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Sources of Bias in Studies among Infertility Clients

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An assumption in case-control studies is that forces of selection are the same for cases and controls. This may not be true for studies of male infertility among infertility clients. Earlier reproductive outcomes may introduce modification of risk behavior or differential referral. Selection bias might also occur when infertile males are compared with fertile males. Partners of sterile men are more likely to have "normal" fertility, while partners of a reference group of normozoospermic men tend to have a lower fertility potential. The latter may lead to overrepresentation of causes of reduced female fertility and introduce bias into estimates of risk factors shared by couples. The relation between cigarette smoking and semen quality was studied in a population of infertility clients from the Netherlands during 1995–1996. To reduce the potential for bias, this relation was studied first in a restricted population less aware of the type of infertility involved. The odds ratio of infertility with smoking was elevated in the restricted population as compared with the total population. Adjustment for smoking by the female partner increased the odds ratios for male smoking as well. These results indicate that bias may occur in clinic-based fertility studies because of different forms of selection. *Am J Epidemiol* 2002;156:86–92.

fertility; infertility; selection bias; semen; smoking

There is an increasing interest in the possible etiologic role of various environmental and lifestyle factors in male infertility (1). Semen analysis has proven to be a useful marker in epidemiologic studies assessing the reproductive toxicity of a variety of exposures (2, 3). Participation rates in sperm studies among men in the general population are usually very low (4), potentially compromising the validity of these studies as a result of selection bias (5).

Clinic-based data have been explored as an alternative to study the relation between semen parameters and "lifestyle" factors (6–10) or occupational exposures (11–16) or, for instance, to study secular time trends in semen quality (17). Yet, there are several potentially important sources of selection bias that can distort inference in such studies. After our review of dozens of published studies among infertility clients, it appears that a detailed discussion of possible biases has received little attention.

The major assumption underlying studies comparing infertility clients with poor semen quality and a reference group of normozoospermic care seekers is that forces of selection are the same for both groups. However, not all infertile couples pursue medical advice, and care seekers are probably not representative of all couples with fertility problems (18–21). Moreover, knowledge of past or present reproductive health may result in modification of present risk behavior (22, 23), and this can distort true associations between exposure and semen characteristics. Ideally, to eliminate both sources of bias, one should use a population of infertility clients completely unaware of the type of infertility involved.

Another specific issue is that in clinic-based reproductive studies the couple is the unit of referral. The fertility potential of female partners of couples that present themselves at a fertility clinic is probably not equally distributed among men with normal semen quality and men with poor semen quality, as depicted schematically in figure 1. Partners of sterile (azoospermic) men probably represent a population of females with a relatively normal fertility potential (24).

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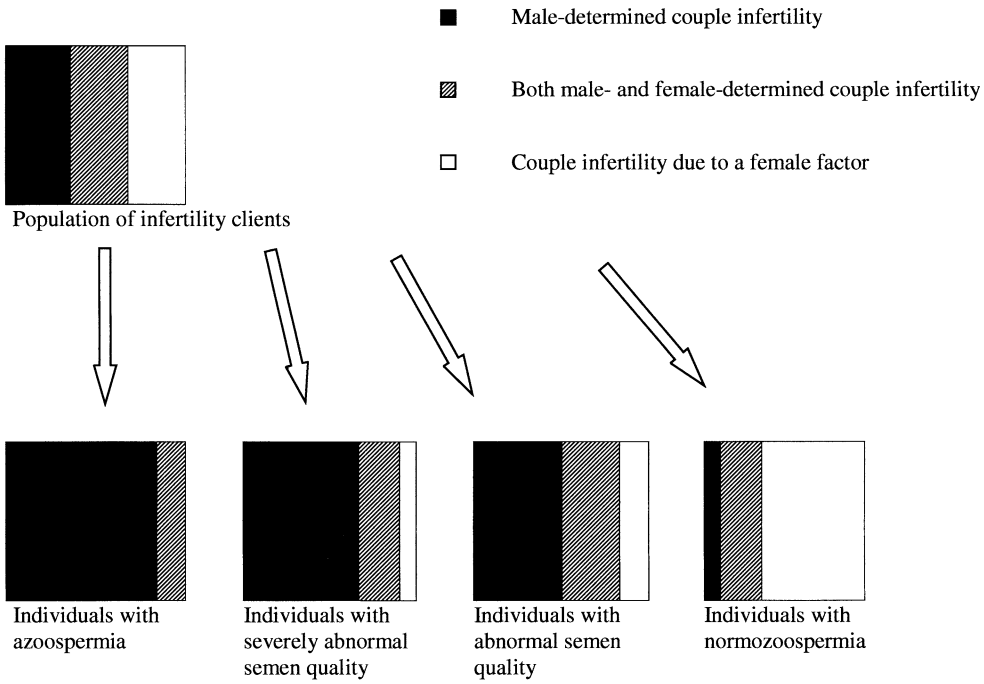

