The Risk of Infertility and Delayed Conception Associated With Exposures in the Danish Workplace

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The association between infertility and a number of occupations and occupational exposures was examined in a case-control study utilizing data collected from medical records and mailed questionnaires. The results suggest that male exposure to heat and female exposure to noise, textile dyes and lead, mercury, and cadmium are associated with infertility. Further research is needed to examine the entire spectrum of abnormal reproductive and developmental outcomes of exposure to these agents and to identify their full effects.

Involuntary infertility is a significant public health problem for which few etiologic factors have been identified. A survey of the prevalence of subfecundity in Denmark reported that a delay in conception of one or more years was experienced by 16% of couples attempting a first pregnancy and 17% of couples attempting a second or subsequent pregnancy.[1]

There is growing evidence that environmental exposures contribute to human infertility. In the late 19th century high rates of sterility were noted among women in the English pottery and lead industries.[2] More recently it has been suggested that female anesthetists may be at higher risk of infertility compared with other female physicians.[3] Evidence has suggested that males exposed to specific agents such as radiation, microwaves, heat, lead, chloroprene and the pesticide DBCP may develop impaired fertility due to alterations in spermatogenesis.[4]

In the study of the occupational effects of physical and chemical agents on human reproduction, relatively few investigations have examined infertility as an outcome of exposure. Rather, research has focused on the visible reactions to reproductive and developmental insult, namely, spontaneous abortion, congenital malformation and childhood cancer. The present study investigated a number of occupations and specific occupational exposures as risk factors in human infertility and delayed conception.

Materials and Methods

This case-control study was based on data collected from case couples who were examined or treated for a problem of infertility at Odense University Hospital, Denmark, during the period 1977-1980, and from control couples who had a healthy child born at the same hospital during the period 1977-1979.

Study Subjects — Eligible study couples for both groups were identified by means of the hospital's inpatient register. According to hospital practice the standard infertility workup included at least one test for which the female partner was admitted to the hospital. Infertile couples who received treatment to reverse an earlier sterilization operation were excluded from the study. Couples who had sought help for a problem of infertility and who later succeeded in achieving pregnancy remained in the case group. Within the control group of fertile couples, parents of infants with a gestational age under 258 days were excluded as were parents of children who had either died or been hospitalized for a serious illness or accident after birth. A total of 1,069 infertile case couples and 4,305 fertile control couples were selected for inclusion in the study.

Geographic Setting — The study was limited to residents of the island of Funen, Denmark, which is served by one large, regional hospital, Odense University Hospital, and six smaller community hospitals in outlying towns. Approximately 10% of the 5 million inhabitants of Denmark live on the island of Funen. Odense is the largest city on Funen, having a population of 170,000. The direct catchment area of Odense University Hospital includes a population of approximately 240,000 residing in Odense and eight adjacent municipalities. Obstetric and gynecological services are available at some of the smaller community hospitals. High-risk pregnancies and special infertility investigations may be referred to Odense from outside its direct catchment area.

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It was necessary to take area of residence into consideration in the analyses because a higher percentage of case couples than of controls resided outside the hospital's direct catchment area. Since an individual's residence also might easily be associated with occupational opportunities, area of residence must be considered a potential confounder.

Data Collection – Sociodemographic data, occupational background and medical and reproductive history were obtained from 927 case and 3,728 control couples, using a self-administered, mailed questionnaire. This represented a response rate of 87% for each group. All information about a couple was solicited from the woman. Questionnaires were sent out during the period November, 1980 to May, 1981. Study women were contacted up to three times if necessary in an effort to enlist their cooperation. The questionnaires were identical for the two groups aside from questions addressed to the infertile case group dealing with the outcome of possible pregnancies occurring after hospital treatment.

The questionnaire was designed primarily to obtain information on the work histories of the women and their spouses and on specific occupational exposures. Couples were asked to identify both the job held in the year prior to hospital admission and the longest-held job up to that time. A classification of occupation was made on the basis of job title, type of workplace and precise description of duties performed. This information was coded according to a five-digit Danish Occupational Code[5] and a five-digit industry code.[6]

The questionnaire assessed occupational exposures to 15 types of chemical and physical agents and three specific work processes in the period prior to hospital admission. Exposure was defined as contact with the agent or performance of the work process a minimum of one time per week for a period of at least one year. The exposures inquired about included anesthetic gases; insecticides; weed killers; degreasers; lacquer, paint or glue; organic solvents; cutting or lubricating oils; dry-cleaning chemicals; textile dyes; lead, mercury or cadmium; asbestos; hairspray or hair dyes; antirust agents; and heat and noise. The work processes of interest were welding of stainless steel, welding of other metals, and working in plastics production.

