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Environmental Toxins and Male Fertility

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Abstract

Purpose of Review Global industrialization has increased population exposure to environmental toxins. A global decline in sperm quality over the last few decades raises questions about the adverse impact of environmental toxins on male reproductive health.

Recent Findings Multiple animal- and human-based studies on exposure to environmental toxins suggest a negative impact on semen quality, in terms of sperm concentration, motility, and/or morphology. These toxins may exert estrogenic and/or anti-androgenic effects, which in turn alter the hypothalamic-pituitary-gonadal axis (HPGA), induce sperm DNA damage, or cause sperm epigenetic changes.

Summary This chapter will discuss the most recent literature about the most common environmental toxins and their impact on spermatogenesis and its consequences on male fertility. Understanding the presence and underlying mechanism of these toxins will help us preserve the integrity of the male reproduction system and formulate better regulations against their indiscriminate use.

Keywords Environment · Environmental toxins · Male infertility · Sperm · Endocrine disrupting chemicals · Thermotoxicity

Introduction

The clinical evaluation of the infertile male is comprised of a patient's history, physical exam, laboratory studies, and select diagnostic studies aiming to identify pathophysiology which adversely affects reproductive function. An infertile patient's reproductive potential is often linked to medical comorbidities, medication use, and past surgeries. Yet, with the infertile couple, we must also consider environmental factors as significant contributors.

For decades, greatly stimulated by public attention following the 1962 publication "Silent Spring," investigators studying human reproduction uncovered key contributors of infertility through environmental, occupational, and animal-based studies. Despite these efforts, a recent meta-analysis by Levine et al. identified a 50% decline in sperm counts of Western men over the last 40 years [1]. As spermatogenesis is more sensitive to environmental contaminants when compared to their female counterparts, this decline may be due to exposures to toxins from industrial, agricultural, and by-products of other technological advancements [2]. This chapter will summarize recent research on the effect of endocrine disrupting chemicals, pesticides, heavy metals, air pollution, hyperthermia, and other new technologies on male reproductive health.

Chemicals

Exposure to chemicals used in agriculture and other industries can greatly influence reproductive fitness. Farmers introduced the widespread use of pesticides to eradicate unwanted insects and increase agricultural yield. Similarly, manufacturers developed newer packaging material which was both more durable and less costly. The toxicology is diverse, ranging from direct effect on gonadal tissue to hormonal modulation. Exposure to some of these chemicals has been shown to render organisms infertile, or, in certain conditions, transfer pathology onto the next generation [2].

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Endocrine Disrupting Chemicals

Endocrine disrupting chemicals (EDCs) are a class of chemical compounds that interfere with any aspect of hormonal action, often exerting estrogen-like and/or anti-androgenic effects. These chemicals may disrupt normal hormonal stimulatory action, inhibitory action, or the elimination of hormones. This can result in the impairment of multiple developmental processes [3]. This diverse group of compounds can be classified into two categories: natural (introduced with food) or synthetic (often used as industrial solvents and their byproducts) [4]. Although environmental EDCs generally exist at low concentrations that may cause a negligible impact on general health, exposure to multiple EDCs could potentially behave synergistically and adversely affect reproductive health [5].

Management of infertility from EDC exposure requires an increased usage of medical resources. In the European Union, EDC infertility care costs nearly €15 billion annually [6]. There is no estimated cost of male infertility from EDC exposure in the USA. EDC exposure-related illness in general is very costly, with a total medical cost of $340 billion in the USA and is $217 billion in the European Union [7].

Polychlorinated Biphenyls

Polychlorinated biphenyls (PCBs) are industrial products previously used as dielectric and coolant fluids. Although PCB production and usage was outlawed decades ago in most countries, their chemical stability and bio-characteristics enabled them to remain a major global environmental problem [8]. PCBs act as xenoestrogens and are highly resistant to degradation. With such chemical stability, they were able to be distributed widely into the environment via air and water [4]. They have been detected all over the world and in many remote regions. PCBs are lipophilic and accumulate readily in fatty tissue, with a reduced clearance rate versus lean tissue. In turn, obese individuals accumulate PCBs significantly more when compared with lean subjects [9].

