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Time to pregnancy among Danish pharmacy assistants

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SCHAUMBURG I, OLSEN J. Time to pregnancy among Danish pharmacy assistants. *Scand J Work Environ Health* 1989;15:222-226. Time to pregnancy was studied as a parameter of couple fertility in a national cohort of all female members (<40 years) of the union of pharmacy assistants from 1979 to 1984. A total of 4 924 women were included in the study. Information on time to pregnancy and exposure was obtained by postal questionnaires in April 1985 (response rate 92 %). Prolonged time to pregnancy according to occupation in production or a dispensary or in product control, bottling, and packing is presented, unexposed pharmacy assistants being used as referents. It was possible to use time to pregnancy in an occupational setting as 95 % of the women were able to state their time to pregnancy and as 90 % of all pregnancies were planned. No association was found between type of work or pharmacy and time to pregnancy, but pharmacy assistants exposed to antibiotics had a slightly increased risk of prolonged time to pregnancy.

Key terms: antibiotics, fertility, occupational exposure, pharmaceutical industry, pharmacy, reproductive outcome.

Fertility problems are a private concern to most couples and may go on unnoticed by others for years. Only one-third of couples experiencing such problems seek medical help (1). In addition only a few studies have sought environmental explanations for impaired couple fertility (2-6). This lack of research is surprising as 16 % of all women trying to become pregnant for the first time experience no conception or conception occurring subsequent to more than one year of normal sexual cohabitation and 17 % of those who succeed in giving birth to a child will experience a delay in a second or subsequent pregnancy (7).

Danish pharmacy assistants have been reported to have a high frequency of infertility (5) in a case-referent study among infertile case couples who had received treatment for infertility compared to reference couples who had given birth to a healthy child born at the same hospital. Female occupation as a pharmacy assistant was associated with a threefold increase in the risk of infertility with evidence of hormonal disturbances [95 % confidence interval (95 % CI) 1.22-7.82].

Work in Swedish pharmaceutical laboratories appears to be associated with an increased risk of spontaneous abortion (8). In a Finnish study from the pharmaceutical industry a high risk of spontaneous abortion among workers exposed to estrogens was found (9). Nurses exposed to cytostatics have an increased risk of spontaneous abortion (10), as well as an increased risk of congenital malformations among their offspring (11). Studies of animal model systems have

indicated that some pharmaceutical products are teratogenic. The use of different drugs in pregnancy have been associated with reproductive failures of various types after intake during pregnancy (12).

These findings prompted the present study, which is part of a larger investigation covering several types of reproductive failures among pharmacy assistants. In this paper only data on time to pregnancy are presented.

The aim of this study was to investigate the distribution of time to pregnancy regardless of outcome according to work process and exposure in order to identify groups of high risk. Time to pregnancy is defined as the period of time it takes a couple having sexual cohabitation without use of contraceptives to achieve a clinically recognized pregnancy.

Subjects and methods

Time to pregnancy was studied in a large unselected group of women defined according to their occupation. A historical cohort with open entry was formed of all members of the national union of pharmacy assistants some time during the period 1 January 1979 to 31 December 1984. These women were identified by means of computerized membership files.

All exposure and outcome data were based upon a postal questionnaire to all union members under the age of 40 years on 31 December 1978. The questionnaire was mailed to 4 924 pharmacy assistants in 1985, and 4 517 were returned, giving a response rate of 92 % covering 2 557 pregnancies in the study period 1979-1984.

In cases of a recognized pregnancy after 1978, the following question concerning time to each pregnancy was asked: "For how long did you try to become pregnant before you succeeded? (Had regular inter-

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Table 1. Number of pregnancies among pharmacy assistants in relation to work process prior to conception and time to pregnancy.