Data collected on reproductive history included maternal age, parity, time needed to achieve conception (or length of infertile period), history of spontaneous and induced abortion, history of conception delay of over one year in an earlier pregnancy, and history and duration of oral contraceptive use. On the basis of data obtained from the questionnaire each woman was classified as a smoker or a nonsmoker in the year of her hospital admission and placed in one of four categories according to her consumption of alcohol during the same time period. Data on women's education were also solicited.

The medical records of all infertile couples were reviewed without knowledge of questionnaire data by a collaborating physician at the Department of Obstetrics and Gynecology and information was abstracted onto a standard form.

Analyses and Results

The data were analyzed using three different approaches. A comparison of the results provides qualitative control, since different methodological problems are addressed in each (see "Discussion" section). The three approaches also supplement each other quantitatively. Statistically nonsignificant results that are positive in all three analyses may be worthy of further investigation. Conversely, a significant result in one approach that is not supported by positive results in other approaches may be a spurious association.

Association of Subfecundity With Reported Exposures – The first analytic approach consisted of between-group comparisons of the reported exposures of case and control couples residing in the hospital's direct catchment area. In this approach, control couples were defined as parents of a healthy child conceived within one year. The case group was restricted to couples who were examined or treated for

Table 1 – General Sociodemographic Characteristics of Selected Subgroups of Cases and Controls

	Cases			
	Male Sperm Abnormalities	Female Hormonal Disturbances	Idopathic Infertile Couples	Controls
Sample size	190	211	94	2,969
Women's age				
Mean	29.9	29.4	29.1	28.5
SD	4.289	3.883	3.344	4.533
Range	22-42	21-39	22-38	17-46
Residence, % Odense	66	71	68	78
Women's education,%				
≤ 9th grade	44	46	40	31
10th/trade school	40	41	45	50
Junior college+	16	12	15	19

infertility of at least one year's duration. The analyses focused on two subgroups of case couples with medical histories that were considered to be potentially related to occupational exposures. These included (1) a male diagnosis indicating abnormalities of sperm density, motility or morphology and (2) a female diagnosis indicating hormonal disturbances (amenorrhea, anovulation, luteal insufficiency or other endocrine malfunctions). These two subgroups were not mutually exclusive as 48 couples were diagnosed as having both of these reproductive disorders. The groups included couples with other multiple diagnoses as well. A third subgroup of interest consisted of couples with an idiopathic complaint of infertility. The basic sociodemographic features of these three subgroups and their controls are shown in Table 1.

Table 2 presents odds ratios and 95% confidence intervals[7] for the above-defined subgroups of case couples compared with controls by reported exposures. As shown, females reporting exposures to cutting oils, dry-cleaning chemicals and lead, mercury and cadmium had three times the risk of idiopathic infe. ility. Females reporting exposure to textile dyes experienced a sixfold increase in risk of idiopathic infertility. Subsequent analyses using logistic regression[8] to control for the possible effects of women's age, women's education, residence and parity produced essentially the same results, as shown in the footnotes to Table 2. The table also shows that reported exposure to heat among males is associated with an increased risk of sperm abnormalities and that reported exposure to noise among females is associated with a twofold increase in the

Table 2 – Odds Ratios (and Their 95% Confidence Intervals) for Selected Subgroups of Subfecund Cases Compared With Fertile Controls by Reported Exposures