The true etiology behind the decreased seminal quality seen with PCB exposure has not been determined and remains an active area of research. Decreased sperm motility may be due to mitochondrial dysfunction from the loss of intracellular ATP, increased ROS generation, and general mitochondrial dysfunction [10]. Also, recent observational studies have suggested a correlation between the levels of PCBs and semen quality. Additional theories suggest an estrogenic, anti-estrogenic, anti-androgenic, or direct effect on spermatogenesis (given PCBs' potential ability to cross the blood-testis barrier) [11]. Peterson et al. identified a significant positive association between serum-PCB and hormonal levels including the testosterone/estradiol ratio, sex hormone binding globulin (SHBG), and follicle stimulating hormone (FSH) with no impact on semen quality variables [12]. Another study showed that environmental levels of PCBs decreased plasma testosterone, free testosterone, the free androgen index, and dihydrotestosterone (T/DHT) (which could be due to PCB-induced increase in 5α-reductase activity) [13].

When examining the mechanism behind PCB deleterious impact on male reproduction, most investigators employed animal models. Bovine spermatozoa subjected to PCB in an in vitro model revealed a dose-dependent association with worse motility, viability, and increased teratozoospermia [14]. Prenatal and lactation PCB exposure in a rat model alters testis histoarchitecture and changes Sertoli cell estrogen and androgen-related gene expression [15]. Prenatal and perinatal exposure to both PCB and certain phthalate metabolites (such as di 2-ethylhexyl phthalate (DEHP)) had a synergetic effect resulting in lower mouse testis weight and reduced seminiferous tubule diameter [16]. Furthermore, mouse Leydig cell PCB exposure increased reactive oxygen species production and interrupted the antioxidant system. In turn, this inhibited 3β-HSD and 17β-HSD enzyme activity resulting in impaired steroidogenesis, especially testosterone biosynthesis [17].

Aneuploidy, which may occur due to an error in meiosis during gametogenesis, may also be associated with exposure to PCBs. High exposure to both DDT and PCB significantly increased the rate of XX18, XY18, and total disomy in adult men [18]. In contrast, recently, Hsu et al. investigated sperm aneuploidy as the potential underlying mechanism of PCB-induced reproductive dysfunction. Despite elevated abnormal morphology with PCB exposure, there was no association between PCB exposure and rates of chromosomal aneuploidy [19].

Bisphenol A

Bisphenol A (BPA) is a high-production-volume chemical that is widely used in the manufacture of consumer products, including baby bottles, plastic containers, and dental sealants. BPA can be detected in a majority of the USA population and populations of many other countries. BPA exposure has been demonstrated through water, air, and dust [20]. The potential risk of BPA to human reproductive health is potentially significant and has led to tighter regulation of BPA usage. In vitro studies demonstrated that BPA exhibits estrogenic, anti-estrogenic (by competition with 17β-estradiol), and anti-androgenic effects [21]. In animal studies, BPA was shown to possess endocrine-disrupting effects. BPA exposure was associated with spermatogenesis failure by downregulating androgen receptor expression and the genes related to spermatogenesis [22]. BPA also caused reduced sperm production, severe damage to the acrosome and mitochondrial activity, reduced the serum concentrations of testosterone, luteinizing hormone (LH) and FSH, and increased the concentration of estradiol [23].

Although occupational and environmental studies have been reported with conflicting results, both forms of exposure have been reported to negatively influence overall reproductive health. Vitku et al. suggested that seminal BPA correlated negatively with sperm concentration, sperm count, and morphology [13]. In contrast, Goldstone et al. showed in a prospective cohort study that BPA exposure was associated with a decrease in DNA fragmentation with no significant change in sperm parameters [20]. This discrepancy between studies could be due sample size, dose of BPA, or duration of exposure.

