OCCUPATIONAL RISKS: STILL A PROBLEM FOR SEMINAL FLUID PARAMETERS? RESULTS OBTAINED FROM A CASE/CONTROL STUDY IN A FERTILITY CLINIC

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ABSTRACT

Introduction: *The reproductive problems involve the male component of the couple in 25-30% of cases.*

Materials and methods: *A case/control investigation was conducted to assess how potential occupational risks could have an effect on this condition. Cases were recruited in an assisted reproduction technology center for male infertility and they were asked to complete a questionnaire and provide a semen sample; controls were fertile men with at least one child conceived spontaneously, with a time to pregnancy <12 months. In total, n= 272 cases and n= 286 controls were recruited. The semen samples were analyzed: volume, concentration and motility were assessed according to the World Health Organization criteria.*

Results: *In the case group, motility was the most altered parameter (86.8% of subjects) followed by concentration (47.7%) and volume (20.2%). The stratification by work activities, conducted considering the possible risk factors (heat in genital area for work like drivers, working at computer for more than 20 hours/week, possible chemical exposure, night shift, hospital workers, armed forces, others), did not evidence higher risk indices in the two groups, even taken into consideration working seniority and age.*

Conclusion: *The study did not highlight any potential risks for reproductive health due to work activities of the subjects, also in consideration of the possible biases related to self-reported data. Although specific occupational exposures are documented risky for the quality of seminal fluid, the preventive measures introduced by the legislation in order to protect workers in the last few decades may have had a role in the results obtained.*

Keywords: *Semen, male fertility, occupational exposure, self-reported exposures.*

DOI: 10.19193/0393-6384_2023_3_93

Received *March 15, 2022;* ***Accepted*** *February 20, 2023*

Introduction

About 10% of the global population is affected by problems related to the reproductive sphere(1). In 25-30% of cases, the cause is related to the male partner of the couple(2), while 25% of cases are still of unknown etiology(3). Recently the quality of the human semen, particularly in the parameter of sperm count, has been reported to be characterized by a significant decline(4), albeit not consistently(5). A recent publication(6) focusing on the temporal trend of seminal fluid parameters in the USA, between 2000 and 2017, has shown that sperm concentration and sperm count have suffered a decline of 2.62% and 3.12% per year, respectively, corresponding to an overall decline in the quality of fluid of 37% and 42% over the 17 years. Based on these observations, sources of risk found in living environments and, especially, in working environments have been considered. Many studies have investigated the quality of seminal fluid in relation to occupational exposure to chemical and physical agents. Indeed, possible occupational risk factors for male reproductive health could be attributable to: physical agents (activities causing heating in the genital area, exposure to radiation, vibrations); chemical agents (paints, solvents, fumes from metal welding, thinners, and pesticides); psychological factors such as stress, and night work (for its capacity to determine a disregulation of circadian rhythms and hormonal alterations)[7, 8].

In this study, we aimed to investigate the association between semen quality and potential self-reported occupational exposure through the administration of a questionnaire, comparing a population of infertile men and a population of fertile subjects.

Materials and methods

Study populations

The Institutional Review Board of the IRCCS San Raffaele Scientific Institute in Milan evaluated and approved the study protocol (identification code 73/INT/2017). The study samples were recruited between March 2017 and February 2018. Infertile men were enrolled at the IRCCS San Raffaele Assisted Reproduction Technology (ART) Centre in Milan. Adult males were interviewed, following the signing of the informed consent, using a specific questionnaire, and a semen sample was collected.

Specific exclusion criteria as "cases" in the study were the following:

- Subjects attending the center for a genetic diagnosis and not for infertility problems;
- Subjects who did not present any altered parameters of seminal fluid compared to the WHO reference values[9];
- Number of days of abstinence, before sample collection, less than three;
- Cases of cryptorchidism without successive execution of orchidopexy[10];
- Subjects unable to produce a usable semen sample (due to difficulty in collection or azoospermia);
- Situations of diagnosed neoplasms that required specific chemotherapy and/or radiotherapy in the genital area.

With respect to the possibility of evaluating the correlation between work activities, and therefore specific self-reported exposures, and the semen quality, possible confounding factors were considered: age[11], smoking[12] and alcohol habits[13], body mass index (BMI)[14] and previous genital pathologies[15-19]. A total of n=572 potentially infertile men were recruited. Subsequently, following the application of the exclusion criteria, the sample was reduced to n=272 cases which fully satisfied the conditions of the study. The controls were enrolled in the Obstetrics and Gynecology Unit of the IRCCS San Raffaele Hospital in Milan.

