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Lifestyle and Environmental Factors Effect on male infertility—An evidence-based Review

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ABSTRACT

Human semen is the end result of a sophisticated biological process hormonally regulated, produced by highly specialized cellular lines that differentiate in embryo but initiate division at puberty and will continue dividing throughout the entire life span of the individual in cycles of 72 days. Semen is a sensitive indicator of environmental, occupational and lifestyle exposures that may be altered by direct toxic effects and hormonal disruption. Damage may happen along the entire human life. However, while some exposures may produce reversible changes, others, especially damage to germinal cells in uterus or prepubertally may result in permanent sequelae. We review the main factors that affect human male fertility and their possible influence in current human reproduction. Some lifestyles, xenoestrogens, heavy metals and volatile organic compounds are already known to compromise reproductive male function. Nonetheless, many questions remain and we still know little about the effect of many other factors on male fertility.

INTRODUCTION

There is mounting evidence that human semen quality and fecundity have been declining during the last decades, at least in large areas of USA and Europe.\textsuperscript{1-10} However, those changes may have not taken place homogeneously.\textsuperscript{11,12} Geographical variations in semen quality support the idea that local specific factors present in some areas but not in others may be responsible for the decline in semen quality.\textsuperscript{13-16} Environmental pollutants, occupational exposures and lifestyle have been explored as possible contributors to those changes.\textsuperscript{17,18} Malfunction of the male reproductive system seems to be a good sensitive marker of environmental hazards\textsuperscript{19} (Figure 10.1).

In this article we review the current evidence on the association between the main occupational and lifestyles exposures and male infertility.
LIFESTYLE FACTORS

Special attention has been devoted in the scientific literature to factors that are well established as health risks, like smoking, alcohol and obesity. Other factors that have also being considered in the literature are drug use, genital heat stress, psychological stress and use of cellular phones, although they have received much less attention and there is less conclusive evidence on their impact on semen quality and male fertility.

Smoking

Cigarette smoke is a known somatic carcinogen and cell mutagen. There is also considerable evidence that smoking adversely affect male reproductive health. The impact of cigarette smoking on male fertility has been a highly controversial issue. Some studies did not find association between smoking and sperm quality\textsuperscript{20} or sperm DNA damage\textsuperscript{21} while others only found effect on sperm volume.\textsuperscript{22} However, methodological issues especially the complexity in adjusting for confounding factors may underlie some of these negative findings. Overwhelmingly, it is now clear that smoking has a
harmful effect on human male fertility. Tobacco effects can be observed at both, microscopic and molecular levels. Microscopically there is an effect on the sperm concentration, motility and morphology. At the molecular level there is increased risk of sperm aneuploidy, higher levels of seminal oxidative stress, alteration of sperm plasma membrane phospholipids asymmetry and sperm DNA fragmentation. Furthermore, maternal smoking during pregnancy may have an adverse and irreversible effect on semen quality in male descendants besides a higher risk of birth defects and childhood cancers in the offspring.

**Alcohol**

Alcoholism has been long associated with reproductive health disturbances such as impotence or testicular atrophy. Spermatogenesis seems to deteriorate progressively with increasing levels of alcohol intake. Chronic alcohol consumption has a detrimental effect on male reproductive hormones and on semen quality. A case-control study conducted in Japan showed that alcohol intake was significantly more common in infertile men than in controls. Alcohol exposures induce reduction of sperm motility and morphology and the response is dose-related. Moreover, there is a higher risk for XY sperm aneuploidy in alcohol drinkers compared to nondrinkers (RR = 1.38; 95% CI: 1.2-1.6). However, we do not know whether all alcoholic beverages have similar adverse effects on semen quality, nor whether there is a safe threshold for alcohol intake. An additional matter of concern is the possible synergistic effect of concurrent toxic habits on male reproduction. A synergistic effect of alcohol and smoking consumption on sperm parameters has been already described, but further research is needed to explore other associations with other lifestyle and occupational or environmental exposures.