Previous human studies looking at the impact of BPA exposure on reproductive health also yielded inconsistent results. Some studies failed to prove any association, while Lassen et al. suggested that higher urinary BPA concentration was associated with significantly higher concentrations of serum LH, testosterone, and estradiol [24]. Such findings may be explained by competitive inhibition of the negative feedback binding of estradiol to the estrogen receptor in the hypothalamus/pituitary. This disinhibition of LH release would, in turn, result in an increased LH level, which would subsequently stimulate increased production of testosterone and estradiol. A cross-sectional study showed that occupational exposure to BPA (via inhalation and dermal contact) was associated with increased prolactin, estradiol, and SHBG levels and reduced inhibin B, androstenedione, and free androgen index levels. These findings, which adversely affect male fertility, might be due to BPA effect by downregulation of the expression of 3-β-hydroxysteroid dehydrogenase [25].

The impact of BPA exposure on male reproduction was described in detail in the review by Manfo et al. which showed that the most detrimental effect is in utero BPA exposure, which causes feminization of male fetuses, atrophy of the testes and epididymides, increased prostate size, shortening of ano-genital distance, disruption of blood-testis barrier, modulating FSH, LH, estradiol synthesis, and the expression and function of estrogen and androgen receptors [26].

Phthalate

Phthalates are multifunctional chemicals used to hold color and scent in consumer and personal care products. Due to the ubiquitous use of phthalate esters, humans are constantly exposed through numerous pathways, including food, air, water, soil, cosmetics, perfumes, food packaging, children's toys, pharmaceutical products, and PVC tubing commonly used for medical therapies [27]. The use of poor-quality plastics, recycled plastics, and plasticizers, such as phthalates, has been a major problem in developing countries [28]. Concerns increased following published reports of phthalate increased exposure for a large proportion of the USA general population [29].

Diethyl phthalate (DEHP) and di-N-butyl phthalate (DBP) are the most commonly used phthalates, both acting in an anti-androgenic manner. DEHP exposure, in particular, is associated with decreased sperm motility [30], increased sperm DNA damage and sperm apoptosis, and decreased serum estradiol and testosterone [31]. In utero phthalate exposure is associated with an alteration of reproductive hormone levels at birth, and the impact of the exposure is dependent on the timing of exposure. A recent study suggested phthalate exposure during the first trimester was associated with elevated estradiol, cryptorchidism, delayed sexual maturation, disturbances in sex ratio, deteriorated quality of semen in F1 generation, and shortening of anogenital distance in males—which represents a prenatal androgen exposure biomarker [32, 33].

Animal studies on phthalate exposure also support the deleterious effect of phthalate exposure on fertility. Exposure during late gestation resulted in a significant reduction in serum testosterone, and exposure in adolescence was associated with an increase of hydrogen peroxide and sperm DNA fragmentation index (DFI) [34, 35]. Results also indicated that the response of testicular steroidogenic cells to phthalate exposure is dependent on the animal species and type of Leydig cells (fetal versus adult). In different experimental approaches, rat fetal Leydig cells were shown to be more sensitive to phthalates than mouse or human cells both in vivo and in vitro [36].

While most observational studies on phthalate exposure in adult subjects showed weak evidence of impaired seminal analysis following phthalate exposure, others showed significantly poor semen quality in terms of decreased motile sperm count, decrease computer-assisted sperm analysis parameters, increased sperm DNA fragmentation index, and increased sperm aneuploidy [37, 38]. The proposed mechanism is direct testicular toxicity and resultant impaired spermatogenesis [39]. A recent meta-analysis on phthalate metabolites also supported the hypothesis that certain products are associated with worse semen parameters and increased sperm DNA damage [30]. Further human studies identified potential detrimental effects of phthalate exposure on semen quality, in both in vitro and in vivo conditions [28].

Interestingly, decreasing phthalate exposure was associated with some recovery of semen and hormone levels, but not all values improved [40]. Further studies suggested that duration of exposure of less than 3 years, even with high exposure, may play a role of recovering semen/hormonal parameter once the exposure source is removed [41].

