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Ectopic pregnancy and occupational exposure of hospital personnel

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Objectives An earlier study found a relationship between occupational exposure to antineoplastic drugs and ectopic pregnancy. The present investigation aimed at confirming this finding in a larger and specifically planned study and at analyzing the relationship between ectopic pregnancy and other chemical or physical agents in the hospital work environment.

Methods A case-referent study (140 cases and 279 referents) was carried out in 1995 in a population of women working in hospitals throughout France. The sample size was computed to have an 80% statistical power to detect a 2-fold increased risk of ectopic pregnancy (odds ratio 2). Information was collected about past and present work conditions (exposures to antineoplastic drugs, solvents, disinfectants, anesthetic gases and ionizing radiation), and known risk factors of ectopic pregnancy. Multivariate analysis was performed using logistic regression.

Results No significant association between occupational exposure and ectopic pregnancy was found, either when past exposure was considered or when exposure was considered within the 3 months before conception. The relationships remained nonsignificant after adjustment for job category and for the known risk factors of ectopic pregnancy.

Conclusions It was concluded that the results of this study should be interpreted as an absence of relationship between exposure to chemical or physical agents and ectopic pregnancy.

Key terms case-referent study, epidemiology, hospital staff.

The incidence of ectopic pregnancy has risen substantially during the past 2 decades, and it is currently 1.5% of all reported pregnancies in western countries (1). Ectopic pregnancy may have serious consequences, in particular by impairing subsequent fertility (2, 3). Several risk factors have been identified (infectious pelvic disease, smoking, tubal surgery, induced conception, age) (2, 4—7), but the etiology of one-third of the cases of ectopic pregnancy remains unknown (7).

We hypothesized that zygotic anomalies might be associated with ectopic pregnancy since it is likely that the transport of an abnormal zygote along the uterine tube is less efficient than that of a normal zygote. The relationship between the woman's age and ectopic pregnancy and that between recurrent spontaneous abortions and recurrent ectopic pregnancies (8, 9) support this hypothesis. It could be tested indi-

rectly by studying the relationship between the risk of ectopic pregnancy and environmental exposure which could increase the proportion of zygotic anomalies.

In a previous paper, we reported a relationship between occupational exposure to antineoplastic drugs and ectopic pregnancy (10). These findings (from a small number of cases) needed to be confirmed by larger studies with the primary objective of assessing this particular relationship. The present paper reports the results of such a study. We tested the hypothesis that occupational exposures would have an effect on the occurrence of ectopic pregnancy. The aim of this study was to analyze the relationship between the occurrence of ectopic pregnancy and occupational exposure in hospitals to agents such as antineoplastic drugs, solvents, disinfectants, anesthetic gases and ionizing radiation, some of which have mutagenic effects.

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Subjects and methods

A case-referent study was carried out in 1995 in a population of women working in hospitals throughout France. The cases and referents were recruited by occupational practitioners during the annual occupational consultation, mandatory in France. The rationale and the design of the study was mailed to 296 occupational practitioners of large and medium-sized hospitals; 104 participated in the study. Recruitment lasted 1 year. The cases were all women working in the participating hospitals who had an ectopic pregnancy between 1 January 1993 and 31 December 1994. For each case, 2 referents were recruited who were the 2 next women visiting the same occupational practitioner and who delivered but had no ectopic pregnancy during the same period.

Sample size

The required sample size was computed for 80% statistical power to detect a 2-fold increased risk of ectopic pregnancy (odds ratio 2) on the assumption that the proportion of exposed women was 20%. We found that 130 cases and 260 referents were required. As about 5% of working women become pregnant each year, as the rate of ectopic pregnancy is 1.5% and as an occupational practitioner sees about 1600 women, this study necessitated the participation of at least 70 occupational practitioners. All the women who were asked by their practitioner except 6 (4 cases and 2 referents) agreed to participate. Finally, we received questionnaires from 140 cases and 279 referents, and thus the size of the sample was satisfactory.

Data collection

The occupational practitioner gave each woman a self-administered questionnaire to collect information on age, educational level, marital status, social status, and work conditions, with emphasis on past and present occupational exposure. We also collected data on known risk factors of ectopic pregnancy, medical and surgical history (including sexually transmitted diseases, inflammatory pelvic diseases, appendectomy, and pelvic or tubal surgery), the woman's reproductive history (previous use of birth control, induced conception cycle), sexual activity, and smoking. After having filled out the questionnaire, the women gave it back to the occupational practitioner.