**Obesity**

A common observation in the Western world is the increased average body mass index (BMI) in the general population that has resulted in an increased prevalence of obesity. Several studies have associated lower WHO semen parameters with obesity. In a follow up study in couples enrolled in the Agricultural Health Study in USA, Sallmén et al found, after adjustment for potential confounders, that male BMI was associated with infertility (defined as no pregnancy after 12 months of unprotected intercourse). They found a dose-response relationship between infertility and male BMI and that association was similar for older or younger men. Other authors have found that semen parameters (mainly sperm counts, motility or sperm DNA integrity) and/or reproductive hormones (testosterone, inhibin B, estradiol) are affected in men with BMIs above or below normal levels.
Maternal BMI may also have an effect on the future semen parameters of the male offspring, although the issue is far from being elucidated. In a follow-up study Ramlau-Hansen et al. found an inverse dose response between maternal BMI and son’s Inhibin B hormone. Besides, point estimates for sperm concentration, semen volume, percent motile sperm, testosterone and FSH suggested impaired semen quality in sons of overweight mothers, though the values did not reach statistical significance. The study may not have had enough power to detect real differences and the evidence remains inconclusive.

Recreational Drug Use

There are very few articles exploring the effect of recreational use of cocaine or cannabis, on semen quality and the male reproductive system, and our knowledge is still very preliminary. In 1990, Bracken et al.57 assessed the association of cocaine use with sperm concentration, motility, and morphology. After adjustment for potential confounders, cocaine use for five or more years was more common in men with low sperm motility, low concentration or large proportion of abnormal forms; while cocaine use within the previous 2 years was twice more frequent in men with oligozoospermia. Authors concluded that given the high prevalence of cocaine use in their male population, the history of cocaine use should be ascertained during diagnostic interviews. Whan et al.58 investigated the effects of delta-9-tetrahydrocannabinol (Delta-9-THC) on human sperm function in vitro showing reduced sperm progressive motility and acrosome reaction. Recently, Badawy et al.59 investigated the effects of Delta-9-and Delta-8-THC on sperm mitochondrial O₂ consumption (respiration) showing that this compounds are potent inhibitors of mitochondrial O₂ consumption in human sperm. Overall, these studies emphasize the potential adverse effects of recreational drugs on male fertility although clearly more observational studies are needed.

Genital Heat Stress

Normal sperm production depends on an optimal testicular temperature maintained below body temperature (typically between 34-35°C). Several experimental studies have shown that heat exposures may reduce semen quality. In male llamas (Lama glama) moderate increases in temperature alters spermatogenesis and all sperm parameters, while showing in histological analysis a higher destruction of tubules and a lower spermatogonial proliferation rate. In humans, occupational activities that require sedentary postures increase scrotal temperature. In observational studies it has been found that individuals involved in activities that increase
scrotal temperature have poor sperm morphology.\textsuperscript{68} Other activities like seating over a heated floor\textsuperscript{69} or recreational exposures to wet heat (jacuzzi or hot baths) also result in impaired semen quality.\textsuperscript{70} However, these effects may be reversible once the exposure to heat is ended.

It has also been studied whether the type of underwear used increases scrotal temperature. Jung et al\textsuperscript{71} found that scrotal temperature in volunteers wearing wool trousers and shirts fitting to body size were significantly higher for tight versus loose fitting. However, whether that temperature increase results in reduced semen quality remains to be studied. Finally, nocturnal scrotal cooling in infertile men with a history of testicular maldescent and oligozoospermia seems to have a positive effect in improving semen quality after 8 weeks, suggesting that nocturnal scrotal cooling might be a therapeutic option in some patients.\textsuperscript{72}

