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Spontaneous abortions among women working in the pharmaceutical industry

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SUMMARY A register based study was conducted on the pregnancy outcome of female workers in eight Finnish pharmaceutical factories to determine whether they had a higher risk of spontaneous abortion than the general population or matched controls. Information about all female workers who had been employed in the factories during the years 1973 or 1975 (four factories) to 1980 was obtained from the employers. The workers' pregnancy data were collected from the nation wide hospital discharge register and polyclinic data of hospitals from 1973 to 1981. The total number of 1795 pregnancies included 1179 deliveries, 142 spontaneous abortions, and 474 induced abortions. The spontaneous abortion rate (the number of spontaneous abortions × 100, divided by the number of spontaneous abortions plus the number of births) during employment was 10·9% and before/after employment 10·6%. The rate for all the women in the corresponding central hospital districts was 8·5% during the study period. A case-control study was also carried out in which the cases were 44 women who had had a spontaneous abortion during employment in the pharmaceutical factory. Three age matched female pharmaceutical factory workers who had given birth to a child were chosen as controls for every case. The information about occupational exposures was collected from questionnaires completed by the occupational physician or nurse at the factory. The response rate was 93%. Exposure to chemicals was more common among the cases than among the controls. For methylene chloride, a solvent commonly used in the pharmaceutical industry, the increase in odds ratio was of borderline significance (odds ratio 2·3, $p = 0·06$). In a logistic regression model (which included oestrogen exposure, solvent exposure by frequency of the usage, and heavy lifting) the odds ratio was increased for oestrogens (odds ratio 4·2, $p = 0·05$) and for continuous heavy lifting (odds ratio 5·7, $p = 0·02$). The odds ratio for spontaneous abortions was greater among those exposed to four or more solvents (odds ratio 3·5, $p = 0·05$) than among those exposed to one to three solvents (odds ratio 0·8, $p = 0·74$).

It has been suggested that some forms of occupational exposure are harmful to pregnant women and affect the outcome of pregnancy.[1-3] Work in hospital laboratories[4 5] and in pharmaceutical laboratories[6] has been associated with an increased risk of spontaneous abortion. The harmful agents have not been identified but organic solvents have been suspected.

Studies based on registered pregnancy data have shown a slightly increased risk of spontaneous abortion in laboratory assistants[7] and workers in university laboratories (not statistically significant).[8] In a Danish study of employment no category of laboratory work was found to carry a significantly increased risk of spontaneous abortion.[9] An increased risk of spontaneous abortion has been found, however, in the pharmaceutical industry among members of the Union of Chemical Workers.[10]

Laboratory work during pregnancy has been associated with congenital malformations in the offspring in several studies,[6 11-14] but some negative results have also been published.[8 15] A slight (not statistically significant) excess of malformations was found in the offspring of women employed in the pharmaceutical industry,[10] but the observation was based on only a few cases.

In the pharmaceutical industry the workers may be exposed to various chemicals and solvents both in the production departments and in the laboratories. In this study we set out to determine whether such work-

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ers experience a higher rate of abortion, using recorded data on spontaneous abortions and a professional assessment of exposure by occupational health personnel.

Materials and methods

The study population was obtained from the personnel records of eight Finnish pharmaceutical factories during the years 1973 or 1975 (four factories)—1980. The workers were linked by personal identity number to the nation wide hospital discharge register and hospital polyclinic data to obtain the information required about the workers' pregnancies, including births and spontaneous and induced abortions for 1973 to 1981. The use and reliability of the register has been described earlier.[7 16 17]

Date(s) of employment and of its termination were collected from the factory files for all women who had had a spontaneous abortion or who had given birth to a child. The study group for the case-control phase was selected from women who had been employed for at least one week during the first trimester of pregnancy. All the women treated for spontaneous abortion (ICD-8 codes 643 and 645) were defined as cases. If the woman had had two or more spontaneous abortions only one was randomly selected. Three controls were selected for every case from women who had given birth (ICD-8 codes 650–662) but only one pregnancy per woman was included. The controls were matched with the case on age at time of conception within two and a half years using the nearest available matching. Three controls were available for all but two cases.