Occupational exposure assessment

The exposure was self-reported by the women. The following 2 reference periods were investigated: the 3 months preceding the beginning of the pregnancy and the rest of the woman's occupational life. Five distinct kinds of exposure were assessed: antineoplastic drugs, solvents, disinfectants, anesthetic agents and ionizing radiation. The frequency of the exposure to antineoplastic drugs was self-assessed on a 4-point scale, from never to very often. The questionnaire included a list of medical products (all antineoplastic drugs),

and the women were allowed to specify the name of the products they used. They also specified whether or not they prepared perfusions, and, if so, the average number per week, and, if they administered perfusions to patients, and the average number per week. For the preparation of perfusions the protective system was described. Solvent exposure (direct use of solvents or work in a room where solvents were used) was self-assessed on a 5-point scale describing daily exposure from never to 4 hours or more a day. The questionnaire included a list of solvents that the respondent had to read and then specified the name of the solvents to which she was exposed. The protective system against solvent exposure, if any, and the tasks using solvents (dilution, cleaning) were described. Exposure to disinfectants was described by a yes or no question asking whether the job included cleaning or sterilization tasks using disinfectants other than solvents. In case of a positive answer the respondent had to specify the name of the chemical agent from a list of disinfectants (other than solvents). Exposure to anesthetic agents (direct use or work in a room where these agents were used or exhaled) was described by a 5-point scale, in duration, from never to 6 hours or more a day. The name of the anesthetic agents and the system of protection, if any, were specified. Exposure to ionizing radiation was described by a frequency scale, in 4 points, from never to very often. The reasons for exposure to ionizing radiation (radiology, therapy, diagnosis) and the system of protection were reported.

Statistical analysis

For the analysis, 2 indicators of exposure were considered, a 3-class variable to take past and present exposures into account (exposed in the 3 months before conception, exposed only in the past, never exposed) and a 3-class variable describing the intensity of current exposure (heavy, moderate or none). Generally speaking, heavy exposure corresponded to regular handling or using (daily or often or very often) without a protective device.

The associations between risk factors and ectopic pregnancy were measured by odds ratios. Confounding was addressed with standard methods of stratified analysis (Mantel-Haenszel procedure) (11). Multivariate analysis was performed using unconditional logistic regression. The logistic regression models included job description — nurses, nursing helpers, service workers (mainly cleaners, porters and kitchen staff) and other occupations (mainly clerical staff) — and the known risk factors of ectopic pregnancy — prior genital infection (clinical infectious pelvic disease or *Chlamydia trachomatis* seropositivity), smoking at the time of conception, and previous pelvic surgery. Furthermore, we considered the woman's age (because the probability of having experienced any investigated past event is dependent on the duration of potential exposure), previous spontaneous abortion, previous induced abortion, induced pregnancy, and previous pregnancies (because the number of previous deliveries tends to be systematically

greater among cases, as women stop working more often after delivering than after an ectopic pregnancy or an abortion). We did not include the variables prior ectopic pregnancy, prior tubal surgery, or appendectomy in this model, as they are included in the factors prior genital infection and previous pelvic surgery.

Results

Among the 140 cases, 93% included tubal ectopic pregnancy, and the treatment was conservative for 40%; 32% of the cases had an intrauterine device at the time of conception. The mean duration of the pregnancy was 5.6 weeks. Among the 279 referents, the mean duration of gestation was 39.0 weeks and the mean birthweight was 3301 g.

The comparisons between the cases and referents are shown in table 1 for the potential risk factors. Women over 35 years of age, women with at least 1 previous delivery, women with 2 or more previous spontaneous abortions, women with a previous induced abortion, and women with previous pelvic surgery were significantly more numerous in the case group than in the reference group. The established risk factors of ectopic pregnancy (5) were found in this sample with expected magnitudes for the corresponding odds ratios. For instance, the odds ratio associated with previous infectious pelvic disease was 2.48 [95% confidence interval (95% CI) 1.18—5.25] and that corresponding to smoking more than 10 cigarettes a day was 2.15 (95% CI 1.28—3.61).

No significant association between occupational exposure and ectopic pregnancy was found, either when we considered past exposure or when we considered exposure within the 3 months before conception. The relationships between occupational exposures and ectopic pregnancy remained nonsignificant after adjustment for other occupational exposures, for category of job, and for the known risk factors of ectopic pregnancy (table 2). The results were similar when either intensity or frequency of exposure within the 3 months before conception was taken into account (table 3).

Discussion

For this study, we chose a population of women working in hospitals because it includes a large proportion of women potentially exposed to substances, some of which have known mutagenic effects (12) or have been shown to be associated with adverse pregnancy outcome (13—16). In addition, it allowed comparison of the results with those of our previous study (10). Among the 296 occupational practitioners asked to participate in the study, 163 did not, often because they did not have enough time. This lack of participation was unlikely to have induced selection bias as

the participants were spread throughout the country and worked in hospitals of various sizes and as the referents were recruited from the same hospital as the cases.

