

Occupational and Lifestyle Exposures on Male Infertility: A Mini Review

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Abstract: Human semen quality may be declining due to environmental pollutants, occupational exposures or changes in lifestyle. Nonetheless, we still know little about the impact of those factors on male fertility. Some heavy metals, volatile organic compounds or xenoestrogens may compromise reproductive male function. This process could take place along the human life cycle and not only in certain stages of development. We review the main factors that affect human male fertility and their possible influence in current human reproduction.

Keywords: Male infertility, heavy metals, xenoestrogens, occupational exposures.

INTRODUCTION

Several studies have suggested that human semen quality and fecundity is declining [1-13]. However, changes in semen quality may not develop uniformly [14-16]. Geographical differences in semen quality support the idea that local factors present in some areas but not in other may be influencing declines in semen quality [17-20]. Environmental pollutants, occupational exposures and lifestyle have been explored as possible contributors to those changes [21-23].

Volatile organic compounds (VOCs) [24], certain halogenated compounds [25], several heavy metals [26-28] or xenoestrogens like some polychlorinated biphenyls (PCBs) [29-31], organochlorine compounds (pesticides) [32-33] and phthalate esters (PEs) [34] may compromise reproductive male function.

Chemicals could adversely affect male reproductive system by, either disrupting the gonadal endocrine axis [9, 35] or, the spermatogenesis process (Fig. 1). Any of those mechanisms would result in poor semen quality [26, 36, 37]. Recent studies suggest that sperm DNA integrity may be altered by environmental exposure to some toxic chemicals [38, 39]. DNA fragmentation may be an excellent marker for exposure to potential reproductive toxicants and a diagnostic tool for male infertility [40, 41].

Occupational activities involving exposure to specific chemicals or expositions to toxicants may impair male reproductive health and cause infertility in humans [27, 37, 42-58].

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 more contradictory and less well documented. Only few studies have explored differences between infertile males attending fertility clinics and controls [27, 45, 50, 59-61] and findings are inconclusive. While some studies found differences between fertile and infertile males in their occupational activities (such as, welding, being a white collar professional or exposure to metals), their exposure to chemicals (like solvents) or to physical agents (like electromagnetic fields or heat), other studies did not find significant differences to the same or similar exposures.

In this work we review the current evidence on the association between occupational and lifestyles exposures and male infertility.

METALS

Exposure to metals (mainly lead and cadmium) has been long associated with low sperm motility and density, increased morphological anomalies and male infertility [24, 62]. Males employed in metal industries had a decreased fertility when compared with other workers as shown by a delayed pregnancy and reduced semen quality [26, 36, 45, 63-69]. Akinloye *et al.* [68] 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 ($p < 0.001$). A statistically significant inverse correlation was observed between serum Cd levels and all biophysical semen parameters except sperm volume. The results of that study support previous findings concerning cadmium toxicity and male infertility. Naha *et al.* [69] studied the blood and semen