A questionnaire was sent to the factory physicians to determine the occupational exposures of the study subject during the first trimester of pregnancy. The physicians or their nurses completed the questionnaire forms using information obtained from the health cards, labour protection chiefs, and the foremen of the departments. They were not informed whether they were dealing with a case or a control. The questionnaire form requested information on the individual worker's occupation and main tasks, and exposure to solvents (aliphatic solvents, alicyclic solvents, toluene, xylene, benzene, chloroform, methylene chloride, and other solvents), antineoplastic agents and carcinogens, hormones (oestrogens, androgens, progestogens), and antibiotics. Information on whether the work included heavy lifting ($\geqslant$ 10 kg) and whether the posture at work was sedentary or standing was also sought, as were individual worker's chronic diseases before and during pregnancy and acute diseases during pregnancy as well as their medication, smoking, and previous pregnancies. Information on smoking and previous pregnancies, however, was available for only 25% and 41% of the women, respectively, and was therefore not used in the analyses.

The questionnaires were checked and any incomplete or unclear answers were clarified by recontacting the occupational health services. The material was coded without knowing who was a case or a control.

The estimated odds ratios for exposure were calculated with the logistic regression model for individually matched data based on the conditional maximum likelihood.[18] The p values for separate variables were evaluated by comparing the respective standardised regression coefficients with normal distribution.

A solvent score variable was formed to analyse the intensity of exposure to all solvents. The exposure frequency of each solvent was scored as follows: daily = 5·0 points, three to four times a week = 3·5 points, one to two times a week = 1·5 points, and less than once a week = 0·5 points. The points given to each solvent were summed and this solvent score variable was used in the logistic models in three categories: no points, 0·5–4·5 points, and $\geqslant$5·0 points.

Results

In the first phase of the study the spontaneous abortion rate was compared according to whether the women were employed in the pharmaceutical factories during the first trimester of pregnancy. During 1973–80, 1795 pregnancies among women employed included 1179 deliveries, 142 spontaneous abortions, and 474 induced abortions. Because the employment time was not required for those who had had an induced abortion only, the rates for spontaneous abortions during employment and before/after employment were calculated as follows: rate of spontaneous abortions (%) = the number of spontaneous abortions × 100 divided by the number of spontaneous abortions plus the number of births. The rates for the employed (10·9%) and non-employed (10·6%)

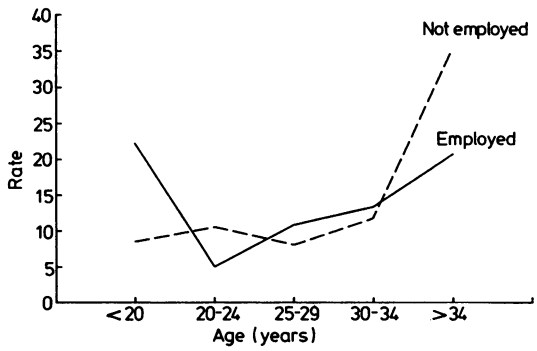

Fig 1 *Age specific rates of spontaneous abortions by employment in the pharmaceutical industry during pregnancy.*

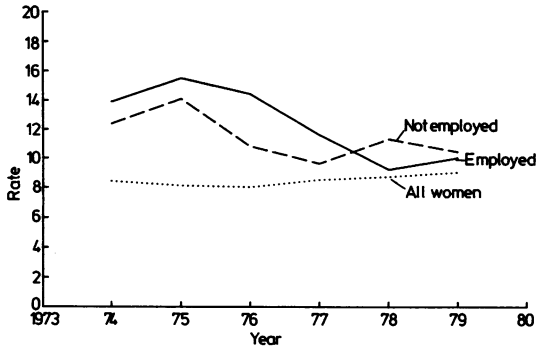

Fig 2 *Three year moving average rates of spontaneous abortions among the workers of pharmaceutical factories and among all women in the respective hospital districts.*

during the pregnancy were similar. The rates were high for the oldest age group (35 or more) of the non-employed, and for the youngest age group (under 20) of the employed (fig 1).