FIGURE 1. Illustration of hypothetical distribution of male and female partner fertility potential among normozoospermic men and men with abnormal semen parameters in a population of infertility clients. The total population of infertility clients is arbitrarily assumed to consist of approximately 33% male-determined couple infertility (dark bar), approximately 33% both male- and female-determined couple infertility (upper-right diagonal), and approximately 33% couple infertility due to a female factor (white bar).

However, female partners of men with completely normal semen parameters are expected to have a much lower fertility potential. In the absence of a clear male factor, the driving force to visit the clinic is most likely a reduced female fertility. This phenomenon may lead to overrepresentation of female characteristics associated with reduced female fertility compared with an ideal reference category. This may introduce bias when determinants of male fertility are studied that are shared by couples and are also causes of female infertility, as is for instance the case for smoking habits (25, 26). The methodological problem has been hypothesized (27, 28), but the actual impact of this type of selection bias on the results of clinic-based studies has never been evaluated. This type of bias is absent when subjects are drawn from the general population, because the female fertility potential is likely to be equally distributed among cases and controls when using this source population. However, the identification and recruitment of couples with male-determined infertility and couples with normal fertility among a general population are, practically, extremely difficult.

Using data originally collected from a study on semen quality from infertility clients in relation to occupational exposures (29), we explore in this study the potential impact of the above-described sources of bias. The data are suitable for assessing selection bias, because we were able to restrict the total study population to couples less aware of the type of infertility involved. Information on specific risk factors for men and their spouses was available, which enabled us to evaluate selection bias-related determinants of male and female infertility that may be shared by couples.

MATERIALS AND METHODS

The study population consisted of male partners in couples having their first consultation at an infertility clinic in the Netherlands in the period between May 1995 and September 1996. Written informed consent was obtained from all couples (male and female partners). We obtained approval from the institutional review board of the university hospital. Before the visit to the infertility clinic, men and their partners were asked to fill in a questionnaire for information on sociodemographic characteristics, lifestyle habits, and details on their current occupation(s). The total sample of males approached for this study was 1,042, with 832 participating. Hence, the response rate was approximately 80 percent. Men who did not provide a semen sample or who had overt and known pathology unlikely to be caused by lifestyle factors, that is, maldescended testes, history of vasectomy or vasovasostomy, history of chemotherapy, radiation therapy, infections, endocrine hypogonadism, and sexual dysfunction, were excluded from the study. A total of 637 men fulfilled these inclusion criteria. Of the 637 subjects, 627 were used in the analyses because 10 had missing values for variables concerning the number of cigarettes smoked or

female risk factors. The duration of infertility ranged from less than 1 year to 20 years.