Pesticides and Herbicides

Over the past several decades, the development and utilization of herbicides and pesticides in agriculture has become commonplace. The overall basis of pesticides and herbicides is to

selectively present toxicity to organisms that impede crop yields. Unfortunately, human and other animal species also experience toxic effects from these chemicals [42]. Similar to EDCs, the toxic effect depends upon the dose, frequency, type of exposure, and the genotypic characteristics of the exposed subjects [43]. The biochemical structure of certain pesticides mimics that of endogenous reproductive hormones, allowing for potential as hormonal ligands with the ability to bind to receptors integral to reproductive health and function. There are many hypothesized mechanisms of pesticide-induced subfertility. While we have characterized the impact of many, our understanding of agriculturally utilized environmental toxins is far from complete.

Organophosphates

Organophosphates (OP) are widely utilized, with more than 200 different compounds available in the marketplace. They account for 45% of the registered pesticides in the USA and ~ 50% in the European Union [44]. Although the toxic effects of human OP exposure have been well studied, their full impact on male reproductive health is less understood [42]. OP inhibit acetylcholinesterase activity and reduce monoamine levels needed for adequate HPGA activity and, therefore, gonadal function [9, 45]. Additionally, OP have the potential for direct toxicity to male hormones or to mimic the male gonadotropins, which supports the hypothesis that OP is considered as endocrine disrupting chemical [46].

A review by Mehrpour et al. investigating the negative impact of OP exposure reported a reduction of sperm counts, motility, viability and density, an increase in sperm DNA damage, and an increase in abnormal sperm morphology [47]. OP exposure also was shown to cause a reduction of testosterone, an increase of FSH, and an increase in LH levels [48]. Furthermore, OP exposure was associated with reduced weight of testes, epididymis, seminal vesicle, and ventral prostate. OP exposure also caused seminiferous tubule degeneration, decreased level and activity of the antioxidant enzymes in testes, and inhibited testicular steroidogenesis [47].

Several recent epidemiologic studies supported the negative impact of occupational and environmental OP exposure on semen parameters, including worse sperm motility and morphology. These studies, however, had inconsistent results when looking at the impact of OP on hormone levels (including testosterone, estradiol, prolactin, and gonadotropins) [49, 50]. This discrepancy could be attributed to different organophosphate usage, magnitude of exposure, and epidemiologic design of the studies [49, 50].

Dichlorodiphenyl-Dichloroethylene

Despite been banned in 1972 across the industrialized world, dichlorodiphenyl-dichloroethylene (DDT) and its main metabolite, *p,p′*-dichlorodiphenyl-dichloroethylene (*p,p′*-DDE), are still used in developing countries, mainly for malaria vector control [51]. Both DDT and DDE persist in the environment well and bioaccumulate in fatty tissues of fish, birds, and humans [51]. DDT has an estrogenic potential, and DDE has the ability to bind to estrogenic receptor. Both have anti-androgenic function and exert their impact by blocking the androgen receptor and interfering with estrogen metabolism [47].

Some investigators found no significant association between blood levels of pp′-DDE and sperm DNA methylation or impairment in fertility following occupational exposure to DDT [52] [53]. Pant et al. earlier suggested that the pathogenesis behind decreased semen quality parameters in nonoccupational exposure to DDT might be to reactive oxygen species (ROS), lipid peroxidation (LPO), and mitochondrial dysfunction resulting in oxidative stress [54]. Additionally, Mehrpour et al. also suggested that occupational exposure resulted in inhibition of spermatogenesis, reduction of testis weights, reduction of sperm counts, sperm motility, sperm viability, sperm density, inducing sperm DNA damage, and increasing abnormal sperm morphology [47].