Because hygienic conditions had allegedly been improved in the factories during the 1970s the spontaneous abortion rate for each year was calculated (fig 2). The three year moving average rates decreased over the study period from about 15% to about 9·5%. The decrease was also observed for the pregnancies conceived before or after employment in the pharmaceutical industry. By contrast, the general spontaneous abortion rate in the central hospital districts, where the pharmaceutical industry was located, remained constant at about 8·5% during the study period.

There were 10 congenital malformations among the women ever employed; five occurred to the women working in the pharmaceutical industry during pregnancy (prevalence 1·18% of the births) and five to those not working there during pregnancy (prevalence 0·66% of the births). The malformations were of different types. Because of the small numbers no inquiries were made about their exposures.

Table 1 *Distribution of spontaneous abortion (cases) and normal births (controls) by occupation among women employed in the pharmaceutical industry (%)*

Occupation	*Cases (n = 44)*	*Controls (n = 130)*
Pharmaceutical workers and packers	25	25
Laboratory assistants	20	20
Pharmacists	11	13
Chemists	5	5
Cleaners	9	7
Clerical staff and kitchen workers	20	22
Other	9	6
Unknown	—	2
Total	99	100

In a case-control study exposure data were sought for the 44 women who had had a spontaneous abortion during their employment in a pharmaceutical factory and for the 130 women who had had a normal birth during employment. Completed questionnaires were received for 93% of the women but not from three cases (6·8%) or from nine controls (6·9%).

The distribution of occupations was similar among the cases and the controls (table 1). Table 2 shows the frequency of different chemical exposure among the cases and the controls. Exposure to chemicals was more common among the cases than the controls. Exposure in the study population was most commonly to solvents. The odds ratios for spontaneous abortions were higher than unity for most of the chemical exposures (table 3). For methylene chloride the increase in odds ratio was of borderline significance (odds ratio 2·3, p = 0·06). The odds ratios were high also for aliphatic (such as pentane, hexane, heptane, petroleum ether, or other aliphatic hydrocarbon mixtures) and alicyclic (cyclohexane, terpenes) hydrocarbons and for benzene but the num-

Table 2 *Frequency of chemical exposure among the cases and the controls*

Exposure	*Exposed cases/all cases (%)*	*Exposed controls/all controls (%)*
Solvents:	12/38 (31·6)	26/119 (21·8)
Aliphatic hydrocarbons	5/38 (13·2)	6/119 (5·0)
Alicyclic hydrocarbons	5/38 (13·2)	5/119 (4·2)
Benzene	3/38 (7·9)	5/119 (4·2)
Toluene	7/38 (18·4)	14/119 (11·8)
Xylene	3/38 (7·9)	4/119 (3·4)
Chloroform	9/38 (23·7)	18/119 (15·1)
Methylene chloride	11/38 (28·9)	17/119 (14·3)
Other solvents	8/38 (21·1)	17/119 (14·3)
Antineoplastic agents	3/41 (7·3)	3/120 (2·5)
Oestrogens	6/39 (15·4)	7/121 (5·8)
Progestogens	2/39 (5·1)	5/121 (4·1)
Androgens	2/39 (5·1)	5/121 (4·1)
Antibiotics	7/40 (17·5)	20/120 (16·7)
Carcinogens*	11/38 (28·9)	21/119 (17·6)

*Antineoplastic agents, arsenic trioxide, asbestos, benzene, chloroform, dimethyl sulphate, dioxane, formaldehyde solution, carbon tetrachloride, trichloroethylene.

Table 3 *Odds ratio of spontaneous abortions for chemical exposures, matched univariate analysis*

Exposure	*Odds ratio*	*95% CI*	*p Value*
Solvents:	1·5	0·7–3·5	0·32
Aliphatic hydrocarbons	2·5	0·6–9·6	0·19
Alicyclic hydrocarbons	3·2	0·7–13·8	0·13
Benzene	2·4	0·5–12·0	0·30
Toluene	1·6	0·6–4·5	0·36
Xylene	2·0	0·4–10·6	0·42
Chloroform	1·6	0·6–4·2	0·32
Methylene chloride	2·3	1·0–5·7	0·06
Other	1·6	0·6–4·3	0·39
Antineoplastic agents	2·8	0·6–14·0	0·21
Oestrogens	3·1	0·8–11·4	0·09
Progestogens	1·1	0·2–5·5	0·94
Androgens	1·1	0·2–5·5	0·94
Antibiotics	1·2	0·7–2·3	0·48
Carcinogens	1·8	0·7–4·2	0·21