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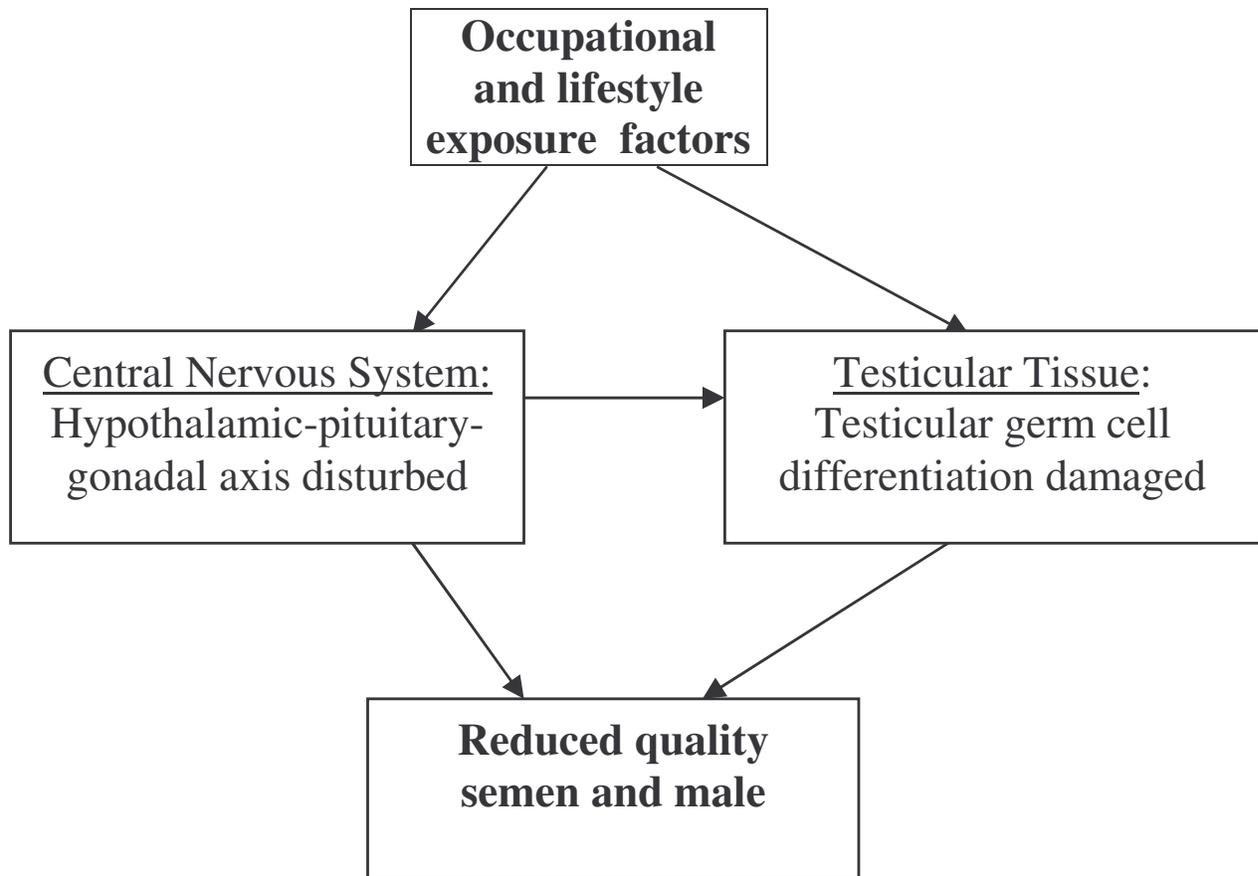


Fig. (1). Pathways showing the relationship between occupational and lifestyle exposure factors and male infertility affectionation.

lead level concentration among battery and paint factory workers. Their results included oligozoospermia, concomitant lowering of sperm protein and nucleic acid content and increased percentage of sperm DNA haploids ($P < 0.001$), suggesting a diminution of sperm cell production after occupational lead exposure. Additionally, there was a decreased sperm velocity, reduced gross and forward progressive motility with high stationary motile spermatozoa ($P < 0.001$) suggesting retarded sperm activity among the exposed workers. Finally, they also found increased incidence of teratozoospermia associated with high blood and semen lead levels ($P < 0.001$).

Other reports have shown a significantly negative correlation between blood lead concentration and semen quality [28, 70-72]. Benoff *et al.* [70] determined the relationships between seminal lead levels and acrosome status and artificial insemination cycle fecundity (AI f) in semen donors. Seminal plasma lead levels and AI f were strongly negatively correlated. It is been suggested that the measurement of seminal plasma lead and P-stimulated acrosome loss, among other determinations, may provide a useful prognosis on the fertility status of potential donors as well as on infertile male patients. Telisman *et al.* [71] measured in 149 healthy industrial workers aged between 20-43 years semen quality and reproductive endocrine function. The group included 98 subjects with light to moderate occupational exposure to lead (Pb) and 51 with no occupational exposure. The overall study results indicated that even moderate exposures

to Pb (Blood Pb $< 400 \mu\text{g/L}$) and cadmium (Cd) (Blood Cd $< 10 \mu\text{g/L}$) significantly reduced human semen quality without conclusive evidence of a parallel impairment of the male reproductive endocrine function. Eibensteiner *et al.* [72] examined lead exposure ($n = 43$) and semen quality ($n = 18$) among traffic police officers in Arequipa (Peru) where leaded gasoline is used. Mean blood lead (PbB) was $48.5 \mu\text{g/dL}$. PbB was associated with declines in several semen parameters (sperm morphology, concentration and total number of sperm). However, only sperm motility and viability differed significantly between the $\leq 40 \mu\text{g/dL}$ and $> 40 \mu\text{g/dL}$ categories and decreased with increasing PbB in a simple linear regression. Traffic police are a target group for excessive ambient lead exposure and the results of this study support earlier findings on the male reproductive toxicity of lead. Nonetheless, as authors point out, results should be taken cautiously since numbers were small and they were unable to control in the analyses for all potential confounders due to incomplete data.