Heavy Metals

Heavy metals are broad spectrum of compounds, ubiquitous in nature, that interfere with many aspects of general and reproductive health. Due to their wide use in many industries, these toxicants are released into the environment by different pathways and are one of the most common categories of contaminants in the environment. Lead, cadmium, and mercury are three metals of concern. They exert negative impact on reproductive health either by direct effect on the target gland or indirect effect. Some heavy metals have demonstrated potent estrogenic and androgenic activities in vivo and in vitro by directly binding estrogen and androgen receptors, and lead to a decrease in sperm concentration and motility [55]. Heavy metal exposures increase the formation of reactive oxygen species, leading to oxidative stress, inducing DNA damage, and disrupting the blood-testis barrier causing apoptosis of spermatozoa [56].

Cadmium is known as endocrine disruptor and is able to exert reproductive toxicity in males even at a low level of exposure. While it is found in cereals, grains, and green leafy vegetables, cadmium exposure can occur from contact with dyes, ceramics, plastics, fertilizers, and cigarettes [2]. Cadmium-induced reproductive toxicity is mediated by multiple mechanisms, including structural damage to the testis vasculature and blood-testis barrier, inflammation, cytotoxicity on Sertoli and Leydig cells, oxidative stress (mainly by means of mimicry and interference with essential ions), apoptosis, interference with selected cell signaling pathways,

epigenetic regulation of genes involved in the regulation of reproductive function, and disturbance of the HPGA [57].

Air Pollution

Air pollution is widely acknowledged for its detrimental effect on general health, including cardiovascular and respiratory disease [58, 59]. The International Agency for Research on Cancer even classified air pollution as carcinogenic to humans [60]. Air pollution is a mixture of multiple pollutants originating from a myriad of natural and anthropogenic sources, such as respirable particulate matter (PM_{10}), fine particulate matter ($PM_{2.5}$), and gases like NO_2, SO_2, and O_3 [60].

A recent review showed weak evidence correlating outdoor air pollution with semen quality. However, there was a strong association between air pollution and poor sperm morphology, and in most studies, at least one of the seminal parameters was affected [61]. Another review showed increased epigenetic changes and sperm DNA damage in men exposed to air pollution. Although both epigenetic changes and sperm DNA damage could disturb spermatogenesis, this hypothesis needs to be explored further. Radwan et al. observed negative association between exposure to certain pollutants like PM_{10} and $PM_{2.5}$ and the proportion of Y/X chromosome bearing sperm. The authors hypothesized that air pollution may interfere in sex distribution by altering the testicular functioning leading to an excess of X sperm production in exposed males [62].

Hyperthermia

Most male mammals, including humans, evolved testes that are located outside the body cavity to maintain a temperature 2–8 °C below core body temperature [63]. Testicular function is highly dependent on this cooler scrotal temperature, and the lack of thermoregulation causes testicular hyperthermia and genital heat stress. Therefore, raising the scrotal temperature can negatively impact spermatogenesis. As spermatogenesis is a highly regulated process, any insult can result in a varying degree of impairment. Results from heat exposure range from a decrease in sperm count to complete azoospermia, a decrease in sperm motility, or an increase in DNA protamination (which is responsible for correct sperm DNA condensation and integrity during the latter phases of spermatogenesis) [64].

Pathology that elevates the testicular temperature, like cryptorchidism and varicocele, has been shown to impede spermatogenesis [65, 66]. Repetitive testicular heat stress leads to Leydig cell stress-mediated apoptosis through excessive stress on the cell's endoplasmic reticulum. This loss of Leydig cell function subsequently reduces local testosterone production necessary for normal spermatogenesis [67]. In a recent animal study, testicular hyperthermia was applied for 15 min daily and resulted in a significant reduction in testicular weight, increase in multinucleated giant cells, increase in degenerative Leydig cells, increase in destructive spermatocytes and spermatids within degenerative seminiferous tubules, and apoptosis of germ cells [68].