Main work in the same year as waiting time to pregnancy ^a	Time to pregnancy			Total
	0—6 months	7—12 months	> 12 months	
Production	359	33	58	450
Dispensary	365	47	39	451
Identification/control	84	7	7	98
Bottling	17	2	1	20
Packing	19	0	2	21
Other work	138	13	17	168
Counter and administrative work (reference)	557	74	86	717
All pregnancies	1 995	233	329	2 557

^a Since work histories and terminated pregnancies were recorded only from 1979, 632 pregnancies had to be excluded because no data on work history were available for that time period.

course without the use of any contraception).” The question was followed by seven closed-answer categories: Became pregnant in spite of use of contraception, 0—6 months, 7—12 months, 13—24 months, 25—36 months, more than 3 years, don’t know. Furthermore a number of questions were asked concerning main occupation during each year from 1979 to 1984. More-detailed questions concerning work tasks during pregnancy, type of pharmacy, exposure, duration of work, etc, were asked.

The unit of analyses in the present context was pregnancy (not the woman). However, the majority of women (70 %) had only one pregnancy during the study period.

Working as a pharmacy assistant in Denmark requires three years of education as an apprentice in a pharmacy including theoretical courses in pharmacology and human biology. All persons licensed as pharmacy assistants must join the union, except for those employed in the pharmaceutical industry (8 %). The work implies different processes: production and laboratory work, dispensary work, product control, bottling, packing, and counter work. In Denmark a large amount of ordinary drugs and mixtures is produced in factories, but they are packed in glasses or bottled at the pharmacy. Besides, all extemporaneous preparations or chemicals used by dermatologists, veterinarians, or dentists are produced in the laboratory in the pharmacy. Some work tasks include exposure to pharmaceutical products, solvents, heavy metals, etc, whereas others lead to no exposure. Pharmacy assistants with mainly counter and administrative work were considered unexposed and were therefore used as referents.

The data were analyzed by means of stratified analyses with the Mantel-Haenszel test statistics and an unconditional logistic regression model (13). All indicated confidence limits are 95 % limits.

Results

The distribution of time to pregnancy according to the main type of work in the same year is shown in tables

Table 2. Work process as a pharmacy assistant and time to pregnancy. Estimates of the risk ratios^a for prolonged waiting time to pregnancy (7—12 months and more than 12 months) compared with 0—6 months and with counter and administrative workers as the reference group (logistic regression model). (OR = odds ratio, 95 % CI = 95 % confidence interval)

Main work during time to pregnancy	Time to pregnancy			
	7—12 months		> 12 months	
	OR	95 % CI	OR	95 % CI
Production	0.69	0.4—1.1	1.03	0.7—1.5
Dispensary	0.97	0.7—1.5	0.70	0.5—1.0
Identification/control	0.63	0.3—1.5	0.55	0.2—1.3
Bottling	0.90	0.2—4.1	0.36	0.1—2.9
Packing	—	—	0.62	0.1—2.8
Other work	0.71	0.4—1.3	0.79	0.5—1.4

^a Adjusted for parity (0, ≥ 1 children), year of graduation, smoking (0, 1—9, ≥ 10 cigarettes daily), and alcohol consumption (0—9, ≥ 10 drinks/week).

1 and 2. The risk estimates for prolonged conception time were calculated with pharmacy assistants with administrative and counter work as referents. The risk estimates were controlled for parity, age, smoking, and alcohol consumption. None of the work tasks led to a statistically significantly increased risk of prolonged time to pregnancy.

Since the study was intended to cover a wider range of reproductive failure, more-detailed exposure information was collected for every pregnancy in the study period. The pharmacy assistants had rather stable work conditions within a shorter time span, and in this group 85 % had the same type of work within a two-year period. With this information known, it was considered of value to present data on time to pregnancy according to work process during pregnancy. Exposure in pregnancy is of course a proxy measure for the exposure prior to time to pregnancy. The estimate of risks for prolonged conception time is shown in tables 3, 4, and 5.

The women were also asked if they had been exposed to a number of different unsealed drugs or chemicals in open boxes during their time of pregnancy. Exposure to antibiotics, heart medicine, hormones, antidiabetics, antiepileptics, and heavy metals showed an increased

Table 3. Number of pregnancies among pharmacy assistants in relation to work process during pregnancy and time to pregnancy.