The criteria observed for recruitment were: volunteers aged >18, male partners of couples with spontaneous conception with a time to pregnancy of less than 12 months. From an initial total of n=412 men who volunteered for the study, the sample was subsequently reduced to n=286 subjects after the application of the inclusion criteria.

Questionnaire design, contents and administration

An ad hoc questionnaire, structured in three parts, was defined for the specific purpose of this study. The first part was aimed to gather the general information regarding the study participants: age, place of residence, smoking or alcohol habits, as well as a series of information related to their living environment (use of medications and nutritional habits, with particular attention to their use of canned products and plastics to contain food).

The second part was dedicated to the collection of the subject's clinical data, particularly regarding the endocrine system, congenital, infectious, and other pathologies that might have adversely affected the male reproductive system.

The third part was aimed at collecting all the information related to the working activities, with a sub-division between current and previous working activities. The potential exposure risk involved in the subjects' current and past occupation, as well as the length of time they had been employed in that role were investigated.

Analysis of the semen samples

All the infertile subjects were asked to produce a sample of seminal fluid in a sterile container, after at least 3 days of abstinence from sexual intercourse. After semen liquefaction (approximately 30 minutes at 37 °C), volume, concentration, and motility were assessed according to the World Health Organization criteria[20]. The volume was measured by weight, assuming a semen density of 1.0 g/mL. A hemacytometer (Bioanalytic GmbH, Germany) was used to estimate the sperm concentration. The volume of seminal fluid was dispensed using Gilson Microman M25, M50, or M250 pipettes (Gilson UK, Luton UK), depending on the need for dilution. Motility was estimated as the percentage of the rapidly, slowly progressive and non-progressive spermatozoa by counting 200 spermatozoa in at least

5 fields of potency per replicate. This was followed by applying the checklist of SEMinal QUAlity studies (SEMQUA), to increase the accuracy and transparency of the study[21]. A quality control program, both internal and external to the laboratory, was conducted in accordance with the European Society of Human Reproduction and Embryology (ESHRE) guidelines[22] for a random and systematic control of errors and inter-laboratory differences.

All the laboratory personnel was trained according to the ESHRE Special Interest Group in andrology - basic course for semen analysis.

Statistical analysis

The statistical analysis was performed with the SPSS® version 25 software (IBM, Armonk, NY, USA). The use of parametric or non-parametric tests, where appropriate, made it possible to evaluate the difference among groups in the various categories and stratifications. Descriptive analyses were conducted for the characteristics of the case/control population, and the differences between the two samples were verified with the Mann-Whitney U test and the Chi-Square test. For the population of infertile men, a seminal parameters description was also performed. The sperm concentration results were elaborated using the natural logarithm of the value obtained, to describe the numerical element in a simpler way. The values of the seminal fluid parameters were stratified by work duties. To highlight any differences among the various classes, considering that the values of the seminal fluid parameters do not distribute normally, the Kruskal-Wallis test was used.

The Odds Ratios were determined (raw and adjusted for confounding factors) related to the work duties and risk factors highlighted, as well as in relation to the living environment (use of plastic containers for food storage, nutritional habits such as soy intake, or the use of canned foods). The length of service was also considered. Three classes of time were highlighted (≤5, 5-15, >15 years) to evaluate how seniority in the role could affect an exposure to a specific risk. Finally, the parameters of seminal fluid in the cohort of men performing night work have been described.

Results

The basal characteristics of cases and controls are shown in Table 1; statistically significant differences between the two groups are also highlighted.