Exposure Material	Men With Sperm Abnormalities	Women With Hormonal Disturbances	Women With Idiopathic Infertility	Men With Idiopathic Infertility
Anesthetics	0.3 (0.1, 2.2)	0.8 (0.3, 2.0)	2.2*(1.0, 5.2)	1.4 (0.3, 5.0)
Pesticides	0.8 (0.4, 1.7)	0.7 (0.2, 2.4)	1.1 (0.3, 4.6)	1.5 (0.7, 3.3)
Weed killers	0.6 (0.3, 1.4)	0.3 (0.1, 1.9)	1.3 (0.3, 5.5)	1.3 (0.6, 2.9)
Degreasers	1.1 (0.8, 1.6)	1.1 (0.7, 1.9)	1.2 (0.6, 2.6)	0.8 (0.4, 1.3)
Lacquer, paint, glue	1.2 (0.9, 1.7)	1.1 (0.7, 1.7)	1.4 (0.8, 2.6)	1.1 (0.7, 1.8)
Other organic solvents	1.1 (0.8, 1.7)	1.0 (0.5, 1.8)	1.6 (0.7, 3.3)	0.8 (0.4, 1.5)
Cutting, lubricating oils	1.2 (0.9, 1.8)	1.1 (0.3, 3.7)	3.5†(1.3, 9.3)	1.1 (0.6, 1.8)
Dry-cleaning chemicals	1.0 (0.5, 2.0)	1.3 (0.5, 3.3)	3.0‡(1.2, 7.4)	0.2 (0.0, 1.4)
Textile dyes	0.9 (0.2, 3.7)	1.7 (0.7, 3.9)	6.2§(3.2, 11.9)	. . .
Lead, mercury, cadmium	0.9 (0.5, 1.6)	0.3 (0.1, 1.3)	2.9‖(1.4, 6.3)	0.8 (0.3, 1.8)
Asbestos	1.5 (0.9, 2.4)	1.4 (0.3, 5.8)	3.2 (0.8, 12.7)	1.3 (0.7, 2.7)
Hairspray or dye	1.1 (0.3, 3.4)	1.4¶(0.9, 2.0)	1.3 (0.7, 2.4)	0.7 (0.1, 5.1)
Antirust agents	1.0 (0.7, 1.6)	1.3 (0.3, 5.5)	1.4 (0.2, 10.7)	0.9 (0.5, 1.7)
Plastic manufacturing	1.7 (0.8, 3.6)	1.4 (0.5, 3.9)	0.8 (0.1, 5.8)	2.2 (0.9, 5.4)
Welding of stainless steel	1.7#(1.0, 2.8)	. . .	. . .	1.2 (0.5, 2.8)
Welding of other metals	1.0 (0.7, 1.4)	1.2 (0.3, 5.0)	. . .	1.4 (0.9, 2.3)
Heat	1.8**(1.2, 2.6)	1.2 (0.6, 2.5)	1.8 (0.8, 4.3)	1.6††(0.9, 2.7)
Noise	1.3‡‡(0.9, 1.8)	2.2§§(1.5, 3.1)	2.4‖‖(1.4, 4.0)	1.3 (0.8, 2.0)

Figures after adjustment for women's age, education, residence and parity:

* 1.7 (0.7, 4.0)
† 3.4 (1.2, 10.1)
‡ 2.7 (1.0, 7.1)
§ 5.2 (2.3, 11.5)
‖ 2.6 (1.1, 5.9)
¶ 1.4 (0.9, 2.1)
# 1.7 (0.9, 2.9)
** 1.9 (1.2, 2.8)
†† 1.6 (0.9, 2.8)
‡‡ 1.3 (0.9, 1.9)
§§ 2.1 (1.4, 3.2)
‖‖ 2.2 (1.3, 3.9)

Table 3 – Odds Ratios (and Their 95% Confidence Intervals) for Selected Subgroups of Cases Compared With All Other Cases (n = 256) by Reported Exposures