Subsequently, we applied more restrictive inclusion criteria to create a subpopulation that is as unaware as possible of the type of infertility involved. These additional exclusions were done irrespective of the semen quality data. The underlying concept is that differential care seeking of cases and controls and modification of risk behavior are avoided when couples are completely "blind" with respect to their fertility status. To this end, couples that previously sought help for problems related to their fertility at a specialist level were excluded. Furthermore, couples with a female partner who was experiencing an abnormal menstrual cycle (less than 23 or more than 35 days) or who had a history of pelvic inflammatory disease or couples with a surgically sterile female partner were excluded. These couples may have different reasons to seek care (30) and have presumably some knowledge of their current fertility status. Finally, secondary infertile couples were not included in the restricted population. Only a very low percentage of secondary infertile couples have been shown to seek specialist care (20), which increases the potential for selection bias substantially.

After enrollment, demographic and clinical data on both partners were collected. All physicians of the university hospital worked according to a standard protocol and had to fill in the diagnostic data on a standard history and physical examination form. The diagnostic process in the couples started with a semen examination. Procedures for semen evaluation were according to the World Health Organization protocol (31). The abstinence period for each person was between 2 and 7 days. The reference group comprised subjects with normozoospermia. These subjects had a sperm concentration of 20×10^6/ml or more, 50 percent or more spermatozoa with forward progression or 25 percent or more spermatozoa with rapid progression, and 14 percent or more spermatozoa with normal forms. Cases were defined as subjects with semen parameters that did not fulfill one or more of the criteria for normozoospermia. Hence, these subjects had a sperm concentration below 20×10^6/ml, less than 50 percent spermatozoa with forward progression and also less than 25 percent spermatozoa with rapid progression, less than 14 percent spermatozoa with normal forms, or abnormal values for more than one parameter (case definition A). To increase the contrast between cases and controls and to reduce the influence of intraindividual variability of semen parameters (32), we used a stricter case definition including subjects with a semen concentration below 5×10^6/ml, less than 10 percent spermatozoa with forward progression, less than 5 percent normal forms, or abnormal values for more than one parameter (case definition B). A rigid case definition comprised persons with azoospermia (case definition C).

Adjusted odds ratios between cigarette smoking and abnormal semen parameters were calculated by means of logistic regression analysis. Separate analyses were made for the total and restricted study population. First, variables potentially related to male infertility were considered in the analyses as confounders. These variables included alcohol (≥2 drinks a day), coffee or tea consumption (≥8 cups (1,200 ml) of coffee or tea a day; in accordance with Wilcox et al. (33), 2 cups of tea were counted as being equal to 1 cup of coffee), education (high school or less), and various occupational exposures. In addition, the most important and well-documented risk factors for female infertility were considered in the logistic models: female age (≥36 years) and smoking (25, 26, 34). Variables that changed the crude association by more than 10 percent were controlled for in the multiple regression analyses. Male and female former smokers were treated as nonsmokers in the analyses, except in the analysis for former smokers. Subjects who smoked cigars or pipes were also considered as nonsmokers, except in the analysis dealing with cigar or pipe smokers. We measured the agreement between risk factors present for male and female partners using the kappa statistic.

RESULTS

Exclusion of secondary infertile couples, couples that previously sought help at a specialized level for problems related to their fertility, couples with females experiencing symptomatic problems, or surgically sterile females resulted in a restricted population of 195 subjects (table 1). The age of the female partner decreased substantially when additional inclusion criteria were taken into account. Approximately 15 percent and 10 percent of the female partners were 36 years of age or more in the total and restricted populations, respectively. The number of smoking male and female partners among couples in the population slightly decreased across the various exclusion steps.

Table 2 shows crude odds ratios for abnormal semen parameters in relation to two important risk factors for female infertility, that is, female age and smoking. Odds ratios did not deviate very much from unity in the total study population. Among the restricted population, men with abnormal semen parameters had younger partners. Partners of men with severely affected semen parameters (case definitions B and C) were also less likely to smoke, although confidence intervals were wide.