The reference group was made up only of pregnancies ending in delivery. Thus women with an intrauterine pregnancy who decided to interrupt it were systematically not included. In contrast, the ectopic pregnancy group included women who could have decided to interrupt their pregnancy if it were not ectopic. The absence of induced abortions in the reference group is liable to have induced selection bias into the study of factors associated with the decision to interrupt a pregnancy, such as obstetrical history or age. To limit this bias, a strategy commonly used in the field of epidemiology of ectopic pregnancy was applied, that is, the analysis was conducted among the cases and the referents who were married or living as a couple, and with no contraception at the time of conception (17), the proportion of which was greater among the referents than among the cases because of the large number of women with an intrauterine device among those suffering ectopic pregnancy (in our study it led to a restriction of the analysis to 84 cases and 267 referents). We verified that results concerning occupational exposure were identical with this strategy of analysis.

We did not find any association between exposure to chemical or physical agents at work and ectopic pregnancy. This result could be explained either by a true absence of association or by a lack of statistical power, by recall bias about exposure, or by a level of exposure too low to have a detectable effect.

The lack of statistical power was unlikely as the number of subjects (140 cases and 279 referents) and the proportion of exposed subjects (14% to 43% according to the agent — table 4) were large enough for a power of 80%. (See the Subjects and Methods section.) Moreover the estimated odds ratios for occupational exposure were generally close to 1 with moderately large confidence intervals. If the absence of statistical significance had been due to a lack of statistical power, higher odds ratios with large confidence intervals would have been expected.

The exposure was evaluated through a self-administered questionnaire, and thus the women's answers could have been inaccurate. A pretest of the questionnaire showed that the women understood the questions clearly and had no difficulties in answering them. Women working in hospitals are generally aware of the products they handle and thus are able to report their exposure without substantial error. Moreover, table 4 shows that the exposures reported were in accordance with the kind of job held by the women (eg, no service workers and only 1 "other" worker declared past or present exposure to antineoplastics), and therefore there was indirect evidence of the absence of reporting bias. We restricted the analysis to nurses and medical staff; these groups are the women who are likely to report their exposures the most accurately. Although the sample was smaller,

Table 1. Distribution of risk factors for ectopic pregnancy among the cases (N = 140) and referents (N = 279) and the odds ratios (OR) and 95% confidence intervals (95% CI).

Factors	Referents		Cases		Crude OR	95% CI
	N	%	N	%		
Previous pelvic infectious disease						
No	263	95	121	88	1	
Yes	14	5	16	12	2.48	1.18—5.25
Woman smoking at the time of conception						
No	204	73	90	64	1	
1—9 cigarettes/day	36	13	14	10	0.88	0.45—1.71
≥ 10 cigarettes/day	38	14	36	26	2.15	1.28—3.61
Age						
≤ 24 years	22	8	7	5	1.11	0.44—2.80
25—29 years	129	46	37	26	1	
30—34 years	86	31	45	32	1.82	1.09—3.05
≥ 35 years	41	15	51	37	4.34	2.50—7.52
Previous deliveries						
0	127	46	43	31	1	
≥ 1	149	54	96	69	1.90	1.24—2.93
Previous spontaneous abortions						
0	224	81	107	78	1	
1	43	16	17	12	0.82	0.45—1.52
≥ 2	8	3	14	10	3.66	1.49—9.00
Previous induced abortions						
No	253	92	116	85	1	
Yes	22	8	21	15	2.08	1.10—3.94
Induced pregnancy						
No	252	92	124	89	1	
Yes	23	8	15	11	1.33	0.67—2.63
Previous pelvic surgery						
No	256	92	110	79	1	
Yes	23	8	30	21	3.04	1.69—5.46
Exposure to antineoplastic drugs						
None	218	80	113	82	1	
Only in the past	22	8	15	11	1.32	0.66—2.63
In the 3 months before conception	33	12	10	7	0.58	0.28—1.23
Exposure to solvents						
None	177	64	93	67	1	
Only in the past	14	5	6	4	0.82	0.30—2.19
In the 3 months before conception	84	31	41	29	0.93	0.59—1.46
Exposure to disinfectants						
None	160	58	74	53	1	
Only in the past	17	6	10	7	1.27	0.56—2.91
In the 3 months before conception	98	36	55	40	1.21	0.79—1.87
Exposure to anesthetic gases						
None	234	85	120	87	1	
Only in the past	11	4	6	4	1.06	0.38—2.95
In the 3 months before conception	29	11	12	9	0.81	0.40—1.64
Exposure to ionizing radiation						
None	185	67	96	69	1	
Only in the past	13	5	5	4	0.74	0.26—2.14
In the 3 months before conception	77	28	38	27	0.95	0.60—1.51

the results were similar. There was no trend between the occupational exposure level and the risk of ectopic pregnancy. Furthermore, if there had been recall bias, it is likely that it would have been an underreporting of exposure among the referents, and it could not explain our results (18, 19).