Recently, Telisman *et al.* [73] reported reproductive toxicity of low-level lead exposure in men with no occupational exposure to metals. In this study semen quality, seminal plasma indicators of secretory function of the prostate and seminal vesicles, sex hormones in serum, and biomarkers of lead, cadmium, copper, zinc, and selenium body burden were measured in 240 Croatian men 19-52 years of age. After adjustment in multiple regression a significant associations was found between blood lead (BPb) and reproductive pa-

rameters, 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 $\mu\text{g/L}$, range 11-149 $\mu\text{g/L}$ in the 240 subjects) that are similar to those of the general population worldwide. Other articles, however, are less conclusive and show no apparent adverse effects of lead or cadmium exposure on semen quality or decreased fertility [74-76].

VOLATILE ORGANIC COMPOUNDS

Semen quality in workers exposed occupationally to hydrocarbons like toluene, benzene and xylene (BTX) present anomalies, including alterations in viscosity, liquefaction capacity, sperm count, sperm motility, and the proportion of sperm with normal morphology compared with unexposed males [77-79]. Similarly, exposure to solvents may affect human seminal quality [22, 57] proportionally with the range of exposure [61].

XENOESTROGENS

Xenoestrogens have also been identified as endocrine disruptors, that not only might cause the "testicular dysgenesis syndrome" (TDS), but also disturb meiosis in developmental germinal cells [9, 80]. Sharpe and Skakkebaek [80] 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. The maintenance of tightly regulated estrogen levels is essential for its completion.

Analysis of maternal and fetal biological fluids have shown that xeno and phytoestrogens cross the placenta barrier into fetal circulation and that they can bioaccumulate in fetal organs, such as the brain [81]. In their study, Foster *et al.* (2000) [81] performed analysis on amniotic fluid samples ($n=53$) from women ($n=51$) undergoing routine amniocentesis. Analyses included common PCB congeners, the DDT metabolites p,p'-DDE, and o,p'-DDE as well as the pesticides: hexachlorobenzene (HCB); and the three isomers of hexachlorocyclohexane (α , β and γ -HCH). The limit of quantitation (LOQ) for PCBs was 0.01 ng/ml and for the other organochlorines contaminants was 0.1 ng/ml. The contaminants α -HCH with a mean (\pm SD) concentration of 0.15 ± 0.06 (ng/ml) and p,p'-DDE with a mean (\pm SD) concentration of 0.21 ± 0.18 ng/ml were detected in the amniotic fluid. PCB specific congeners were detected with a much lower frequency and levels were in the range of the LOQ. Overall one in three amniotic fluid samples tested positive for at least one environmental contaminant. Therefore, the authors conclude that approximately one in three fetuses in the Los Angeles area is exposed in uterus to endocrine environmental contaminant modulators. The consequences of that exposure remain unknown at this time.

It has also been described that these compounds cross a blood-tissue barrier similar to that of the testis, suggesting that intratubular germ cells might be exposed [82,83]. Genistein, the principal soy isoflavone, has estrogenic activity and

is widely consumed. Doerge *et al.* (2000) [82] measured placental transfer of genistein in rats as a possible route of developmental exposure. Pregnant Sprague-Dawley rats were administered genistein orally. Concentrations of genistein aglycone and conjugates were measured in maternal and offspring serum and brain. Although fetal or neonatal serum concentrations of total genistein were approximately 20-fold lower than maternal serum concentrations, the biologically active genistein aglycone concentration was only 5-fold lower, and fetal brains contained predominately genistein aglycone at levels similar to the maternal brain. These studies show that genistein aglycone crosses the rat placenta and can reach significant levels in fetal brains.

Juhler *et al.* [84] investigated the hypothesis that farmers that have a high intake of organic grown commodities would have a high semen quality due to their expected lower levels of dietary pesticides intake. In their conclusions authors reported that estimated dietary intake of 40 groups of pesticides did not seem to entail a risk of impaired semen quality, but as they recommended, cautions should be taken in trying to generalize these negative results to populations with higher dietary exposure levels or intakes of different groups of pesticides.