Exposure Material	Men With Sperm Abnormalities (n = 258)	Women With Hormonal Disturbances (n = 305)	Women With Idiopathic Infertility (n = 129)	Men With Idiopathic Infertility (n = 129)
Anesthetics	0.7 (0.2, 3.1)	0.6 (0.2, 1.5)	1.1 (0.4, 3.0)	1.4 (0.3, 6.4)
Pesticides	1.2 (0.6, 2.8)	3.4 (0.4, 27.1)	4.0 (0.4, 37.3)	1.6 (0.7, 4.0)
Weed killers	1.8 (0.7, 4.6)	2.6 (0.3, 22.9)	4.0 (0.4, 37.5)	2.6*(1.0, 6.9)
Degreasers	1.1 (0.7, 1.7)	0.8 (0.4, 1.5)	0.9 (0.4, 1.9)	0.8 (0.4, 1.4)
Lacquer, paint, glue	1.3 (0.9, 2.0)	0.7 (0.4, 1.3)	1.1 (0.5, 2.1)	1.1 (0.7, 1.9)
Other organic solvents	1.0 (0.6, 1.6)	0.9 (0.4, 2.0)	1.4 (0.6, 3.2)	0.8 (0.4, 1.4)
Cutting, lubricating oils	1.1 (0.7, 1.7)	0.8 (0.2, 3.4)	2.0 (0.5, 8.0)	1.1 (0.6, 1.8)
Dry-cleaning chemicals	1.2 (0.5, 2.7)	0.7 (0.2, 2.3)	1.8 (0.5, 5.8)	0.7 (0.2, 2.1)
Textile dyes	2.9 (0.3, 25.6)	1.0 (0.3, 2.9)	3.2†(1.2, 8.7)	. . .
Lead, mercury, cadmium	0.9 (0.5, 1.8)	0.4 (0.1, 1.4)	1.9 (0.7, 5.2)	0.7 (0.3, 1.7)
Asbestos	1.2 (0.6, 2.2)	0.8 (0.2, 4.2)	1.4 (0.2, 8.2)	1.0 (0.5, 2.2)
Hairspray or dye	0.8 (0.2, 2.9)	1.5‡(0.9, 2.4)	1.0 (0.5, 2.0)	0.4 (0.1, 3.1)
Antirust agents	1.0 (0.6, 1.6)	1.7 (0.2, 18.4)	. . .	0.7 (0.4, 1.5)
Plastic manufacturing	1.0 (0.4, 2.4)	0.5 (0.2, 1.4)	0.2 (0.0, 1.1)	1.2 (0.5, 3.2)
Welding of stainless steel	1.1 (0.6, 2.1)	0.8 (0.1, 13.5)	. . .	0.6 (0.2, 1.5)
Welding of other metals	0.8 (0.5, 1.3)	1.1 (0.3, 5.1)	0.7 (0.1, 6.3)	1.0 (0.6, 1.6)
Heat	1.3 (0.8, 2.1)	0.6 (0.3, 1.2)	0.9 (0.4, 2.1)	0.9 (0.5, 1.7)
Noise	1.1 (0.7, 1.6)	0.7 (0.5, 1.1)	0.8 (0.5, 1.5)	0.8 (0.5, 1.3)

Figures after adjustment for women's age and area of residence

* 2.6 (1.0, 7.3)

† 3.0 (1.0, 8.7)

‡ 1.3 (0.7, 2.2)

risk of hormonal disturbances as well as a twofold increase in the risk of idiopathic infertility. No male exposures were observed to be associated with elevated risks of idiopathic infertility.

The second approach in analyzing the data consisted of within-group comparisons of reported exposures of case couples. The three subgroups described above were compared with infertile couples with conditions unlikely to be caused directly by occupational exposures: displaced testis, variococele, history of mumps as an adult (in the male partner), blocked fallopian tubes, endometriosis, fibroids, malformation of the uterus, or history of chemotherapy, radiation therapy or gonorrhea. The analysis included all case couples with a history of infertility of at least one year's duration who resided on Funen, whether or not they lived within the hospital's direct catchment area. As shown in Table 3 the exposure histories of the case and reference groups are for the most part quite similar. The one exception is a statistically significant threefold risk of idiopathic infertility among couples reporting female exposure to textile dyes. A number of the confidence limits in Table 3 are wide, reflecting the small number of exposed individuals.

A third approach to analyzing the data consisted of a within group comparison of the 3,728 couples from the control group. After experiencing a delay in conception of more than one year, 436 couples had given birth to a healthy child. The reported exposures of these couples were compared with those of the remaining couples who had conceived a healthy child within one year (i.e., the same control group as in the first approach). No residence restriction was applied; subjects could, in principle, come from all of Funen although 90% of the subjects resided within the hospital's immediate catchment area.