Work process (more than 10 h/week) during pregnancy ^a	Time to pregnancy			Total
	0—6 months	7—12 months	> 12 months	
Production	420	48	69	537
Dispensary	576	76	91	743
Identification/control	97	8	7	112
Bottling	48	4	5	57
Packing	93	12	14	119
Other	100	10	26	136
Counter and administrative work (reference)	463	58	84	605
All pregnancies	1 995	233	329	2 557

^a Pregnancies among women working 10 h/week (or less) during pregnancy in one of the stated categories have been excluded. Pregnancies may occur more than once to the same woman.

Table 4. Work process as a pharmacy assistant and time to pregnancy. Estimates of risk ratios^a for prolonged waiting time to pregnancy (7—12 months and 12 months or more) compared with 0—6 months and with counter and administrative workers as the reference group (logistic regression model).

Work process (more than 10 h/week) during pregnancy	Time to pregnancy			
	7—12 months		> 12 months	
	OR	95 % CI	OR	95 % CI
Production	0.91	0.6—1.4	0.93	0.7—1.3
Dispensary	1.08	0.7—1.6	0.96	0.7—1.3
Identification/control	0.63	0.3—1.4	0.40	0.2—0.9
Bottling	0.67	0.2—2.0	0.60	0.2—1.6
Packing	1.01	0.5—2.1	0.88	0.5—1.7
Other work	0.80	0.4—1.6	1.40	0.8—2.3

^a Same adjustments as in table 2.

point estimate for prolonged conception time (table 5). Only women working with antibiotics had a borderline statistically significantly increased frequency of prolonged time to pregnancy in comparison with that of the unexposed persons [odds ratio (OR) 1.34, 95 % CI 1.0—1.8].

Discussion

For the past 10 years studies of reproductive outcome have focused mainly on congenital malformations and hospitalized spontaneous abortions. However, these outcomes only represent a few of the potential haz-

Table 5. Exposure to unsealed drugs and chemicals and time to pregnancy. Estimates of risk ratios^a for prolonged waiting time to pregnancy (12 months or more) compared to all others (logistic regression model). All unexposed persons were used as the reference group. Each pregnancy may be recorded more than once.

Exposure more than once per week	No pregnancies according to time to pregnancy			Odds ratio	95 % confidence interval
	0—6 months	7—12 months	> 12 months		
Antibiotics	542	65	102	1.34	1.0—1.8
Heart medicine	38	5	6	1.18	0.4—3.8
Cancer drugs	8	—	—	—	—
Anticoagulants	18	1	2	0.99	0.2—5.3
Sex hormones	38	6	4	0.76	0.2—2.7
Other hormones	104	14	14	1.08	0.5—2.3
Antidiabetics	23	1	3	1.31	0.3—6.8
Psychopharmaca	50	9	8	0.94	0.3—2.7
Pain killers	255	31	35	0.97	0.6—1.6
Antiepileptics	107	17	13	0.84	0.4—1.9
Antirheumatics	43	7	7	1.17	0.4—3.7
Solvents	283	24	35	0.74	0.5—1.2
Pesticides	65	8	7	0.91	0.3—2.5
Heavy metals	50	5	7	1.30	0.5—3.5
Preservatives	341	41	48	0.9	0.6—1.3
Unexposed	1 124	132	193	1.0	—

^a Adjusted for the same variables as in table 2 and adjusted for all other exposure in the study.

ards to reproduction. There is still a serious need for new methods of measuring the adverse effects of occupational and environmental hazards to reproduction.

Couple fertility should also be considered as a reproductive end point for research. However, it involves several biological processes, ie, production of egg and sperm, transport of cells, fertilization, transport of fertilized egg to the uterus, implantation, and development until the time of clinically recognized pregnancy. Consequently, taking only successful reproduction as a measure of environmental influence might blur the association. A recent prospective study of 221 women intending to conceive showed that 31 % of all pregnancies verified by the urinary concentration of human chorionic gonadotrophin were lost. Of these, two-thirds of the pregnancies were lost before they had been clinically recognized (14).