Table 3 shows the odds ratios and 95 percent confidence intervals for current smoking among the total and restricted populations according to various case definitions. The risk for smoking was clearly elevated in the restricted population as compared with the total population. Correction for potential risk factors for male infertility had little effect on the association between smoking and abnormal semen characteristics, and these factors were therefore eliminated from further consideration. The smoking habits of both members of a couple were positively associated (kappa statistic = 0.46, 95 percent confidence interval: 0.39, 0.53), and female smokers were unequally distributed among cases and controls. Adjustment for smoking by the female partner increased the odds ratios for male smoking substantially. The confounding effect of this female risk factor of infertility was more profound when we used a strict case definition. Additional adjustment for female age had no effect on the observed associations. Moreover, female age did not act as an effect modifier, because stratified analyses excluding couples with female partners 36 years of age or older showed the same results.

TABLE 1. Characteristics of the study population across various levels of exclusion, the Netherlands, 1995–1996

	Cases A*		Cases B†		Cases C‡		Controls§		Overall	
	No.	%	No.	%	No.	%	No.	%	No.	%
Total population	422		173		43		205		627	
Female age, ≥36 years	68	16.1	18	10.4	4	9.3	29	14.1	97	15.5
Female smoking	137	32.5	58	33.5	12	27.9	67	32.7	204	32.5
Male smoking	153	36.3	75	43.4	20	46.5	64	31.2	217	34.6
Primary infertile couples	328		132		38		157		485	
Female age, ≥36 years	38	11.6	9	6.8	3	7.9	17	10.8	55	11.3
Female smoking	105	32.0	39	29.5	9	23.7	47	29.9	152	31.3
Male smoking	119	36.3	53	40.2	16	42.1	46	29.3	165	34.0
Primary infertile couples without previous specialist consultations	180		73		21		86		266	
Female age, ≥36 years	14	7.8	2	2.7	1	4.8	11	12.8	25	9.4
Female smoking	56	31.1	18	24.7	3	14.3	25	29.1	81	30.5
Male smoking	63	35.0	27	37.0	9	42.9	24	27.9	87	32.7
Restricted population¶	141		58		17		54		195	
Female age, ≥36 years	10	7.1	1	1.7	0	0	9	16.7	19	9.7
Female smoking	41	29.1	13	22.4	1	5.9	14	25.9	55	28.2
Male smoking	51	36.2	23	39.7	7	41.2	12	22.2	63	32.3

* Sperm concentration below 20×10^6/ml, less than 50% spermatozoa with forward progression and also less than 25% spermatozoa with rapid progression, less than 14% spermatozoa with normal forms, or abnormal values for more than one parameter.

† Sperm concentration below 5×10^6/ml, less than 10% spermatozoa with forward progression, less than 5% spermatozoa with normal forms, or abnormal values for more than one parameter.

‡ Azoospermia.

§ Sperm concentration of 20×10^6/ml or more, 50% or more spermatozoa with forward progression or 25% or more spermatozoa with rapid progression, and 14% or more spermatozoa with normal forms.

¶ Primary infertile couples: no previous consultation at a specialist level and no symptomatic problems.

In fact, the combination of the additional exclusion criteria that we applied and the adjustments made for smoking by the female partner had a clear effect on the estimated risks for male smoking. When using the total study population and without consideration of confounding due to female risk factors for infertility, we found that the odds ratio was 1.12 for 1–9 cigarettes a day, 1.83 for 10–19 cigarettes a day, and 2.01 for 20 or more cigarettes a day. Among subjects in the restricted population and with adjustment for smoking by the female partner, these odds ratios were almost doubled and were 2.01 for 1–9 cigarettes a day, 3.40 for 10–19 cigarettes a day, and 3.51 for people who smoked 20 or more cigarettes a day (case definition B; table 4). Parallel results were seen when using case definitions A and C.