The results of this approach are presented in Table 4. Three of the findings are consistent with the results reported in the main case-control comparison. The risk of conception delay was 1.7 times greater for women reporting exposure to lead, mercury and cadmium and 1.7 times greater for women reporting exposure to noise than for women who had not reported such exposures. Among men, reported exposure to heat was associated with a 1.8 times greater risk of delayed conception. Several other exposures that were statistically significant at the .05 level were found to be associated with increased risk of conception delay. The odds ratio was 2.4 for women engaged in welding, 2.5 for women reporting to have worked with

Table 4 – Odds Ratios (and Their 95% Confidence Intervals) for Delayed Conception by Reported Exposures

Exposure Material	Men	Women
Anesthetics	0.9 (0.4, 2.0)	1.6*(1.0, 2.6)
Pesticides	1.1 (0.7, 1.7)	1.2 (0.6, 2.4)
Weed killers	0.9 (0.6, 1.4)	1.0 (0.5, 2.3)
Degreasers	1.1 (0.9, 1.4)	0.7 (0.5, 1.1)
Lacquer, paint, glue	1.0 (0.8, 1.3)	1.0 (0.7, 1.4)
Other organic solvents	1.2 (0.9, 1.5)	1.1 (0.7, 1.6)
Cutting, lubricating oils	1.2†(0.9, 1.5)	1.2 (0.5, 2.6)
Dry-cleaning chemicals	1.2 (0.7, 1.9)	1.6 (0.9, 2.9)
Textile dyes	2.2‡(1.1, 4.2)	1.0 (0.4, 2.2)
Lead, mercury, cadmium	1.3§(0.9, 1.8)	1.7‖(1.1, 2.8)
Asbestos	1.2 (0.8, 1.7)	1.3 (0.4, 3.7)
Hairspray or dye	0.6 (0.2, 1.8)	1.0 (0.7, 1.3)
Antirust agents	1.2 (0.9, 1.6)	2.5¶(1.1, 5.3)
Plastic manufacturing	1.7#(1.0, 2.9)	2.1**(1.2, 3.9)
Welding of stainless steel	1.0 (0.6, 1.6)	1.1 (0.1, 8.8)
Welding of other metals	1.4††(1.1, 1.8)	2.4‡‡(1.1, 5.1)
Heat	1.8§§(1.4, 2.4)	1.5‖‖(1.0, 2.4)
Noise	1.3¶¶(1.0, 1.6)	1.7##(1.3, 2.3)

Figures after adjustment for women's age, women's education, area of residence, parity, women's smoking and drinking habits and past use of oral contraceptives

* 1.4 (0.9, 2.3)
† 1.2 (0.9, 1.5)
‡ 2.4 (1.2, 4.9)
§ 1.3 (0.9, 1.8)
‖ 1.7 (1.0, 2.8)
¶ 2.5 (1.1, 5.7)
# 1.6 (0.9, 2.8)
** 1.9 (1.0, 3.7)
†† 1.3 (1.0, 1.7)
‡‡ 2.7 (1.2, 6.3)
§§ 1.9 (1.5, 2.6)
‖‖ 1.4 (0.9, 2.3)
¶¶ 1.3 (1.0, 1.6)
1.9 (1.4, 2.6)

antirust agents, 1.6 for women working with anesthetic gases, 2.2 for males with reported exposure to textile dyes, 1.4 for males engaged in welding metals other than stainless steel and 1.3 for males with reported exposure to noise.

The footnotes to Table 4 present results adjusted for the potential confounding effects of women's age, women's education, women's smoking history, oral contraceptive usage, parity and residence. Age at time of contact was entered in full years. Smoking, alcohol consumption, history of oral contraceptive use and residence were entered as dichotomous variables. Education was measured in two categories. A specific occupational exposure was included in each analysis as a dichotomous variable (i.e., exposed *v* nonexposed). Study subjects who had responded "don't know" to a specific exposure question were excluded from that analysis, as were subjects for whom information was unavailable. On average 5% of women and 11% of men were thus excluded from questions relating to their respective exposures.

After adjustment for the above potential confounders by means of logistic regression, the odds ratios of delayed conception for women with reported exposure to anesthetic gases and for women with reported employment within the plastics manufacturing industry did not differ significantly from 1.0 at the .05 level.

Association of subfecundity With Occupations – For case and control couples residing within the direct catchment area of Odense University Hospital, odds ratios of selected categories of subfecundity were calculated for occupations of females and their spouses for jobs held in the year preceding hospital admission and for their longest-held occupations prior to hospital admission. The control group consisted of couples who conceived a child within one year. The control group was further restricted to couples whose female partner was 20 years of age or older at time of study contact to more closely approximate the age distribution of case couples. The analyses are based on a three-digit level of detail of occupational codes.

