Lifestyle factors and male infertility: an evidence-based review

Jaime Mendiola¹, Alberto M. Torres-Cantero¹², Ashok Agarwal³

¹Division of Preventive Medicine and Public Health, School of Medicine, University of Murcia, Espinardo (Murcia), Spain
²Center for Reproductive Medicine, Glickman Urological and Kidney Institute and OB-GYN and Women’s Health Institute, Cleveland Clinic, Cleveland, Ohio, USA

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Abstract

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

Key words: semen quality, food intake, heavy metals, occupational exposures, xenoestrogens.

Introduction

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

In this article we review the current evidence on the association between the main occupational and lifestyle exposures and male infertility.
Lifestyle factors

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

Smoking

Cigarette smoke is a known somatic carcinogen and cell mutagen. Considerable evidence also exists that smoking adversely affect male reproductive health, although the impact of cigarette smoking on male fertility has been a highly controversial issue. Some early studies did not find an association between smoking and sperm quality [20] or sperm DNA damage [21] while another only found effects on sperm volume [22]. However, methodological issues, especially the complexity in adjusting for confounding factors, may underlie some of these negative findings.

The harmful effects of cigarette smoking on human male fertility are now clear [23], Tobacco effects can be observed at both microscopic and molecular levels. Microscopically, sperm concentration, motility and morphology are affected [24-31]. At the molecular level, an increased risk of sperm aneuploidy [32, 33], higher levels of

Figure 1. Pathways showing the relationship between occupational and lifestyle exposure factors and male infertility injury
spermatozoa morphology, and the response is dose-related [44]. Moreover, the risk for XY sperm aneuploidy is greater in alcohol drinkers compared to nondrinkers (RR=1.38, 95% CI: 1.2-1.6) [33]. However, whether all alcoholic beverages have similar adverse effects on semen quality, or whether there is a safe threshold for alcohol intake is unknown.

An additional 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 described, but further research is needed to explore other associations with other lifestyle and occupational or environmental exposures [45, 46].

**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 World Health Organization (WHO) semen parameters with obesity [47, 48]. In a follow-up study of couples enrolled in the Agricultural Health Study in the United States, 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) [49]. 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 [50-55].

Maternal BMI also may 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 the son’s inhibin B hormone [56]. In addition, point estimates of sperm concentration, semen volume, percent motile sperm, testosterone and FSH suggested impaired semen quality in sons of overweight mothers, although the values did not reach statistical significance. The study may have lacked sufficient power to detect real differences, and the evidence remains inconclusive.

**Recreational drug use**

Very few articles explore the effects of recreational cocaine or cannabis use on semen quality and the male reproductive system, and our knowledge is still very preliminary. In 1990, Bracken et al. assessed the association of cocaine use with sperm concentration, motility and morphology [57]. 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 two years was twice as 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. investigated the effects of delta-9-tetrahydrocannabinol (Delta [9]-THC) on human sperm function in vitro, showing reduced sperm progressive motility and acrosome reaction [58]. Recently, Badawy et al. investigated the effects of Delta [9]-THC and Delta [8]-THC on sperm mitochondrial O2 consumption (respiration), showing that these compounds are potent inhibitors of mitochondrial O2 consumption in human sperm [59]. Overall, these studies emphasize the potential adverse effects of recreational drugs on male fertility although 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) [60]. Several experimental studies have shown that heat exposure may reduce semen quality [61-63]. In male llamas (Lama glama) moderate increases in temperature alter spermatogenesis and all sperm parameters, while showing on histological analysis a higher destruction of tubules and a lower spermatogonial proliferation rate [64]. In humans, occupational activities that require sedentary postures increase scrotal temperature [65-67]. In observational studies, individuals involved in activities that increase scrotal temperature have
been found to have poor sperm morphology [68]. Other activities such as sitting over a heated floor [69] or recreational exposure to wet heat (Jacuzzi or hot baths) also result in impaired semen quality [70]. However, these effects may be reversible once the exposure to heat is ended.