**Psychological Stress**

The impact of male psychological stress on semen quality is an area of great interest in which further research is needed, especially population based studies. At molecular level, the mechanisms of stress-related semen quality alterations have not been fully elucidated. Eskiocak et al\textsuperscript{73} showed that some seminal antioxidant contents (glutathione and free sulfhydryl) as well as motility and morphologically normal spermatozoa decrease in healthy subjects undergoing examination stress. There are a few prospective studies with general population showing that there is a small or nonexistent effect of a man’s daily life psychological stress on his semen quality.\textsuperscript{74,75} In couples attending fertility clinics, Zorn et al\textsuperscript{76} found a weak association between psychological factors and impaired semen quality. In males involved in IVF procedures the quality of the semen sample obtained the day when eggs retrieval was performed was significantly worse than the first sample analyzed in the same patients. The decline in semen quality in the second sample was attributed to the psychological stress involved in that clinical process.\textsuperscript{77,78}

**Cellular Telephone Use**

There has been an increasing concern about the possibility that the use of cell phones could affect our health and the male reproductive system. A few observational studies have shown that the prolonged use of cell phones may have negative effects on sperm parameters like sperm count, motility, viability, and normal morphology.\textsuperscript{79-81} The impact of the radiofrequency electromagnetic waves on semen quality still needs further investigation, including research in animal and in vitro models to better understand the mechanisms that are involved in this particular exposure.\textsuperscript{82-85}
Endocrine Disruptor Compounds (EDCs) like some polychlorinated biphenyls (PCBs), organochlorine compounds (pesticides), or phthalate esters (PEs), several heavy metals like lead or cadmium and several air pollutants (polycyclic aromatic hydrocarbons [PAHs], dioxins) have been shown to compromise reproductive male function (Table 10.1).

<table>
<thead>
<tr>
<th>Oral/food exposures</th>
<th>Organochlorine compounds (pesticides)</th>
<th>PCBs</th>
<th>Phthalates (plasticizers)</th>
<th>Heavy metals</th>
<th>Dioxins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air/inhalation exposures</td>
<td>Organochlorine compounds (pesticides)</td>
<td>PAHs</td>
<td>PCBs</td>
<td>Solvents</td>
<td>Heavy metals</td>
</tr>
<tr>
<td>Skin exposures</td>
<td>Phthalates (cosmetics)</td>
<td>PCBs</td>
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PAHs = polycyclic aromatic hydrocarbons, PCBs = polychlorinated biphenyls.

The alteration of the male reproductive system may result from gonadal endocrine disruption or by damaging the spermatogenesis process directly. Unsurprisingly, occupational activities involving exposures to some of those specific chemicals and toxins are associated with infertility. But, although there is a growing body of literature relating the effect of specific substances on semen quality, the relationship between environmental chemical exposures and male infertility is not always available. Several studies have explored compared men’s semen parameters and occupational exposures in male partners of infertile couples attending fertility clinics. In this way an association has been found between welding and reduced semen quality (sperm count and motility). In other case-control studies infertile men had been more frequently exposed to organic solvents, electromagnetic fields (engineering technicians, etc.) and heavy metals than normozoospermic controls. Recently, studies have suggested that environmental toxins alter sperm DNA integrity. DNA fragmentation may be an excellent marker of exposure to reproductive toxicants and a diagnostic tool for potential male infertility.
Endocrine Disruptor Compounds (EDCs)

EDCs besides causing the “testicular dysgenesis syndrome” (TDS), disturb meiosis in developmental germinai cells. Sharpe and Skakkebæk have suggested that the male reproductive system is most vulnerable to estrogenic agents during the critical period of cell differentiation and organ development in fetal and neonatal life. In this period, the testes are structurally organized, establishing Sertoli cell and spermatogonia numbers to support spermatogenesis that will be initiated at puberty. Endogenous hormones have a vital role in fetal life and to ensure future fertility. The maintenance of tightly regulated estrogen levels is therefore essential for its completion. Exposure to the wrong hormones (male fetus exposed to female hormones) or inadequate amounts of these, could affect the reproductive system, by resulting in fertility problems in adulthood. Moreover, due to their chemical composition, EDCs are able to cross a blood-tissue barrier in the testis, suggesting that intratubular germ cells may also be directly exposed.