	Cases (272)	Controls (286)	P value
Average age±DS (range)	42.1±5.2 (30-57)	37.5±5.2 (18-51)	0.000*
BMI[1] (%)			
Underweight	0.0	0.3	0.091
Normal	46.0	52.8	
Overweight	45.2	36.0	
Obese	8.5	5.6	
Missing	0.4	5.2	
Smoke (%)			
Yes	29.4	22.4	0.148
Previously	19.9	22.0	
No	50.7	54.9	
Missing	0.0	0.7	
Alcohol consumption (%)			
Never	14.7	10.5	0.082
Daily	4.4	7.3	
Weekly	19.5	26.9	
Occasionally	59.6	53.8	
Missing	1.8	1.4	
Residence area (%)			
Urban	75.0	87.1	0.003*
Rural	14.3	6.3	
Coast	2.6	0.3	
Industrial	0.7	0.3	
Other	5.5	3.5	
Missing	1.8	2.4	
Use of plastic containers for fat food storage (%)			
Never	62.1	56.6	0.012*
Daily	3.3	5.9	
Weekly	12.5	18.5	
Monthly	17.3	17.8	
Missing	4.8	1.0	
Eating canned food at least weekly	26.9	42.3	0.001*
Eating soya products at least weekly	10.3	12.9	0.465
Working activity			
Employees, professionals, computer operators	54.4	47.6	0.095
Drivers, workers with a prolonged sitting positions	10.7	10.8	
Farmers, artisans, dental technicians	15.8	17.1	
Health workers	3.7	7.7	
Armed forces	2.9	2.4	
Other	12.1	11.5	
Missing	0.4	2.8	
Average seniority in employment ±SD[2] (Range)	13.9.±.6.6 (2-38)	10.0±5.9 (0-27)	0.000*

Table 1: Characteristics of the study samples.
*[1]BMI, body mass index; [2]SD, standard deviation; *Significant values of the Mann-Whitney Test for continuous variables and of the χ^2 test for qualitative variables.*

The comparison between the two populations showed some differences: namely, cases were older than controls and had a higher working seniority.

The controls seemed to reside principally in urban areas and had a greater tendency to use canned foods and store food products in plastic (possible sources of exposure to plasticizers in living environments). Table 2 shows the values of the seminal fluid parameters of cases, compared with the reference values of the WHO[14]. The complexity of obtaining a semen sample from fertile subjects made it necessary to use the WHO reference values as comparison data and not the experimental results on the control sample.

The experimental findings about semen of infertile men were stratifying for working activities, grouped according to their specific type of risk, and shown in Figure 1.

		Seminal data (272)		
		Volume (ml)	Concentration (Ln)	Motility (%)
Average		2.4	16.1	22.8
Median		2.0	16.5	20.0
Standard deviation		±1.2	±1.7	±12.8
5° percentile		1.0	12.2	5.0
95° percentile		4.0	18.1	50.0
Quartile	<25°	1.5	15.4	10.0
	25°-50°	2.0	16.5	20.0
	50°-75°	3.0	17.2	30.0
	>75°	8.0	18.8	60.0
WHO 2010 reference levels		≥ 1.5	≥16.5	≥ 40.0
Out of Range		58 (21.3%)	130 (47.8%)	237 (87.1%)

Table 2: Values of seminal fluid parameters of cases.

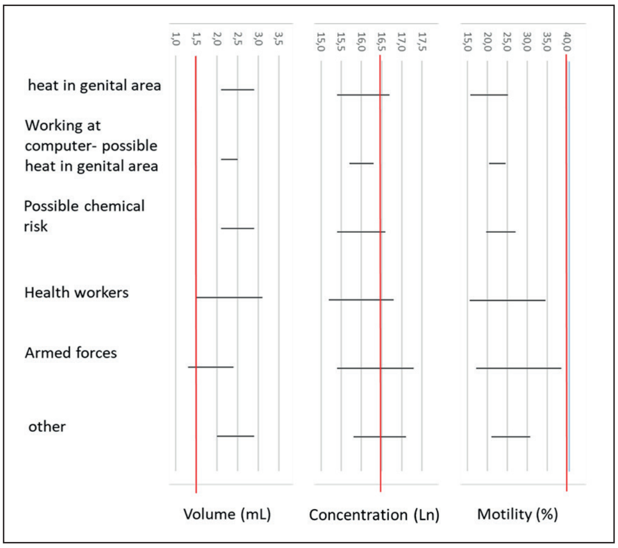

Figure 1: Parameters of the seminal fluid in relation to the declared work activities. The red line corresponds to the WHO normality limit.

This stratification provides for:

• Activities in which it is possible excessive heating of the genital area occurs;

• Activities conducted at video display screens;

• Possible exposure to chemical agents;

• Health activities, in which the potential presence of risk for night work, stress, and possible chemical risk is configured;

• Military, activities in which there may be risks from stress and nocturnal working.