An increase in time to pregnancy may indicate impaired conception or early pregnancy loss due to both male and female factors. Animal studies have shown that environmental exposures can interfere with the biological processes of mating and early intrauterine growth. Male workers exposed to 1,2-dibromo-3-chloropropane experienced reduced couple fertility — this reduction, in fact, went on unnoticed for several years (15).

The measurement of time to pregnancy has to rely on self-reported data, and in our material only 3.6 % was not able to state the length of time to pregnancy within the categories 0–6 months, 7–12 months, 13–24 months, 25–36 months, and more than three years; 7.2 % became pregnant in spite of the use of contraceptives. Close to 90 % of the Danish pharmacy assistants had planned pregnancies only. Having planned their pregnancies also means that they would be more likely to remember the length of time to pregnancy. These women are well educated, have substantial biological knowledge, have easy access to contraceptives, and have very few pregnancies.

Baird et al (16) compared their own retrospectively collected data on time to pregnancy (2) to the distribution in a group of women followed prospectively after the removal of intrauterine devices as described by Tietze (6). The distribution of time to pregnancy was similar in the two groups. Time to pregnancy regardless of outcome among the group of pharmacy assistants did not differ from that of a population of birth-giving Danish women as reported by Olsen et al (17).

This study shows that it is possible to collect data on time to pregnancy in an unselected group of women defined by their occupation. Baird & Wilcox (2) investigated a population of volunteers, and Rachootin and her co-workers (5, 17) a group of hospitalized women. This study also shows that women do not find these questions too private since the response rate was 92 %. We have no information on frequency of intercourse, which might induce confounding. However, as these women plan their pregnancies and have suffi-

cient biological insight, we do not expect time to pregnancy to rely heavily on the frequency of intercourse. Timing of intercourse in relation to ovulation is probably much more important than frequency of intercourse, and we do not expect sexual activity to be different in the groups compared. However, for future investigations we recommend that questions on the level of sexual activity be asked. Women should also be asked about the number of months or cycles to pregnancy, since this information makes it possible to detect smaller changes in the time to pregnancy.

In this study women exposed to antibiotics were identified with an increased risk of prolonged time to pregnancy. This result was rather unexpected and needs further investigation. However, the biological meaning of this phenomenon could be that small amounts of antibiotics over long periods of time might enforce superinfections or infections in the genital tract which might alter acidity and interfere with the mobility of sperm and thereby also interfere with conception rate. However, it is probable that this association is purely due to chance since it was the only statistically significant result in a fairly large number of tests.

None of the work processes among pharmacy assistants were associated with a higher risk of delayed time to pregnancy. This finding could be due to a number of factors. Work conditions among pharmacy assistants may be too similar for the identification of any single risk group. In addition our exposure data may be too crude, and the number of women in the study does produce rather limited scientific information for some of these specific work tasks. Furthermore, prolonged time to pregnancy is a crude diagnosis with several different etiologic components, a feature it shares with spontaneous abortions, low birthweight, preterm birth, etc.

Controlling for confounding was only partly possible, since the majority of alternative causes of sterility or prolonged time to pregnancy was unknown. Age, parity, smoking, and drinking habits are known to influence time to pregnancy (2, 4, 17), but had only limited confounding influence on the results. Although information on smoking and drinking habits are related to each pregnancy, we do not expect these habits to be different during time to pregnancy or between the groups compared. In addition, a Danish study showed that only 10 % stopped smoking or drinking during pregnancy, and in the third trimester still 40 % smoked and 82 % consumed alcohol (18, 19).

Since 1981 pregnant women in Denmark have been entitled to job transfer or maintenance allowances if the work exposures are considered hazardous to the unborn child. Had pharmacy assistants made use of this possibility our results might have been underestimated. However, the awareness among pharmacy assistants of possible reproductive hazards in the work environment was low during the study period, and only five pharmacy assistants in the study group made use of maintenance allowance.