Table 5 – Male Occupations *Not* Associated With an Increased Risk of Idiopathic Infertility, Infertility With Evidence of Sperm Abnormalities or Delayed Conception

Auditors, accountants, cashiers
Bank employees
Bricklayers
Construction engineers
Electrical engineers
Electricians
Farmers
Fitters
Gardeners
Gas, water, power and sanitation line installers
Locksmiths
Machinists, metal turners
Meat packers
Mechanical engineers
Military and civil defense personnel
Office workers
Painters, wallpapers, flooring workers
Post office workers, telephone operators, travel agents
Physicians
Sales clerks
Salesmen
Shipyard and storehouse workers
Steel construction workers
Street maintenance workers
Teachers
Warehousemen
Welders
Unknown

Male occupations were represented by 55 categories of job titles and female occupations by 43 categories. Three subgroups were examined for evidence of an increased risk of subfecundity for male occupations: (1) male partners of pairs with idiopathic infertility, (2) men with medical evidence of sperm abnormalities, and (3) fathers of children conceived after more than one year. Table 5 presents the list of male occupations that were *not* associated with an elevated risk of subfecundity in any of the three groups studied. Table 6 presents occupations in which a positive association was observed in one or more of the study groups. Likewise, Tables 7 and 8 present the results of the corresponding analyses for females divided into three study groups: (1) female partners of pairs with idiopathic infertility, (2) women with medical evidence of hormonal disturbances, and (3) mothers of children conceived after more than one year.

Most of these findings are based on very small numbers. Odds ratios and their 95% confidence intervals are presented in the footnotes to Tables 6 and 8 for those positive findings in which at least 20 controls were observed in a specific occupational category.

Discussion

This study was designed to test and generate hypotheses regarding possible occupational etiologies of infertility. It

Table 6 – Male Occupations Associated With an Increased Risk of Idiopathic Infertility, Infertility With Evidence of Sperm Abnormalities or Delayed Conception ($p<.05$)

Occupation	Idiopathic Infertility		Sperm Abnormalities		Delayed Conception	
	A*	B†	A	B	A	B
Fishermen	X	X	X	X		
Machine repairmen			X	X	X	
Carpenters	X‡	X§				
Pilots	X	X				
Economists	X	X				
Sheet metal workers			X	X		
Inspectors, guards			X	X		
Typesetters			X	X		
Forest rangers			X	X		
Blacksmiths			X‖	X		
Company directors					X¶	X#
Dental assistants					X	X
Political scientists, sociologists	X					
Programmers		X				
Mechanics		X**				
Food industry workers		X				
Machine technicians			X			
Cooks			X			
Property managers			X			
Dairy workers			X			
Packagers, bottlers			X			
Electronics technicians				X		
Dry cleaners				X		
Librarians				X		
Production foremen					X††	
Foundry workers					X	
Shoe repairmen					X	

* A indicates occupation in year prior to hospital admission

† B indicates longest held occupation prior to hospital admission

Odds ratios and their 95% confidence intervals

‡ 3.17 (1.48, 6.80)

§ 2.86 (1.39, 5.88)

‖ 4.18 (1.80, 9.67)

¶ 1.96 (1.17, 3.28)

2.05 (1.27, 3.32)

** 8.82 (3.02, 25.77)

†† 1.95 (1.09, 3.49)

Table 7 – Female Occupations *Not* Associated With an Increased Risk of Idiopathic Infertility, Infertility With Evidence of Hormonal Disturbance or Delayed Conception

Bank employees
Cleaning ladies
Cooks
Gardeners
Hairdressers
Keypunch operators
Laboratory technicians
Nurses
Packers and bottlers
Physical and occupational therapists
Post office workers, telephone operators, travel agents
Teachers
Technical artists
Unknown

was recognized from the beginning that this work would be a preliminary, but necessary, step in pointing the way toward further, more focused research.