DISCUSSION

The results of these analyses indicate that conclusions regarding the role of smoking in male infertility are affected by the population selection criteria, the case definition, and correction for female causes of infertility. Had we used the total population without adjustment for risk factors for female infertility, we would have found smaller effects as compared with the results obtained when using the restricted population and adjusting for partner's smoking status. The discrepancies in risk estimates for smoking in the overall comparisons and the subgroup analyses may stem from the various types of selection bias discussed below.

Not all infertility problems come to medical attention, and the proportion of care seekers is especially low among infertile couples who are pursuing a second, third, or subsequent pregnancy (18–21). The possibility of selection bias therefore cannot be excluded, and it seems likely that confining the analysis to primary, asymptomatic infertile couples without a previous detailed infertility work-up decreases the likelihood of differential forces of selection among exposed and nonexposed cases and controls. The potential for modification of (perceived) risk behavior (22, 23) is probably also reduced in the restricted population, because these couples are less aware of the type of infertility involved. Thus, the higher risk estimates found among couples in the restricted population must be given greater credence than those of the total population.

TABLE 2. Crude odds ratios for abnormal semen parameters in relation to age and smoking by the female partner in the total study population and the restricted population, the Netherlands, 1995–1996

	Total population		Restricted population	
	OR*	95% CI*	OR	95% CI
Case definition A†				
Female smoking	0.99	0.69, 1.41	1.17	0.58, 2.38
Female age, ≥36 years	1.17	0.73, 1.87	0.38	0.15, 1.00
Case definition B‡				
Female smoking	1.04	0.68, 1.60	0.83	0.35, 1.96
Female age, ≥36 years	0.71	0.38, 1.32	0.09	0.01, 0.72
Case definition C§				
Female smoking	0.80	0.39, 1.65	0.18	0.02, 1.47
Female age, ≥36 years	0.62	0.21, 1.87	0	—¶

* OR, odds ratio (calculations based on the control group with the following characteristics: sperm concentration of 20×10^6/ml or more, 50% or more spermatozoa with forward progression or 25% or more spermatozoa with rapid progression, and 14% or more spermatozoa with normal forms); CI, confidence interval.

† Sperm concentration below 20×10^6/ml, less than 50% spermatozoa with forward progression and also less than 25% spermatozoa with rapid progression, less than 14% spermatozoa with normal forms, or abnormal values for more than one parameter.

‡ Sperm concentration below 5×10^6/ml, less than 10% spermatozoa with forward progression, less than 5% spermatozoa with normal forms, or abnormal values for more than one parameter.

§ Azoospermia.

¶ There was an empty cell for the combination of female age of ≥36 years and case definition C.

TABLE 3. Estimated odds ratios for abnormal semen parameters and male cigarette smoking in the total study population and the restricted population, the Netherlands, 1995–1996*

	Total population					Restricted population				
	No.†	OR‡	95% CI‡	OR	95% CI	No.	OR	95% CI	OR	95% CI
Case definition A§										
Male smoking	153	1.25	0.88, 1.79	1.34	0.90, 2.00	51	1.98	0.96, 4.11	2.07	0.95, 4.51
Female smoking	137			0.86	0.58, 1.29	41			0.90	0.42, 1.93
Case definition B¶										
Male smoking	75	1.69	1.11, 2.57	1.97	1.20, 3.24	23	2.30	1.00, 5.27	2.99	1.17, 7.67
Female smoking	58			0.73	0.44, 1.21	13			0.51	0.19, 1.38
Case definition C#										
Male smoking	20	1.92	0.98, 3.74	2.62	1.22, 5.61	7	2.45	0.77, 7.81	4.58	1.20, 17.47
Female smoking	12			0.50	0.22, 1.14	1			0.09	0.01, 0.87

* Smoking by the male partner was entered alone and simultaneously with female smoking into logistic regression models.

† Number of cases with the particular risk factor.

‡ OR, odds ratio (calculations based on the control group with the following characteristics: sperm concentration of 20×10^6/ml or more, 50% or more spermatozoa with forward progression or 25% or more spermatozoa with rapid progression, and 14% or more spermatozoa with normal forms); CI, confidence interval.