CI = Confidence interval.

ber of women exposed to these solvents was small. An increased risk, although not significant statistically, was associated with exposure to oestrogens (odds ratio 3·1, p = 0·09). From other working conditions (table 4) continuous lifting of heavy loads was associated with an excess of spontaneous abortions, but the statistical significance was borderline (odds ratio 3·6, p = 0·06). Working position (sedentary, standing, or both) was not associated with a risk of abortion.

Because the odds ratios for solvent exposure for all and for the individual solvents were increased, further analyses considered the frequency of exposure. Table 5 shows the odds ratio for abortion for the three most common solvents by frequency of exposure.

Those exposed at least once a week and less than once a week were compared with those not exposed to the solvent in question. The odds ratios for methylene chloride and toluene increased with frequency of use, lending support to causality; for chloroform the reverse was the case (table 5). When the exposure was characterised by the number of solvents used, the odds ratio for spontaneous abortion was greater among those exposed to four or more solvents than among those exposed to one to three solvents (table 5). The analysis of exposure using the solvent score variable (see materials and methods) gave parallel results: the odds ratio for abortion increased with increasing intensity of exposure.

A multivariate analysis was conducted in order to control for the effect of exposures on each other. When oestrogen exposure, solvent exposure by frequency of usage (solvent score), and lifting heavy loads were included in the same logistic regression model, the odds ratio was increased for oestrogens (odds ratio 4·2, p = 0·05) and for continuous heavy lifting (odds ratio 5·7, p = 0·02) (table 6). The odds ratio was increased also for the higher solvent score but it was not statistically significant.

Diseases and medication during early pregnancy showed no significant association with spontaneous abortions, although slightly increased odds ratio were found for chronic diseases and for their medication (table 7). The lack of information on diseases and medication was relatively high, varying from 23% to 35%; yet the percentages were similar for the cases and the controls in the different categories.

Discussion

This study showed no appreciable differences between the frequencies of spontaneous abortion among those who had been employed in the pharmaceutical industry during the first trimester of pregnancy and those who had not. When interpreting this result some factors which may have diluted the effects of occupational exposures might be considered. Firstly,

Table 4 *Odds ratio of spontaneous abortions for standing work and heavy lifting, matched logistic analysis*

Model	*Type of work*	*Cases No (%)*	*Controls No (%)*	*Odds ratio*	*95% CI*	*p Value*
1	Sedentary work	13 (31·7)	43 (35·5)	1·0		
	Varying work	19 (46·3)	53 (43·8)	1·3	0·6–2·9	0·56
	Standing work	9 (22·0)	25 (20·7)	1·4	0·5–4·4	0·54
2	Heavy lifting (≥ 10 kg)					
	None	29 (70·7)	90 (75·6)	1·0		
	Seldom	6 (14·6)	24 (20·2)	1·0	0·4–2·9	0·98
	Continuously	6 (14·6)	5 (4·2)	3·6	1·0–13·7	0·06

Table 5 *Odds ratio of spontaneous abortions by number of solvents or frequency of exposure, matched logistic analysis*

Model	*Exposure*	*Cases No (%)*	*Controls No (%)*	*Odds ratio**	*95% CI*	*p Value*
1	Exposure to:					
	1–3 solvents	4 (10·5)	17 (14·3)	0·8	0·3–2·6	0·74
	⩾4 solvents	8 (21·1)	9 (7·6)	3·5	1·0–12·4	0·05
2	Methylene chloride:					
	< once a week	5 (13·2)	10 (8·4)	2·0	0·6–6·6	0·28
	⩾ once a week	6 (15·8)	7 (5·9)	2·8	0·8–9·5	0·10
3	Chloroform:					
	< once a week	5 (13·2)	9 (7·6)	1·8	0·5–6·4	0·35
	⩾ once a week	4 (10·5)	9 (7·6)	1·4	0·4–5·1	0·57
4	Toluene:					
	< once a week	2 (5·3)	7 (5·9)	1·2	0·2–6·9	0·83
	⩾ once a week	5 (13·2)	7 (5·9)	1·9	0·6–6·4	0·32
5	Solvent score:					
	0·5–4·5 points	6 (15·8)	18 (15·1)	1·1	0·4–3·2	0·80
	⩾ 5·0 points	6 (15·8)	8 (6·7)	2·4	0·7–7·7	0·15