The most convincing evidence of associations obtained from this study are: (1) male exposure to heat (associated with sperm abnormalities in the case-control comparison and delayed conception in the within-group comparison of controls); (2) female exposure to noise (associated with hormonal disturbances and idiopathic infertility in the case-control comparisons and delayed conception in the within-group comparison of controls); (3) female exposure to textile dyes (associated with idiopathic infertility in the case-control comparison as well as the within-group comparison of cases); and (4) female exposure to lead, mercury and cadmium (associated with idiopathic infertility in the case-control comparison and delayed conception among controls).

These associations, which were fairly consistent in the present study, seem plausible in light of experimental, clinical and epidemiological evidence in the literature. The effect of heat in inhibting sperm production has been well documented. A testicular temperature 34 to 35 °C (4 to 5 °F lower than body temperature) is necessary for spermatogenesis.[9] Although the injurious effects of heat on spermatogenesis generally are completely reversible, effects may persist for up to three months following exposure.[9]

Noise has been shown to have a number of nonauditory systemic effects, including vasoconstriction and increased secretion of adrenal cortical hormones which may indicate a physiological response to stress.[10,11] After exposing gravid rats to noise levels of 70 to 94 dB for six minutes of every hour during each day of pregnancy, Geber[12] reported total litter resorption in 40% to 50% of the pregnancies, reduction in litter size by two fetuses per litter and increased congenital malformations. He proposed that these results were brought about by increased levels of maternal epinephrine and norepinephrine and decreased uteroplacental and fetal blood flow in response to noise.

Noise may also increase the toxic effect of chemicals when both are administered simultaneously. An experimental study has reported that noise levels of 50 to 60 dB combined with exposure to carbon monoxide at 0.66 mg/m^3 caused significant physiological changes in laboratory animals, whereas the isolated effect of 50- to 60-dB noise levels or of carbon monoxide in a concentration of 0.66 mg/m^3 did not cause any changes.[13]

Harmful effects of lead on human fertility, pregnancy, and fetal development have been reviewed by Rom.[2] In the past lead was sometimes used by women as an abortifacient. Some of the textile dyes and dye intermediaries are well recognized as human carcinogens[14] and it is possible that carcinogens might have an antifertility effect, especially if they act to produce genetic damage of germ cells.

Several methodological problems are encountered in the present study, which examined a wide range of occupations and exposures with the hope of identifying some real associations. In such a large number of comparisons, some associations might be spurious. This problem, referred to as the problem of simultaneous inference, was one of the reasons for supplementing the main case-control study with findings from within-group comparisons of case and of control couples, respectively. The strength of evidence for a real association increases when findings are observed to be consistent in the multiple comparisons afforded by the present study.

A large number of employment categories appear to be overrepresented among couples experiencing infertility and delayed conception. It is difficult to interpret these findings as many of these associations undoubtedly are not of causal nature. The overrepresentation of some female occupational categories among infertile couples may reflect special employment or advancement opportunities possible for women who are childless or have small families. (Because of the small numbers involved it was not possible to adjust for parity and age as potential confounders.) Although negative findings have also been reported, one cannot claim that these occupations are "safe" with regard to their effects on human fertility, again due to the small size of the sample.

It should be noted also that the occupational demands of some jobs or of couples working different shifts might limit opportunities for sexual contact. None of the comparisons have been standardized for sexual activity.

Several potential sources of bias in the present study are worth noting:

Selection Bias – Medical treatment is not sought by all couples who are infertile. A previous study of medical care-seeking behavior showed that only one third of infertile couples with a delay in conception of over two years sought hospital treatment.[15] If factors related to the decision to seek medical care for a problem of infertility (for example, education and area of residence) were also associated with occupational exposures, they could be a source of confounding in the main comparison of cases and controls. This could lead, for example, to a spurious positive association between a particular exposure and infertility. Under these conditions, however, one would not expect to find a corresponding positive association in the within-group comparison of controls because confounding here would be operating in the opposite direction in this study.