§ Sperm concentration below 20×10^6/ml, less than 50% spermatozoa with forward progression and also less than 25% spermatozoa with rapid progression, less than 14% spermatozoa with normal forms, or abnormal values for more than one parameter.

¶ Sperm concentration below 5×10^6/ml, less than 10% spermatozoa with forward progression, less than 5% spermatozoa with normal forms, or abnormal values for more than one parameter.

Azoospermia

TABLE 4. Estimated odds ratios for abnormal semen parameters and smoking by the male partner* as defined by the number of cigarettes smoked a day in the total study population and the restricted population, the Netherlands, 1995–1996

	Total population					Restricted population				
	No.†	OR‡	95% CI‡	OR	95% CI	No.	OR	95% CI	OR	95% CI
1–9 cigarettes/day	14	1.12	0.53, 2.36	1.28	0.59, 2.78	5	1.50	0.37, 6.02	2.01	0.46, 8.90
10–19 cigarettes/day	33	1.83	1.03, 3.25	2.19	1.16, 4.13	10	3.00	0.87, 10.40	3.40	0.95, 12.20
≥20 cigarettes/day	28	2.01	1.07, 3.78	2.47	1.23, 4.96	8	2.40	0.67, 8.64	3.51	0.83, 14.76
Female smoking	58			0.70	0.42, 1.17	13			0.51	0.18, 1.44

* Smoking by the male partner was entered alone and simultaneously with female smoking in the logistic regression models. The analyses were based on case definition B (sperm concentration below 5×10^6/ml, less than 10% spermatozoa with forward progression, less than 5% spermatozoa with normal forms, or abnormal values for more than one parameter).

† Number of cases with a particular risk factor.

‡ OR, odds ratio (calculations based on the control group with the following characteristics: sperm concentration of 20×10^6/ml or more, 50% or more spermatozoa with forward progression or 25% or more spermatozoa with rapid progression, and 14% or more spermatozoa with normal forms); CI, confidence interval.

Reproduction involves the interaction between both partners and, among men attending an infertility clinic, this can result in a special type of selection bias for male correlates of female causes of infertility (27, 28). Smoking is an important and well-established risk factor for female infertility (25, 26), and male smoking habits are related to the smoking status of the female partner. Because the fertility potential of female partners is probably unequally distributed among cases and controls (see figure 1), this may lead to biased estimates. To obtain an unbiased estimate for the association between smoking and male infertility, it is therefore necessary to measure and adjust for female smoking. The change in the estimated odds ratio for abnormal semen characteristics with smoking after adjustment for the partner's smoking status indeed suggests the presence of confounding.

Several design options have been used in clinic-based studies of male infertility. Infertility clients with poor semen quality have been compared with normozoospermic care seekers, with care seekers who have a known pathology unlikely to be caused by lifestyle factors, or with an external control group of fertile couples. The bias as shown in this study may to some extent be present in all these different clinic-based designs. One can greatly reduce the possibility of this type of selection bias in clinic-based studies by restricting both cases and controls to infertile care-seeking couples with a specific and clearly defined cause of female infertility (e.g., double-sided tubal occlusion). However, this strategy may be more easily stipulated than fulfilled. The diagnostic process generally starts with a semen examination but, in practice, not every couple will receive a complete medical evaluation. The diagnostic process itself is often cut short by the occurrence of pregnancy (30). Alternatively, this type of bias is not likely to be present in studies of semen quality in the general population. Unfortunately, participation rates of sperm studies in the general population are very low (4).

The bias as shown in this paper may also be present in clinic-based studies of reduced female fertility. In these studies a reciprocal phenomenon may occur. The male-partner fertility potential may not be equally distributed among couples with female fertility problems and a reference group of couples with normal female fertility. Obviously, also in these studies causes of reduced fertility may be correlated between partners, so that the relation between female infertility and its underlying causes may be biased. Hence, the presented bias has a broader applicability, and adjustments for male factors might be necessary in clinic-based studies on female infertility.