Endogenous hormones have a vital role in fetal life and ensure future fertility. Exposure to the wrong hormones (female fetus exposed to male hormones) or inadequate amounts of these, could affect the reproductive system, and genitalia may not develop correctly resulting in fertility problems in adulthood [85, 86].

Recently, Aksglaede *et al.* [87] published a review about the sensitivity of the child to sex steroids and the possible impact of exogenous estrogens. Some of the conclusions were that children 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 effects in adult life. The authors concluded that 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 [88].

A recent study carried out by Swan *et al.* [89] suggests that maternal beef consumption, and possibly xenobiotics (anabolic steroids) in beef may alter testicular development in uterus and adversely affect reproductive capacity. Sperm concentration was inversely related to mother's weekly beef intake. In sons of "high consumers" (>7 beef meals/week), sperm concentration was 24.3% lower than that of men whose mothers ate less beef [89, 90].

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 [91, 92], but little is known about the possible synergistic or additive effects of these compounds in humans [93].

A recent work published by the Nordic Cryptorchidism Study Group, studied the human association between mater-

nal 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 [94].

A further recent change in the Western diet is the increased use of soy-based infant formula milk (SFM) for the increasing numbers of babies that are lactose-intolerant [83]. Infants on SFM have a phytoestrogen (a kind of xenoestrogen) intake per kg bodyweight 6-11 times higher than that seen in adults consuming a high phytoestrogen diet [95]. Plasma levels of phytoestrogen are a thousand fold greater than those of endogenous estradiol raising concerns about the effects of prolonged neonatal exposure to such high concentrations of estrogens and its potential disruption of male reproductive tract [96].

Consequently, it is being speculated that male reproductive anomalies (hypospadias, cryptorchidism) [97, 98] and the global fall in sperm counts [1] have both a causal link in the marked increased of phytoestrogens in our diet brought about by the western adoption of a fast food culture [99, 100].

Though, traditionally, estrogen were perceived as having a minor role in male reproduction, it is now clear that estrogens have a major role in male gonadal development, spermatogenesis and fertility [101]. Evidence coming from animal models [102] and human studies has shown that increasing levels of phytoestrogens intake can disrupt both the normal development [103] and the function of the male reproductive system [80]. However, we have found only one report in which adult males were given phytoestrogen supplements (isoflavone) and only for a short period of time (20 days) without finding an effect on semen quality [104].

Similarly, only a few references are found on observational studies relating semen quality and food intake. A poster communication to the American Society of Reproductive Medicine (ASRM) 62nd Annual Meeting in New Orleans 2006 found that the proportion of men with low intake of fruits and vegetables (<5 servings/day) was greater among infertile men than controls (83% vs 40%, $p=0.0036$). In that study men with the lowest intake of dietary antioxidants had the lowest sperm motility [105]. From the same group, Song *et al.* [106], in another communication described the beneficial effects of dietary intake of plant phytoestrogens on semen parameters and sperm DNA integrity in infertile men. They concluded that population based studies and basic research are both needed to confirm and clarify the mechanism of the effects of phytoestrogens on sperm physiology.

A recent oral communication presented at the ASRM 63rd Annual Meeting in Washington 2007 by Chavarro *et al.* [107], reported a cross-sectional study exploring the association of soy foods and soy isoflavones intake with semen quality parameters. They suggested that higher intake of these foods was associated with lower sperm concentration.

Therefore we concur that more research is needed to explore the influence and effect of environmental pollutants,

occupational and lifestyles characteristics on reproduction and fertility in males throughout the life cycle, from pre and peri-natal exposures to early infancy, childhood, puberty and adulthood. Ideally a prospective design would be more suitable to address the effect of possible exposures along each stage of development on male fertility.

Finally, there is an increasing awareness in the general population, as well as preliminary evidence, on the effect of simultaneous exposure to compounds such as food additives, toxicants, contaminants, outdoor and indoor air pollutants, endocrine disruptors such as pesticides or xenoestrogens and hazardous substances in the workplace. Therefore it is crucial to develop toxicity studies able to address complex mixtures of chemicals, both for hazard identification as well as for risk assessment of these chemical mixtures at present.

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Received: February 11, 2008

Revised: March 25, 2008

Accepted: March 25, 2008

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