Bias Related to Nonresponse – If occupationally exposed women in the case group had a high response rate while exposed women in the control group failed to return their questionnaires, the odds ratio would be overestimated. This overestimation might affect the case-control compari-

Table 8 – Female Occupations Associated With an Increased Risk of Idiopathic Infertility, Infertility With Evidence of Hormonal Disturbance or Delayed Conception ($p<.05$)

Occupation	Idiopathic Infertility		Hormonal Disturbance		Delayed Conception	
	A*	B†	A	B	A	B
Joiners, cabinetmakers			X	X	X	
Spinners	X	X			X	X
Weavers	X	X			X	
Machine knitters	X	X			X	
Dry cleaners			X		X	
Electricians				X	X	
Tanners					X	X
Tire vulcanization workers					X	X
Typesetters			X	X		
Debt collectors			X	X		
Pharmacy assistants			X‡	X§		
Auditors, accountants, cashiers			X‖	X¶		
Shipyard and storehouse workers	X	X				
Fitters	X					
Production managers	X					
Crane operators		X				
Rope, net and sailmakers			X			
Shoemakers			X			
Welders			X			
Restaurant administrators				X		
Plastic industry workers				X		
Office workers				X#		
Seamstresses					X**	
Anatomist, genetists					X	
Sales clerks						X††
Waitresses						X
Steel production workers						X
Cutters (fabrics, leather)						X
Photographers				X		

* A indicates occupation in year prior to hospital admission
† B indicates longest held occupation prior to hospital admission

Odds ratios and their 95% confidence intervals
‡ 3.09 (1.22, 7.82)
§ 2.84 (1.12, 7.19)
‖ 2.82 (1.40, 5.66)
¶ 2.27 (1.03, 4.99)
# 1.59 (1.13, 2.23)
** 2.46 (1.31, 4.65)
†† 1.39 (1.00, 1.93)

sons presented in Table 2, but would be less likely to affect the analyses presented in Tables 3 and 4, which are based on within-group comparisons.

Data were available to study this issue in greater detail. Hospital information for all eligible study women included their general type of employment as reported to their local tax board. This information is known to be inaccurate in that it is not necessarily updated on changing jobs. However, the data are useful in providing a broad occupational category of employment for individuals at some point in their work history. Table 9 presents the response rate among case and control couples according to these employment categories. Fairly similar percentages are observed, although slightly more case than control couples responded from the service and farming/fishing/forestry categories and fewer case than control couples responded from the industry/transportation/skilled worker group.

Information Bias — It is possible that case couples, in searching for an explanation of their infertility, were more likely than controls to report a minimal exposure (which did not meet the study's criteria). This potential problem of overreporting was investigated through the use of an independent method of assessing occupational exposures — namely, from reported occupations. A Danish translation of

Table 9 – Response Rate Among Study Subjects Distributed by Type of Employment of Women

Type of Employment	Total No. of Eligible Study Subjects		Respondents	
	Cases	Controls	Cases, No. (%)	Controls, No. (%)
Research, technical skills	262	1,226	247 (94)	1,127 (92)
Office work	189	702	173 (92)	650 (93)
Sales	81	288	76 (94)	265 (92)
Service	116	331	99 (85)	266 (80)
Farming, fishing, forestry	5	20	5 (100)	16 (80)
Industry, transportation, skilled work	236	749	191 (81)	634 (85)
Unknown	180	989	136 (76)	770 (78)
Total	1,069	4,305	927 (87)	3,728 (87)

Table 10 – Percent of Self-reported Exposures That Could Also be Defined by Occupation in Case and Control Groups

Exposure Material	Cases, %	Controls, %	χ^2 (1 *df*)*
Insecticides			
Women	14	14	0.23
Men	32	41	0.44
Asbestos			
Women	13	0	1.28
Men	49	52	0.75
Lead, mercury, cadmium			
Women	65	70	0.01
Men	53	57	0.01

* Test of uniform association of self-reported and occupationally defined exposures using the log-linear model and testing that the three-factor interaction is equal to 0

an American computer-based occupation-exposure linkage system[16] was made to examine the reporting patterns of case and control couples with respect to a few selected exposures: (1) insecticides, (2) lead, mercury and cadmium, and (3) asbestos. The occupationally defined exposures are based on suspected exposure in the job reported in the year prior to hospital admission or in the longest-held job up until that time. This does not correspond with the criterion used to define self-reported exposures which was one exposure per week, for at least one year, anytime prior to hospital admission. Furthermore, the validity of the Danish occupation-exposure linkage has not been tested. In spite of these difficulties, if the present study showed appreciable case-control differences in the agreement between self-reported and occupationally defined exposures, information bias might be suspected. Table 10 demonstrates that the case-control differences are quite similar and thus do not provide evidence of information bias.

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