowing for a margin of safety, women should not have more than one standard drink a day (70-85 g absolute alcohol a week), and only as much as this if abstinence is not feasible.

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What makes insulin injections painful?

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The pain induced by subcutaneous administration of insulin may depend on the size and the sharpness of the needle or on the volume of the injection; the latter has been used to argue in favour of using highly concentrated insulin (100 U/ml).[1] We assessed the pain of subcutaneous injection in diabetic patients being treated with insulin.

Patients, methods, and results

Sixty three patients aged 16-40 years with a history of insulin treatment of 0·5-21 years who were participating in a diabetes education programme volunteered for the study. For study purposes sterile insulin free Nordisk Insuject Testmedium (Novo-Nordisk, Bagsvaerd, Denmark) was injected subcutaneously by 51 patients. Insuject Testmedium and regular human insulin (Velasulin H, Novo-Nordisk, Valby, Denmark) had been found previously to evoke identical pain responses in another 12 of the patients (Wilcoxon signed rank test, $p=0·89$). In a double blind fashion, 0·025 ml, 0·1 ml, 0·1 ml, 0·2 ml, 0·25 ml, and 0·5 ml of the fluid were injected by Disetronic insulin pens (Disetronic, Biergdorf, Switzerland) into an abdominal skin fold.[2] The 0·1 ml injection was administered in duplicate to test the reproducibility of the patients' pain scoring. The sequence of the injections was randomised by drawing cards; coding was carried out by a person (DML) who did not take part in the injection procedures. Disetronic pens were used because their design does not permit observation of how much fluid is being expelled when the plunger is pushed for injection.

The pens were loaded with the test fluid, adjusted, and masked by a person unaware of the experimental procedures; they were furnished with 26 1/2 gauge Microlance needles (Beckton-Dickinson, Dublin, Ireland) which were renewed before each injection. Furthermore, 12 patients inserted either 27 gauge NovoPen needles (Nipro, Osaka, Japan), 27 gauge insulin syringe-needle units (Omnikan, Braun, Melsungen, Germany), or 28 gauge insulin syringe-needle units (Plastipak Microfine IV, Becton-Dickinson, Heidelberg, Germany) without injecting any fluid. The needles were either sharp (unused) or blunt (after piercing five times the rubber membrane of a human regular insulin vial (Hoechst, Frankfurt, Germany); they were inserted subcutaneously in a double blind, randomised fashion. Immediately after they had completed the experimental procedures the patients were asked to record graphically any perceived pain on a visual analogue scale by making a single mark on a 21 cm line (0=no pain at all; 21=worst pain).[3]

The table summarises the results. There were no significant differences in pain perception among the five different volumes (Friedman's analysis of variance by ranks, $\chi^2=6·95$, $df=5$, $p>0·5$). Thirteen of the 51 patients (25%) reported no pain at all with any injected