The association between type of underwear and increased scrotal temperature also has been studied. Jung et al. found that scrotal temperature in volunteers wearing wool trousers and shirts fitted to body size was significantly higher for tight vs. loose-fitting clothing [71]. 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 on improving semen quality after eight weeks, suggesting that nocturnal scrotal cooling might be a therapeutic option in some patients [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 the molecular level, the mechanisms of stress-related semen quality alterations have not been fully elucidated. Eskiocak et al. showed that some seminal antioxidant contents (glutathione and free sulphydryl), as well as motility and morphologically normal spermatozoa decrease in healthy subjects undergoing examination stress [73]. A few prospective studies in the general population have shown a small or nonexistent effect of the psychological stress of daily life on semen quality [74, 75]. In couples attending fertility clinics, Zorn et al. found a weak association between psychological factors and impaired semen quality [76]. In males involved in IVF procedures, the quality of the semen sample obtained on the day of egg retrieval was significantly worse than the quality of 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 [77, 78].

**Cellular telephone use**

Concerns are escalating about the possible adverse effects of cell phones on human health and the male reproductive system. A few observational studies have shown that prolonged use of cell phones may have negative effects on sperm parameters like sperm count, motility, viability and normal morphology [79-81]. The impact of 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 [82-85].

**Occupational and environmental factors**

Endocrine disruptor compounds (EDCs) such as some polychlorinated biphenyls (PCBs) [86-88], organochlorine compounds (pesticides) [89, 90] or phthalate esters (PEs) [91], several heavy metals such as lead and cadmium [92-94] and several air pollutants [polycyclic aromatic hydrocarbons (PAHs), dioxins] [95, 96] have been shown to compromise reproductive male function (Table I).

Alteration of the male reproductive system may result from gonadal endocrine disruption [97, 98] or by direct damage to the spermatogenesis process (Figure 1) [92, 99]. Not surprisingly, occupational activities involving exposure to some of those specific chemicals and toxins are associated with infertility [93, 99-109]. Although literature relating the effect of specific substances on semen quality is expanding, the relationship between environmental chemical exposure and male infertility is not always available. Several studies have compared semen parameters and occupational exposure in male partners of infertile couples attending fertility clinics [93, 101, 110, 111]. An association has been found between welding and reduced semen quality (sperm count and motility) [93, 110]. In other case-control studies, infertile men had more frequent exposure to organic solvents [108, 109, 111], electromagnetic fields (engineering technicians, etc.) and heavy metals than did normozoospermic controls [93, 109, 112]. Recently, studies have suggested that environmental toxins alter sperm DNA integrity [113, 114]. DNA fragmentation may be an excellent marker of exposure to reproductive toxicants and a diagnostic tool for potential male infertility [115-117].

**Endocrine disruptor compounds**

Endocrine disruptor compounds (EDCs) cause testicular dysgenesis syndrome (TDS) and disturb

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<th>Oral/food exposures</th>
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<th>PCBs</th>
<th>Phthalates (plasticizers)</th>
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<td>Air/inhalation exposures</td>
<td>Organochlorine compounds (pesticides)</td>
<td>PAHs</td>
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meiosis in developmental germinal cells [6, 118]. Sharpe and Skakkebaek 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 [118]. 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 ensuring future fertility. The maintenance of tightly regulated estrogen levels is therefore essential for its completion [97, 118]. Exposure to the wrong hormones (male fetus exposed to female hormones) or inadequate amounts of the correct hormones could affect the reproductive system by resulting in fertility problems in adulthood [119, 120]. Moreover, due to their chemical composition, EDSs are able to cross a blood-tissue barrier in the testis, suggesting that intratubular germ cells also may be directly exposed [121, 122].

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 [121]. In a recent observational study, Chavarro et al. after controlling for potential confounders 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 [123].

Pesticides are another important source of EDCs. Juhler et al. investigated the hypothesis that farmers with high intakes of organically grown commodities would have good semen quality due to their expected lower levels of pesticide exposure [124]. An independent analysis of 40 groups of pesticides found no effects on semen quality. However, the analysis did not take into account the synergistic effect that pesticides in combination may exert on the reproductive system [125, 126].