Besides selection bias other reasons may exist for the apparent differences in risk estimates for smoking in the overall comparison and subgroup analyses. The exclusion of diagnostic groups that are not smoking related may artificially enhance the associations between smoking and semen quality. However, the results show that smoking habits are relatively similar across the study population at large and the various groups of selected subjects. Nonetheless, the exclusion strategy may still have resulted in a more susceptible subgroup, potentially influencing the relation between smoking and semen quality. Hence, we cannot disregard completely the possibility that alternative factors may at least in part be responsible for the observed differences.

The associations of semen quality with smoking habits were stronger if cases were defined according to more stringent cutoff values for semen parameters. There may be different underlying reasons for this phenomenon. Misclassification arising from intraindividual variability of semen parameters may be a considerable source of bias toward the null (32). The attenuation effect is reduced by the application of very strict case definitions. Alternatively, smoking habits may be specifically related to poor semen parameters without being a causal factor in less severe male infertility.

Only a few of the published clinic-based studies on occupational or lifestyle factors (6) compared results of analyses of restricted subsets with results of the main analysis. No other clinic-based studies of smoking and semen quality were found that included important risk factors of female infertility in the analysis. These limitations may explain the conflicting results in clinic-based studies, as opposed to the relatively consistent association between smoking and poor semen quality described in studies among normal men (7, 8). Because smoking habits are strongly correlated within a couple and because female smoking is an important and

well-documented risk factor of female infertility (25, 26), these results probably represent a rather extreme example of selection bias for male correlates of female causes of infertility. Results of studies focusing on specific occupational pollutants (11–16), for instance, may be less vulnerable to this type of bias. Genetic factors (35, 36) are unlikely to be correlated with any determinant of female infertility. If so, clinic-based studies focusing on these factors would not be subject to this bias. Nonetheless, we conclude that, in general, one should be extremely cautious when dealing with such a clinic-based design and apply a more refined analytical approach.