For the sake of simplicity only results from the logistic regression analysis are presented in this report. It should be noted, though, that data were also analyzed by means of Gaussian regression taking into account the full distribution of time to pregnancy and similar conclusions were reached.

Only part of the reproductive spectrum was studied and even only part of the fecundity problem. Thus women who did not want a child and women who tried to become pregnant but did not conceive were not included in the study. Therefore occupational causes of permanent childlessness only are not detectable in a study of this type.

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References

1. Rachootin P, Olsen J. Social selection in seeking care for reduced fecundity among women in Denmark. *J Epidemiol Community Health* 1981;35:262—4.
2. Baird DD, Wilcox AJ. Cigarette smoking associated with delayed conception. *JAMA* 1985;253:2979—83.
3. Baird DD, Wilcox AJ. Effects of occupational exposures on the fertility of couples. In: Stein ZA, Hatch MZ. Reproductive problems in the workplace. Philadelphia, PA: Hanley & Belfus, Inc, 1986:361—74. (Occupational medicine: state of the art reviews vol 1, no 3.)
4. Olsen J, Rachootin P, Schiødt AV, Damsbo N. Tobacco use, alcohol consumption and infertility. *Int J Epidemiol* 1983;12:179—84.
5. Rachootin P, Olsen J. The risk of infertility and delayed conception associated with exposure in the Danish workplace. *J Occup Med* 1983;25:394—402.
6. Tietze C. Fertility after discontinuation of intra uterine and oral contraception. *Int J Fertil* 1968;13:385—9.
7. Rachootin P, Olsen J. Prevalence of socioeconomic correlates of subfecundity and spontaneous abortions in Denmark. *Int J Epidemiol* 1982;11:245—9.
8. Hansson E, Jansa S, Wande H, Källén B, Östlund E. Pregnancy outcome for women working in laboratories in some of the pharmaceutical industries in Sweden. *Scand J Work Environ Health* 1980;6:131—4.
9. Taskinen H, Lindbohm ML, Hemminki K. Spontaneous abortions among women in the pharmaceutical industry. *Br J Ind Med* 1986;43:199—205.
10. Selevan SG, Lindbohm ML, Hornung RW, Hemminki K. A study of occupational exposure to antineoplastic drugs and fetal loss in nurses. *N Engl J Med* 1985;313:1173—8.
11. Hemminki K, Kyyrönen P, Lindbohm ML. Spontaneous abortions and malformations in the offspring of nurses exposed to anaesthetic gases, cytostatic drugs, and other potential hazards in hospitals, based on registered information of outcome. *J Epidemiol Community Health* 1985;39:141—7.
12. Schardein JL. Chemically induced birth defects. New York, New York: Marcel Dekker Inc, 1985.
13. Breslow NE, Day NE. Statistical methods in cancer research; vol I (the analysis of case-control studies). Lyon: International Agency for Research on Cancer, 1980.
14. Wilcox AJ, Weinberg CR, O'Connor JF, et al. Incidence of early loss of pregnancy. *N Engl J Med* 1988;319:189—94.
15. Whorton D, Krauss RM, Marshall S, Milby TH. Infertility in male pesticide workers. *Lancet* 1977;2:1259—61.
16. Baird DD, Wilcox AJ, Clarice RW. Use of time to pregnancy to study environmental exposure. *Am J Epidemiol* 1986;124:470—80.
17. Olsen J, Rachootin P, Schiødt AV. Konceptionstid og alder [Conception time and age]. *Ugeskr Læger* 1983;145:2332—4.
18. Olsen J, Frische G, Kirchheimer H. Gravide kvinders rygevaner [Smoking habits of pregnant women]. *Ugeskr Læger* 1986;148:1846—8.
19. Olsen J, Frische G, Kirchheimer H, Poulsen AO. Alkoholvaner blandt gravide i Odense 1985—1986 [Alcohol habits among pregnant women in Odense 1985—1986]. *Ugeskr Læger* 1987;149:1420—2.

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