The values of the parameters of seminal fluid do not distribute normally, so to evaluate possible differences, the Kruskal-Wallis test was applied. The test results did not show statistically significant differences in any comparison (p>0.05). For the causality study, the Odds Ratio were calculated, between cases and controls, referring to work activities, grouped by type of risk, and to some possible sources of risk in the living environment. The outcome of this evaluation, adjusted for confounding factors, is presented in Table 3.

Working activity	Cases	Controls	OR[1]	95% CI[2]	P value
Possible heat in genital area	29	31	1.0	0.6-1.9	0.891
Working on computers	144	129	1.0	0.7-1.5	0.906
Possible chemical risk	42	44	0.9	0.6-1.6	0.860
Heath sector	10	19	0.8	0.4-2.0	0.715
Armed forces	8	7	0.7	0.2-2.3	0.575
Other	33	30	0.9	0.5-1.8	0.957
Use of plastic containers for fat food	90	107	0.8	0.5-1.2	0.340
Eating canned food at least weekly	185	210	0.7	0.4-1.1	0.128
Eating soya products at least weekly	92	100	0.9	0.7-1.5	0.975

Table 3: Odds Ratio (OR) of possible occupational and non-occupational risk factors and male infertility, adjusted for confounding factors.

[1]OR, Odd Ratio; [2]CI, confidence interval.

The cohort of men only employed in night work, amounting to n= 29 subjects, was subsequently studied in order to evaluate, in detail, whether this specific risk could have a detectable impact. The distribution of the data is presented in Table 4.

		Seminal data (29)		
		Volume (ml)	Concentration (Ln)	Motility (%)
Average		2.0	15.9	22.1
Median		2.0	16.8	20.0
Standard deviation		±1.1	±1.8	±12.9
Quartile	<25°	1.0	15.1	10.0
	25°-50°	2.0	16.8	20.0
	50°-75°	3.0	17.2	30.0
	>75°	5.0	17.7	50.0
WHO 2010 reference levels		≥ 1.5	≥16.5	≥ 40.0
Out of Range		9 (31.0%)	14 (48.3%)	26 (89.7%)

Table 4: Parameters of the seminal fluid in the population of night workers.

The stratification of the findings with respect to the length of service (<5 years, between 5 and 15 years, >15 years) did not produce statistically different comparisons between cases and controls for any specific work duties (Kruskall Wallis test).

A comparison among the values of this sub-cohort with the results of the overall sample without the 29 night workers, showed an increase of the number of out of range samples (volume 20.2 vs 31.0 %; concentration 47.7 vs 48.3 %; and motility 86.8 vs 89.7 %). Nevertheless, this was not considered statistically significant (test of χ^2 for the comparison of volume p value = 0.177; of concentration p value = 0.995; of motility p value = 0.744).

Discussion

The impact of occupational environment on semen parameters has been a focus of some interest. With respect to excessive heat in the genital area, some studies[23] confirm the possibility of a reduction in the quality of seminal fluid, although the investigation involved workers in the steel industry, in which the possible confounding related to chemicals must probably be taken into consideration. Other authors[24] have also identified working at video display terminals as an important risk factor (OR 8.01, 95% CI 4.03-15.87) for the alteration of seminal fluid, due to the prolonged sitting position, although this association remains controversial[25]. Our findings did not confirm this hypothesis of risk source even if with an overall semen parameters with a greater portion out of normal range (volume 3.55 vs 2.4 mL on average; concentration 39.97 vs 9.8 * 106/mL on average; motility 45.81 vs 22.8 % on average, respectively).

Eisenberg et al.[26], in a longitudinal study involving n=456 men aimed at evaluating potentially risky "physical" agents, highlighted the physical effort in working activity as an element linked to the subjects' oligozoospermia, despite having a population that was also exposed to heat (21%), night work (23%), and shift work (16%). Similarly, "manual activity" was associated (OR = 1.28, 95% CI 1.07-1.53) with the reduction of sperm concentration[27]. Concerning night work, numerous studies have been conducted to understand the involvement of this specific working situation on semen quality. A cross-sectional study[28] on n=953 subjects showed a reduction in sperm concentration equal to 29% in men with significant sleep disturbances. El-Halaly et al.[24], presenting a case/control study with n=255 infertile and n=267 fertile men, noted a greater presence of infertile men (OR=3.60, 95% CI 1.12-11.57) in the group of night workers. Not all researchers, however, confirmed this hypothesis[26, 29], and our results follow these last researches, in fact, we found no statistically significant difference among this group of men and the other in other working classes.