*Comparison with subjects not exposed to solvents.

all the female personnel of the pharmaceutical factories, exposed and non-exposed, were included in the analysis. Secondly, we had no information about jobs of those not employed in the pharmaceutical industry during the pregnancy. They may have been employed in similar occupations elsewhere. Qualified people, such as laboratory assistants, pharmacists, and chemists tend to continue in the same type of work although the employer may change.

Interestingly the spontaneous abortion rate decreased from about 15% to 9·5% during the study, reaching almost the rate of all women (8·5%). This coincided with technical improvements in the pharmaceutical industry which decreased dust and vapour exposures, as detailed by the occupational physicians. Although decreases in exposure levels may have contributed to the decreasing trend in spontaneous abortions, a similar but less pronounced decrease in spontaneous abortions in the pregnancies taking place before or after employment (see fig 2) suggests that other factors may also be involved. We have observed a declining spontaneous abortion rate in the 1970s for the female members of the Union of Chemical Workers, of which the workers in the pharmaceutical industry constitute one branch.[10] We have been unable to explain such a decrease.

In the case-control part of the study some of the occupational factors, such as frequent use of solvents and methylene chloride, were associated with increased odds ratios. The frequency of use of solvents, including methylene chloride, and the number of different solvents used associated with spontaneous abortions added credibility to the findings. The concentrations of methylene chloride were occasionally high, as it was earlier common to allow the solvent to evaporate into the air of the working environment.

In a previous study Axelsson *et al* found a slight (statistically insignificant) increase in the spontaneous abortion rate for women exposed to organic solvents, including methylene chloride, in laboratories during the first trimester of pregnancy.[8] The results of a Danish study showed no increase in the odds ratio for

Table 6 *Odds ratio of spontaneous abortions for oestrogens, solvents, and heavy lifting in pharmaceutical industry, logistic regression model*

Exposure	*Odds ratio*	*95% CI*	*p Value*
Oestrogens	4·2	1·0–18·2	0·05
Solvent score:			
0·5–4·5 points	0·5	0·1–1·7	0·26
⩾5·0 points	1·9	0·5–7·0	0·33
Heavy lifting (⩾10 kg):			
Seldom	1·3	0·4–3·9	0·65
Continuously	5·7	1·3–26·0	0·02

Table 7 *Odds ratio of spontaneous abortions for diseases and medications, matched univariate analysis*

Disease or medication	*Cases No (%)*	*Controls No (%)*	*Odds ratio*	*95% CI*	*p Value*
Chronic diseases	6 (17·6)	11 (11·7)	1·6	0·5–5·1	0·45
Medication for chronic diseases	5 (15·2)	7 (7·8)	1·8	0·5–6·2	0·38
Acute diseases	13 (38·2)	39 (40·2)	0·9	0·4–2·0	0·72
Medication for acute diseases	6 (20·7)	17 (20·2)	0·9	0·3–2·9	0·84

spontaneous abortion among laboratory workers with alleged exposure to organic solvents, but the time of exposure in the pregnancy was not known.[9]

Exposure to oestrogens showed high odds ratios when analysed individually or in a multivariate model. According to the questionnaires exposure to oestrogens among pregnant women was infrequent, taking place less than once a week. Among the cases two production workers (pill compressing work), two laboratory assistants, and two pharmacists were exposed to oestrogens as were one worker who weighed the raw materials, five laboratory assistants, and one pharmacist among the controls. The exposure characteristics were clarified afterwards by contacting the occupational physicians. In the production departments oestrogens were processed two or three times a year for two or three days. The dates for oestrogen formulation matched the first trimester of pregnancy of the two production workers. The laboratory assistants and the pharmacists handled small amounts of oestrogens in analyses periodically at the intervals of a few weeks. Concentrations of oestrogens had not been measured in the air of the factory or of the laboratories. Nevertheless, it appears likely that at least in the pill compressing department exposure to some oestrogen dust is possible. Although we confirmed that all the cases handled oestrogens to some degree during the first trimester of pregnancy, we cannot exclude the contribution of other factors to the finding. Workers in an oral contraceptive formulating plant in Puerto Rico have been reported to have symptoms of hyperoestrogenism.[19] An increase in first trimester fetal losses has also been observed in women who became pregnant while using oral contraceptives.[20] The harmful effects of the hormone therapy during pregnancy on the offspring have also been described, including disturbances of the development of the fetal genitalia and childhood cancer.[21] Furthermore, oestrogens are potent embryotoxic agents in experimental animals.[21]