Dietary soy foods also have estrogenic activity and may affect semen quality. In animal models, genistein crosses the rat placenta and can reach significant levels in fetal brains. In a recent observational study after controlling for potential confounders, Chavarro et al found an inverse association between soy food intake and sperm concentration, that was more pronounced in the high end of the distribution (90th and 75th percentile of intake) and among overweight and obese men.

Another important source of EDCs are pesticides. Juhler et al investigated the hypothesis that farmers with high intake of organic grown commodities would have good semen quality due to their expected lower levels of pesticides exposures. When 40 groups of pesticides were analyzed independently no effect was found on semen quality. However, the analysis did not take into account the synergistic effect that they may have when combined on the reproductive system. A recent work published by the Nordic Cryptorchidism Study Group, studied the human association between maternal exposure to 27 groups of pesticides and cryptorchidism among male children. In a nested case-control study within a prospective birth cohort, researchers compared 62 milk samples from mothers of cryptorchid boys and 68 from mothers of healthy ones and no significant differences were found for any individual chemical. However, combined statistical analysis of the eight most abundant and persistent pesticides showed that pesticide levels in breast milk were significantly higher in boys with cryptorchidism. Consequently, it is being speculated that male reproductive anomalies (hypospadias, Cryptorchidism) and the global fall in sperm quality might be attributed to the marked increased of EDCs in our water and diet.
In a recent review about the sensitivity of the child to sex steroids and the possible impact of exogenous estrogens, Aksglaede et al. concluded that children before puberty are extremely sensitive to estradiol and may respond with increased growth and/or breast development even at serum levels below the current detection limits, and that those changes in hormone levels during fetal and prepubertal development may have severe (probably non reversible) effects in adult life. The authors concluded that, therefore, a cautionary approach should be taken in order to avoid unnecessary exposure of fetuses and children to exogenous sex steroids and endocrine disruptors, even at very low levels. That caution includes food intake, as possible adverse effects on human health may be expected by consumption of meat from hormone-treated animals.

A recent study published by Swan et al. suggests that maternal consumption of xenobiotics (anabolic steroids) from beef may damage testicular development in uterus in the offspring and adversely affect reproductive capacity of the males. Sons of “high beef consumers” (>7 beef meals/week) had sperm concentrations 24.3% lower than that of men whose mothers ate less beef. General population is exposed to many potential endocrine disruptors concurrently. Studies, both in vivo and in vitro, have shown that the action of estrogenic compounds is additive, but little is known about the possible synergistic or additive effects of these compounds in humans.

**Heavy Metals**

Exposure to metals (mainly lead and cadmium) has been long associated with low sperm motility and density, increased morphological anomalies and male infertility. Males employed in metal industries had a decreased fertility when compared with other workers as shown by a delayed pregnancy and reduced semen quality. Akinloye et al. analyzed the serum and seminal plasma concentrations of cadmium (Cd) in 60 infertile males and 40 normozoospermic subjects. Seminal plasma levels of Cd were significantly higher than serum levels in all subjects. A statistically significant inverse correlation was observed between serum Cd levels and all biophysical semen parameters except sperm volume.

Naha et al. studied the blood and semen lead level concentration among battery and paint factory workers. Their results included oligozoosperma and increased percentage of sperm DNA haploids, suggesting a diminution of sperm cell production after occupational lead exposure. Additionally, there was a decreased sperm velocity, reduced forward progressive motility with high stationary motile spermatozoa, suggesting retarded sperm activity among the exposed workers. Finally, there is also increased
incidence of teratozoospermia associated with high blood and semen lead levels.