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REFERENCES

1. Skakkebaek NE, Giwercman A, de Kretser D. Pathogenesis and management of male infertility. Lancet 1994;343:1473–9.
2. Wyrobek AJ, Gordon LA, Burkhart JG, et al. An evaluation of human sperm as indicators of chemically induced alterations of spermatogenic function. A report of the US Environmental Protection Agency Gene-Tox Program. Mutat Res 1983;115:73–148.
3. Hatch MC, Friedman-Jimenez G. Using reproductive effect markers to observe subclinical events, reduce misclassification, and explore mechanism. Environ Health Perspect 1991;90:255–9.
4. Bonde JP, Giwercman A, Ernst E. Identifying environmental risk to male reproductive function by occupational sperm studies: logistics and design options. Occup Environ Med 1996;53:511–19.
5. Larsen SB, Abell A, Bonde JP. Selection bias in occupational sperm studies. Am J Epidemiol 1998;147:681–5.
6. Bracken MB, Eskenazi B, Sachse K, et al. Association of cocaine use with sperm concentration, motility, and morphology. Fertil Steril 1990;53:315–22.
7. Vine MF, Margolin BH, Morrison HI, et al. Cigarette smoking and sperm density: a meta-analysis. Fertil Steril 1994;61:35–43.
8. Vine MF. Smoking and male reproduction: a review. Int J Androl 1996;19:323–37.
9. Buiatti E, Barchielli A, Geddes M. Risk factors in male infertility: a case-control study. Arch Environ Health 1984:39:266–9.
10. Parazzini F, Marchini M, Luchini L, et al. Tight underpants and trousers and risk of dyspermia. Int J Androl 1995;18:137–40.
11. Rachootin P, Olsen J. The risk of infertility and delayed conception associated with exposures in the Danish workplace. J Occup Med 1983;25:394–402.
12. Mortensen JT. Risk for reduced sperm quality among metal workers, with special reference to welders. Scand J Work Environ Health 1988;14:27–30.
13. Veulemans H, Steeno O, Masschelein R, et al. Exposure to ethylene glycol ethers and spermatogenic disorders in man: a case-control study. Br J Ind Med 1993;50:71–8.
14. Lundsberg LS, Bracken MB, Belanger K. Occupationally related magnetic field exposure and male subfertility. Fertil Steril 1995;63:384–91.
15. Bigelow PL, Jarrell J, Young MR, et al. Association of semen quality and occupational factors: comparison of case-control analysis and analysis of continuous variables. Fertil Steril 1998;69:11–18.
16. Gerber WL, de la Pena VE, Mobley WC. Infertility, chemical exposure, and farming in Iowa: absence of an association. Urology 1988;31:46–50.
17. Adamopoulos DA, Pappa A, Nicopoulou S, et al. Seminal volume and total sperm number trends in men attending subfertility clinics in the greater Athens area during the period 1977–1993. Hum Reprod 1996;11:1936–41.
18. Templeton A, Fraser C, Thompson B. The epidemiology of infertility in Aberdeen. BMJ 1990;301:148–52.
19. Wilcox LS, Mosher WD. Use of infertility services in the United States. Obstet Gynecol 1993;82:122–7.
20. Olsen J, Küppers-Chinnow M, Spinelli A. Seeking medical help for reduced fecundity: a study based upon surveys in five European countries. Fertil Steril 1996;66:95–100.
21. Olsen J, Basso O, Spinelli A, et al. Correlates of care seeking for infertility treatment in Europe. Eur J Public Health 1998;8:15–20.
22. Weinberg CR, Baird DD, Wilcox AJ. Sources of bias in studies of time to pregnancy. Stat Med 1994;13:671–81.
23. Olsen J, Skov T. Design options and methodological fallacies in the studies of reproductive failures. Environ Health Perspect 1993;101(suppl 2):145–52.
24. Emperaire JC, Gauzere-Soumireu E, Audebert AJM. Female fertility and donor insemination. Fertil Steril 1982;37:90–3.
25. Buck GM, Sever LE, Batt RE, et al. Life-style factors and female infertility. Epidemiology 1997;8:435–41.
26. Augood C, Duckitt K, Templeton AA. Smoking and female infertility: a systematic review and meta-analysis. Hum Reprod 1998;13:1532–9.
27. Savitz DA, Pearce N. Control selection with incomplete case ascertainment. Am J Epidemiol 1988;127:1109–17.
28. Wacholder S, McLaughlin JK, Silverman DT, et al. Selection of controls in case-control studies. I. Principles. Am J Epidemiol 1992;135:1019–28.
29. Tielemans E, Burdorf A, te Velde ER, et al. Occupationally related exposures and reduced semen quality: a case-control study. Fertil Steril 1999;71:690–6.
30. Weinberg CR, Wilcox AJ. Reproductive epidemiology. In: Rothman KJ, Greenland S, eds. Modern epidemiology. Philadelphia, PA: Lippincott-Raven, 1998:585–608.
31. World Health Organization. WHO laboratory manual for the examination of human semen-cervical mucus interaction. Cambridge, England: Cambridge University Press, 1993.
32. Tielemans E, Heederik D, Burdorf A, et al. Intraindividual variability and redundancy of semen parameters. Epidemiology 1997;8:99–103.
33. Wilcox A, Weinberg C, Baird D. Caffeinated beverages and decreased fertility. Lancet 1988;2:1453–6.
34. Menken J, Trussel J, Larsen U. Age and infertility. Science 1986;233:1389–94.
35. Lilford R, Jones AM, Bishop DT, et al. Case-control study of whether subfertility in men is familial. BMJ 1994;309:570–3.
36. Pryor JL, Kent-First M, Muallem A, et al. Microdeletions in the Y chromosome of infertile men. N Engl J Med 1997;336:534–9.