Exposure to antineoplastic agents was not common in this series; only three cases and three controls were exposed. The cases were two pill compressing workers and one laboratory assistant; the controls were a grinder and a weigher who were exposed to dusty raw material and one laboratory assistant. All were exposed less than once a week, except for the laboratory assistant, who was exposed once or twice a week. Cyclophosphamide was the main antineoplastic agent produced; methotrexate, busulphan, chlorambucil, and mercaptopurine were prepared in smaller amounts. The increased odds ratio for exposure to antineoplastic agents, although not significant statistically, is in accordance with the results of recent studies on Finnish nurses exposed to cytostatic drugs, where significant increased odds ratio for malformations in the offspring[16] and spontaneous abortions were found.[21a]

For the carcinogens, of which chloroform was the most commonly used, the odds ratio was slightly above unity, but the difference was not significant statistically. The group of carcinogens was heterogeneous and the number of women exposed to each was small.

In addition to chemical exposure the physical demands of the work were of interest. The various working positions (sedentary, standing, or varying) seemed to have no particular effect on the occurrence of spontaneous abortions, whereas heavy lifting seemed to increase the risk. The harmful effects of physical strain on pregnancy have earlier been associated mainly with fetal growth retardation and prematurity[22 23] if the mother has continued heavy work at the end of the pregnancy but negative studies have also been published.[24 25] Preliminary results of a Canadian study show a slightly increased spontaneous abortion rate among women in work that requires heavy lifting (23·6%), when compared with all women (17·7%).[26] In a study of women in laboratory work a slightly but insignificantly increased spontaneous abortion risk (RR 1·36, CI 0·91–2·02) was found for those who reported heavy lifting.[8] How physical strain during early pregnancy could lead to abortion is not clear.

In cross sectional studies concerning the spontaneous abortion rate among working women there may be a selection bias because women who have had a successful pregnancy are more likely to stop working than the women who have had an abortion.[27] In the present study all the female employees of the pharmaceutical factories, including those who had resigned, were included. The longitudinal approach of this study should avoid the selection bias.

The collection of information on the outcomes of pregnancy from questionnaires is sensitive to bias because exposed women seem to be more active in reporting their miscarriages than non-exposed.[28] In this study the information on pregnancy outcome was gathered from registered data of hospitalised abortions, completed with the polyclinic data. For the exposure data the occupational health personnel completed the questionnaires, based on the files of health stations and the information obtained from the foremen. Thus the response and reporting bias is probably minimal. On the other hand, such data may miss some individual exposures during pregnancy, when the usual exposure for the worker is given.

Although all the findings of this study appear biologically plausible and some have previously been suggested we cannot exclude the contribution of chance as relatively many comparisons were done. The power of the study was quite low for most of the

chemical exposures due to the small size of the study population and low frequencies of exposure. The likelihood of detecting a twofold risk varied from 15% for antineoplastic agents to 42% for all solvents as calculated with the method described by Miettinen.[29] The likelihood of detecting a threefold risk varied from 32% to 80% respectively.

The results of this study support the view that organic solvents, and methylene chloride in particular, may have harmful effects on the pregnancy. The dose-response effect seen in connection with solvent exposures add credibility to the finding. The increased odds ratio found for oestrogen exposure must be interpreted with caution because of the small numbers of cases and probably light exposures, according to the description of occupational health personnel. The finding of the harmful effect of heavy lifting in early pregnancy may have some practical consequences but the result should be confirmed in an independent series.

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