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. 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 [127]. This finding has given rise to speculation that male reproductive anomalies (hypospadias, cryptorchidism) [128] and the global fall in sperm quality [1] might be attributed to the marked increased of EDCs in our water and diet [129].

In a recent review about the sensitivity of children to sex steroids and the possible impact of exogenous estrogens, Aksglaede et al. concluded that children are extremely sensitive to estradiol before puberty 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 nonreversible) effects in adult life [130]. The authors concluded, therefore, that a cautionary approach should be taken 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 result from consumption of meat from hormone-treated animals [131].

A recent study published by Swan et al. suggests that maternal consumption of xenobiotics (anabolic steroids) from beef may damage testicular development in utero in the offspring and adversely affect reproductive capacity of the males [132]. Sons of “high beef consumers” (>7 beef meals/week) had sperm concentrations 24.3% lower than those found in sons whose mothers ate less beef [132, 133]. The 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 [134, 135], but little is known about the possible synergistic or additive effects of these compounds in humans [136].

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 [95, 137]. Males employed in metal industries had a decreased fertility when compared with other workers as shown by delayed pregnancy and reduced semen quality [92, 115, 138-144]. Akinloye et al. analyzed the serum and seminal plasma concentrations of cadmium (Cd) in 60 infertile males and 40 normozoospermic subjects [143]. Seminal plasma Cd levels 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 [144]. Their results included oligozoospermia and increased percentage of sperm DNA haploids, suggesting a diminution of sperm cell production after occupational lead exposure. Additionally, sperm
velocity and forward progressive motility were reduced with a high percentage of stationary motile spermatozoa, suggesting retarded sperm activity among the exposed workers. Finally, an increased incidence of teratozoospermia is associated with high blood and semen lead levels.

Telisman et al. conducted a study that compared semen quality of 98 subjects with light to moderate occupational exposure to lead (Pb) to that of 51 men with no occupational exposure. They concluded that even moderate exposures to Pb (blood Pb <400 µg/l) and cadmium (blood Cd <10 µg/l) significantly reduced human semen quality without conclusive evidence of a parallel impairment of the male reproductive endocrine function [145].

Moreover, other reports also have found that blood lead concentration in the general population is negatively correlated with semen quality [94, 145, 146]. Recently Telisman et al. reported reproductive toxicity of low-level lead exposure in men with no occupational exposure to metals [147]. In this study, a significant association was found between blood lead (BPb) and reproductive parameters such as immature sperm concentration, percentage of pathologic sperm, wide sperm, round and short sperm, serum levels of testosterone and estradiol, and a decrease in seminal plasma zinc and 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 al. [152] 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 analyses. These findings are consistent with animal data, but more mechanistic studies are needed.

Occupational and environmental pollutants

Several solvents may affect human seminal quality [17, 107] proportional to the amount and duration 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 also has been observed between exposure to styrene in boat-building factory 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 [159]. Dioxin exposure also is associated with impaired male fertility.

Recently, Mocarelli et al. [96] investigated the reproductive hormones and sperm quality in males 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 and estradiol and an increase in FSH. The other two groups with later exposure (mean age at exposure 13.2 years and 21.5 years of age, respectively) did not have decreased semen parameters. The study suggests that exposure to dioxins in infancy, even at relatively low concentrations, may permanently reduce semen quality.

Conclusions

A growing body of literature shows that a wide variety of substances adversely affects semen quality and may impair human fertility. However, the evidence for adverse effects on fertility is incomplete, and our knowledge is still fairly limited.

Although our knowledge is expanding related to the single effect of individual products, the reality is more complex. Single exposure does not occur, and very few studies address the consequences for semen quality and male infertility of simultaneous, complex exposure to compounds such as food additives, toxicants, contaminants, outdoor and indoor air pollutants, endocrine disruptors and hazardous substances. 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.

Finally, study design does not always facilitate the interpretation of the results. To be useful, studies must be designed in a way that confounding factors can be controlled. Ideally this would include all variables that are known to affect semen quality such as lifestyle, occupational and environmental exposures, and exposure would be tracked along the main developmental stages of the male’s life span.
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