In another study that included 98 subjects with light to moderate occupational exposure to lead (Pb) and 51 with no occupational exposure Telisman et al concluded that even moderate exposures to Pb (Blood Pb < 400 µg/L) and cadmium (Cd) (Blood Cd < 10 µg/L) significantly reduced human semen quality without conclusive evidence of a parallel impairment of the male reproductive endocrine function.146

Moreover, other reports have also found that blood lead concentration in the general population is negatively correlated with semen quality.94, 145, 146 Recently Telisman et al147 reported reproductive toxicity of low-level lead exposure in men with no occupational exposure to metals. In this study, after adjustment, a significant association was found between blood lead (BPb) and reproductive parameters, such as immature sperm concentration, percentages of pathologic sperm, wide sperm, round and short sperm, serum levels of testosterone and estradiol, and a decrease in seminal plasma zinc and in serum prolactin (P < 0.05). These reproductive effects were observed at low-level lead exposures (median BPb 49 µg/L, range 11-149 µg/L in the 240 subjects) that are similar to those of the general population worldwide. However, other articles have been less conclusive in finding adverse effects of lead or cadmium exposure on semen quality or decreased fertility.148-151 With regards to other possible metals affecting fertility; recently, Meeker et al152 assessed relationships between environmental exposure to multiple metals (arsenic, cadmium, chromium, copper, lead, manganese, mercury, molybdenum, selenium and zinc) and human semen quality. The associations involving molybdenum were the most consistent. They found a dose-dependent relationship between molybdenum and declining sperm concentration and morphology in adjusted analysis. These findings are consistent with animal data but more mechanistic studies are needed.

**Occupational and Environmental Pollutants**

Several solvents may affect human seminal quality17,107 proportionally to the amount and time of exposure.108,109 Semen quality in workers exposed occupationally to hydrocarbons like toluene, benzene and xylene present anomalies in viscosity, liquefaction capacity, sperm count, sperm motility, and the proportion of sperm with normal morphology compared with unexposed males.153-155 An association has also been observed between expositions to styrene in boat building factories workers,156 PAH in coke-oven workers,157 and episodic air pollution with an increasing fragmentation of the DNA sperm,158 as well as altered WHO seminal
parameters in young men.\textsuperscript{158,159} Dioxin exposure is also associated with impaired male fertility. Recently, Mocarelli et al\textsuperscript{96} investigated the reproductive hormones and sperm quality in males that were exposed to the accidental dioxin leak in Seveso, Italy, in 1976. Three groups of males exposed at infancy/prepuberty,puberty, and adulthood, respectively were compared with 184 healthy males. Men exposed in infancy/prepuberty (mean age at exposure: 6.2 years) showed reductions in sperm concentration, progressive motility, total motile sperm count, estradiol and an increase in follicle-stimulating hormone. The other two groups with later exposures (mean age at exposure 13.2 years and 21.5 years of age, respectively) did not have deleterious effects on semen parameters. The study suggests that exposure to dioxins in infancy may permanently reduce semen quality even at relatively low concentrations.

**CONCLUSION**

There is a growing body of literature showing that a wide variety of substances adversely affects semen quality, and although evidence is not always there, may impair human fertility. However, our knowledge is still fairly limited.

First of all, because although our knowledge is growing on the single effect of individual products, the reality is more complex, there are no single exposures, and there are very few studies addressing the consequences of simultaneous complex exposures to compounds such as food additives, toxicants, contaminants, outdoor and indoor air pollutants, endocrine disruptors and hazardous substances on semen quality and male infertility. A clear side effect of that lack of information is that we may be underestimating the consequences of exposing the population to a wide variety of products because we are missing the larger broader picture of complex exposures.

Secondly, study design does not always facilitate the interpretation of the results. In order to be useful it is necessary to design studies in a way that control of confounding factors is possible, including all known variables that are known to affect semen quality, such as lifestyle, occupational and environmental exposures, and, it would be desirable, along the main developmental stages of the patient’s life span.

Finally, in order to better characterize risk assessment, it might be useful to revise the ways to better report damage to sperm quality and to quantify the amount of toxic exposures on similar male reproductive endpoints.

**REFERENCES**


LIFESTYLE AND ENVIRONMENTAL FACTORS EFFECT ON MALE