The level of the exposure of women working in hospitals may be too low nowadays to cause a substantial increase in ectopic pregnancy risk. We considered this drawback by excluding the women who were seldom exposed or only ex-

posed when using a protective device from the exposed group. Thus our exposed group contained only women with a medium or high level of exposure. Moreover, when we included the intensity and the frequency of exposure in the analysis, we did not find any trend for the risk of ectopic pregnancy. Occupational exposures in similar populations have previously been studied by other teams. Relationships with adverse pregnancy outcomes (especially spontaneous abortion) have been found with odds ratios of around 2 for

Table 2. Relationships between occupational exposures and ectopic pregnancy: adjusted odds ratios (OR) and 95% confidence intervals (95% CI).

Occupational exposure	Adjusted OR ^a	95% CI
Antineoplastic drugs		
None	1	
Only in the past	1.56	0.65—3.72
In the 3 months before conception	0.95	0.39—2.31
Solvents		
None	1	
Only in the past	0.51	0.14—1.96
In the 3 months before conception	1.04	0.59—1.86
Disinfectants		
None	1	
Only in the past	1.77	0.57—5.54
In the 3 months before conception	1.41	0.82—2.42
Anesthetic gases		
None	1	
Only in the past	0.95	0.25—3.53
In the 3 months before conception	0.78	0.31—1.95
Ionizing radiation		
None	1	
Only in the past	0.69	0.19—2.56
In the 3 months before conception	1.43	0.77—2.64

^a Each odds ratio has been adjusted for the other exposures in the table and for the category of occupation (nurses, nursing helpers, service workers, other), woman's age, previous deliveries, previous pelvic infectious disease, woman smoking at the time of conception, previous spontaneous abortions, previous induced abortions, induced pregnancy, and previous pelvic surgery.

Table 3. Relationships between frequency and intensity of occupational exposures and ectopic pregnancy: adjusted odds ratios (OR) and 95% confidence intervals (95% CI).

Occupational exposure in the 3 months before conception	Adjusted OR ^a	95% CI
Antineoplastic drugs		
None	1	
Moderate	1.69	0.60—4.71
Heavy	0.22	0.04—1.28
Solvents		
None	1	
Moderate	0.93	0.47—1.86
Heavy	1.49	0.63—3.54
Disinfectants		
No	1	
Yes	1.34	0.78—2.31
Anesthetic gases		
None	1	
Moderate	0.50	0.17—1.49
Heavy	2.80	0.62—12.7
Ionizing radiation		
None	1	
Moderate	1.48	0.77—2.83
Heavy	1.98	0.56—7.06

^a Each odds ratio has been adjusted for the other exposures in the table and for category of occupation (nurses, nursing helpers, service workers, other), woman's age, previous deliveries, previous pelvic infectious disease, woman smoking at the time of conception, previous spontaneous abortions, previous induced abortions, induced pregnancy, and previous pelvic surgery.

Table 4. Occupational exposure in the 3 months before the conception or previously according to job category (cases and referents together).

Exposure	Total (N = 419) (%)	Nurses ^a (N = 207) (%)	Nursing helpers (N = 99) (%)	Service workers ^b (N = 64) (%)	Other occupations ^c (N = 49) (%)
Antineoplastic drugs	19.5	37.9	2.0	0.0	2.0
Solvents	34.9	45.2	29.9	34.9	2.0
Disinfectants	43.5	44.9	56.7	50.8	2.0
Anesthetic gases	14.1	25.0	4.1	4.8	0.0
Ionizing radiation	32.1	49.5	18.5	14.5	8.2

^a Nurses: nurses (166), laboratory assistants (10), X ray technicians (12), midwives (6), medical doctors (6), nursery nurses (7).

^b Service workers: nonnursing care workers (58), kitchen staff (4), cleaning staff (2).

^c Other occupations: clerical staff (38), psychologists (3), social workers (2), managers (4), speech therapists (2).

various types of exposure: antineoplastic drugs (20), solvents (21), anesthetic gases (22, 23), and ethylene oxide (24). This phenomenon tends to suggest that the level of exposure that we studied is prone to have detectable adverse effects. The absence of a significant relationship between exposure and ectopic pregnancy in our study is thus probably due to the relationship being weak or nonexistent rather than to the level of exposure being too low for effect.

We thus conclude that our results should be interpreted as an absence of a relationship between exposure to chemical and physical agents (which include some mutagens) and ectopic pregnancy. To explain the discrepancy with the results of our previous study, we suggest that either the earlier results were observed by chance or the levels of occupation-

al exposures were higher, as the pregnancies studied took place some 10 to 20 years earlier.

Finally, the hypothesis that zygotic anomalies could be a cause of ectopic pregnancy is not supported by our study, albeit indirect. A recent paper (25) reached the same conclusion in studying directly the karyotype of ectopic pregnancies, but this study included a very small number of observations.

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