The strongest evidence of the effects on male reproductive health owing to occupational exposure undoubtedly concerns exposure to chemical agents. The involved inorganic compounds are essentially the following: lead[30], in which exposure to doses higher than 40 μg/dl in the blood were associated with reduced sperm motility and concentration as well as altered sperm morphology; boron[31], for which there is experimental evidence in vitro, with any epidemiological confirmation; and chromium[32], for which significantly greater morphological anomalies emerged in the exposed than in the not exposed subjects. Exposure to carbon disulphide was also investigated[33], for which a greater presence of sexual dysfunctions and a reduced quality of seminal fluid was shown in exposed workers. Among the studied organic substances, a specific effect can be found for endocrine disruptors such as: the phthalates[34], particularly di-(2-ethylhexyl) phthalate (DEHP), for which there is evidence of interference on DNA integrity and sperm motility; alkylphenols[35], in particular bisphenol A (BPA), which produces an alteration of the androgenic hormonal structure; pesticides[36], particularly organophosphates and carbamates[37], with greater evidence in chronic exposure, resulting in sperm chromatin damage, reduced fluid quality and hormonal alterations.

We can also cite the exposure to benzene in the petrochemical industry[38, 39], able to induce sperm aneuploidy and a decrease in sperm motility. Among the self-reported occupational exposure, herein collected no specific chemicals were identified or cited, some life habits could be traced to possible exposure to endocrine disruptors, but no higher risks seem to be recognized. Although some occupational risk factors have been identified, it is worth noting how the law to protect workers appropriately reduces possible exposure to these risk factors and, therefore, potential effects may not even be registered[40]. An example of this situation is evident if we consider exposure to radiation: the effect on reproductive health has been extensively documented, but for years there have been no investigations able to highlight the exposure of workers, since this specific exposure is strongly regulated. Therefore, even in the presence of a danger, the risk for the workers is reduced by the prevention and protection measures adopted.

The present investigation to identify possible causal occupational factors, responsible for the reproductive impairment, did not reveal specific contexts of increased risk. The stratification of the biological data in quartiles and a further distribution according to the various tasks, and the length of service, did not produce statistically significant differences (test χ^2 p=0.445 for volume, p=0.744

for t sperm concentration, p=0.917 for spermatozoa motility). Overall, the study did not confirm some data in the literature. In particular, we didn't find job tasks/ activities that could be considered more involved in the etiology or progression of male hypofertility.

Elements of bias to be considered in the present study, potentially influencing the outcomes, are related to:

• The method of data collection: information from the self-reported questionnaire are not objectively verifiable, therefore, if incomplete, incorrect, or false it would not be possible to recognize and eliminate them;

• Occupational exposure to risk factors: this element is collected from the declaration of the individual subject, but it was not possible to conduct inspections in each workplace to understand the real possibilities/probabilities of exposure to specific risks (even if in the same sector, the conditions of exposure may differ);

• The grouping of duties: the statistical processing necessarily requires a grouping of the declared work activities into "homogeneous" groups, that have been made taking into account the possibility of specific risk. Such a grouping obviously represents a procedural choice that could have some inaccuracies linked to incorrect or incomplete descriptions of the work activities in the questionnaire.

Certainly, the possible elements of bias that may be present in the study must be taken into account, but the homogeneous and numerically consistent selection of cases and control groups and the evaluation of the possible confounding factors should have contained the possible issues. This case/control investigation did not enable to confirm some published data[30]. In particular, with respect to the reproductive health risks associated with occupational activities such as those conducted at the computer, no higher risk index emerged compared to the controls; also in other contexts, no greater risk emerged. In addition, the sub-cohort of night workers, while showing higher values than the remaining cohort in the comparison of the parameters of seminal fluid, did not show a statistically significant difference as to allow us to hypothesize a greater involvement of this type of exposure in the onset of male infertility. Although the risk for male reproductive health due to exposure to specific agents is scientifically documented, it must be considered that the real conditions in workplaces require an accurate assessment, as the regulations for the protection of workers is hinged on the elimination or, where this is not possible, on the reduction of exposure and the prevention of risk. This element, which has been consolidated for decades, results in increasingly safe workplaces, with limited potential exposure risks.

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Ethical statement:
The study was approved by the Ethics Committee of the IRCCS San Raffaele Scientific Institute in Milan (identification code 73/INT/2017) and therefore it was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons involved gave their informant consent prior to their inclusion in the study.

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