Many human studies suggested the negative impact of testicular hyperthermia on spermatogenesis. Constant scrotal heat stress can negatively impact sperm DNA integrity and chromatin condensation, as well as sperm count, motility, and morphology [63, 69]. Transient scrotal hyperthermia also can seriously impact spermatogenesis through damage from oxidative stress, although this is usually reversible [70]. These studies indicate that constant heat exposure had a greater effect on spermatogenesis when compared to intermittent heat exposure.

Cell Phones

With continuous innovations in cell phone technology and widespread applications, cell phones have become an essential part of our lives. One active area of research is the potential impact of cell phone usage on general health, including male fertility. Cell phones transmit information to nearby relay base stations or antennas through the emission of radiofrequency electromagnetic waves. The human body also can absorb those waves, and the absorption produces heat [71]. There are reported associations of cell phone usage and effects on the brain and heart [72, 73]. Reported pathologies include headaches, increased resting blood pressure, and alterations to brain activity during sleep [74–76].

Some animal and human studies looking at the effects of cell phone exposure have noted a negative impact on reproductive health, but none have drawn any clear conclusions if this effect is clinically significant. In a few animal studies, electromagnetic and radiofrequency irradiation was associated with significant reductions in seminiferous tubules, testicular weight, sperm count, sperm viability, sperm motility, and sperm total antioxidant. They also reported increased lipid peroxidation, DNA damage, and cell cycle arrest in testicular germ cells [77–79].

A number of human studies also support a link between cell phone use and male infertility. A systematic review and meta-analysis of all relevant studies conducted between 2000 to 2012 concluded that cell phone exposure was associated with reduced sperm motility and viability, with no change in sperm concentration [80]. A meta-analysis of in vitro studies also reported similar findings [81]. Subsequently, Zhang et al. stated that cell phone exposure was associated with reduced sperm concentration and volume [82]. Kesari et al. similarly concluded that electromagnetic exposure can damage Leydig cell function and cause a reduction of serum testosterone level,

shrinkage of seminiferous tubules, and a reduction of sperm motility and count [71].

Laptop Computers

Innovation in computers led to the development of such small, portable computers that can comfortably sit on top of the user lap. This "lap" positioning, although convenient for the user, may be another contributor to male infertility. As the internal temperature of a laptop computer can reach 70 °C, there is potential for reproductive pathogenesis from direct thermotoxicity. Additionally, the laptop on lap positions the scrotum between closed legs, which synergistically generates and traps heat. This can cause genital heat stress that may worsen semen parameters [83]. Interestingly, scrotal shielding with a lap pad between the computer and the user's legs does not protect from scrotal temperature elevation. But not surprisingly, sitting in a modified position with legs apart or reducing the duration of laptop use does decrease scrotal temperature [84].

The human studies on WiFi waves are sparse, and, as a result, the non-thermal effect of laptop computer electromagnetic waves on male reproductive health remains unclear [85]. Animal studies with increased exposure to WiFi waves did show a decrease in seminal vesicles weight, epididymis size, and sperm parameters in a time-dependent pattern (more specifically, sperm concentration, motility, and morphology). A plausible explanation for impaired semen quality from WiFi exposure is the induction of reactive oxygen species, increase in cell apoptosis, and increase in caspase-3 activity in the seminiferous tubules [86, 87].

Conclusion

Present day humans are exposed to a complex variety of environmental toxins. Although restrictions on the use of certain known toxins have been implemented, exposure to many of these toxins continues, either due to continued use or previous environmental accumulation. And while many of these toxins are not toxic at environmental concentrations, there is potential for pathogenesis due to synergetic toxicity mechanisms. Despite strong evidence compiled from environmental and occupational observational studies, there is a lack of strong confirmatory clinical studies. Continued research must be done to better understand the pathogenic mechanisms behind the environmental factors that contribute to infertility. These future studies will shape new environmental policy restrictions aimed to protect human reproduction. As we continue to search for answers, the environment continues to evolve around us, presenting new potential threats and challenges to our reproductive health.

Compliance with Ethical Standards

Conflict of Interest Mahmoud Mima, David Greenwald, and Samuel Ohlander each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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