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REVIEW

Temporal decline of sperm concentration: role of endocrine disruptors

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Abstract

Introduction Male infertility is a widespread disease with an etiology that is not always clear. A number of studies have reported a decrease in sperm production in the last forty years. Although the reasons are still undefined, the change in environmental conditions and the higher exposure to endocrine-disrupting chemicals (EDCs), namely bisphenol A, phthalates, polychlorinated biphenyls, polybrominated diphenyl esters, dichlorodiphenyl-dichloroethylene, pesticides, and herbicides, organophosphates, and heavy metals, starting from prenatal life may represent a possible factor justifying the temporal decline in sperm count.

Aim The aim of this study is to provide a comprehensive description of the effects of the exposure to EDCs on testicular development, spermatogenesis, the prevalence of malformations of the male genital tract (cryptorchidism, testicular dysgenesis, and hypospadias), testicular tumor, and the mechanisms of testicular EDC-mediated damage.

Narrative review Animal studies confirm the deleterious impact of EDCs on the male reproductive apparatus. EDCs can compromise male fertility by binding to hormone receptors, dysregulating the expression of receptors, disrupting steroidogenesis and hormonal metabolism, and altering the epigenetic mechanisms. In humans, exposure to EDCs has been associated with poor semen quality, increased sperm DNA fragmentation, increased gonadotropin levels, a slightly increased risk of structural abnormalities of the genital apparatus, such as cryptorchidism and hypospadias, and development of testicular tumor. Finally, maternal exposure to EDCs seems to predispose to the risk of developing testicular tumors.

Conclusion EDCs negatively impact the testicular function, as suggested by evidence in both experimental animals and humans. A prenatal and postnatal increase to EDC exposure compared to the past may likely represent one of the factors leading to the temporal decline in sperm counts.

Keywords Spermatogenesis · Endocrine disruptors · Sperm concentration · Decline

Introduction

Male infertility and temporal decline of the sperm concentration and count. Search for the etiology

Infertility is defined as the failure of a couple to achieve conception after 12–24 months of unprotected sexual intercourse [1]. It is a widespread condition, which is estimated to affect about 15% of childbearing aged couples [2]. Overall, male factor infertility is identified in half of infertile couples, and it is solely responsible for about 30% of cases [3]. Although several etiologies of male infertility have been identified so far [4], the exact cause could remain unclear despite a comprehensive diagnostic work-up in a relevant percentage of cases. A prospective monocenter study on 1737 male patients with infertility claimed that ~75% of those with oligozoospermia were idiopathic [5]. Similarly,

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another study from Germany carried out on 26,091 men of infertile couples could not find the etiology of spermatogenesis impairment in 72% of them [6]. Other authors have estimated a portion of 30% of unexplained male infertility among all-male infertile patients, and 13.3% in patients with azoospermia [7]. This evidence clearly highlights the importance of research aimed at identifying the etiology of the seemingly idiopathic male infertility.

It is, therefore, noteworthy that several studies published in recent years indicate a worrying decline in sperm production. A meta-regression study by Levine and collaborators performed on 42,935 men who provided their semen samples between 1973 and 2011 reported an overall decline of 52.4% in sperm concentration (−0.70 million/ml/year), and 59.3% in total sperm count (−5.33 million/year) in the last 40 years. The decline was confirmed in unselected men from North America, Europe, Australia, and New Zealand [8]. More recently, a retrospective study on randomly selected samples compared the conventional semen parameters from 2011 to 2015 vs. those form 2016 to 2020, confirming the presence of a worse total sperm count, but not of sperm concentration, motility and morphology [9]. Similarly, a retrospective study on 20,958 sperm analyses of men from different North African countries reported a marked decrease in semen quality in the last decade [10]. Another meta-analysis (MA) carried out on the African population reported a time-dependent decrease of 72.6% in the past 50 years (1965–2015) [11]. Furthermore, the presence of a decline in sperm parameters throughout the decades has also been described in Asian countries [12, 13].

The causes of such a decline have not been elucidated yet. However, due to the increase in industrialization, scientific progress, and technology, the environment has undergone drastic changes in terms of concentration of pollutants, exposure to chemicals, and to substances like endocrine-disrupting chemicals (EDCs) in the last few decades. EDCs are defined as "an exogenous chemical, or mixture of chemicals, that can interfere with any aspect of hormone action" [14]. There is a number of studies that have addressed the role of EDCs in the impairment of sperm parameters. Whether the increase in EDC concentration over time may be responsible for the decline in sperm parameters is currently still not known.

Aim of the study

This narrative review aims to provide a comprehensive description of the effects of exposure to EDCs on testicular development, spermatogenesis, the prevalence of structural abnormalities of the male reproductive tract (cryptorchidism, testicular dysgenesis, hypospadias), and testicular tumor. To accomplish this, we reviewed both animal and human evidence. The mechanisms through which EDCs can impact the male reproductive apparatus were also discussed. Finally, to facilitate a better comprehension of these mechanisms, we briefly outlined key events happening during prenatal and postnatal testicular development and spermatogenesis.

Male reproductive function

Physiology of prenatal testicular development

Gonadal differentiation is identifiable around the 7th week of gestation. The seminiferous tubules, originating from the mesonephros, contain large germ cells that divide actively. The smaller, anti-Müllerian hormone (AMH) secreting Sertoli cells (SCs) are present surrounding these primordial germ cells [15]. Leydig cells differentiate and start producing testosterone between the 8th and the 9th week of gestation. These cells move in the inter-tubular space at the 14–15th week of gestation when half of the testicular volume is made of Leydig cells. Their proliferation and maturation are responsible for the differentiation of gonocytes into pre-spermatogonia [15].

SCs are the first cells to differentiate in the undifferentiated gonad and coordinate the series of events that lead to sex differentiation. Indeed, in the XY gonad, pre-SCs express the *Sry* gene, which is required for male sex differentiation. This gene triggers the expression of *Sox9* gene, which in turn regulates the expression of AMH from the SCs and represses ovarian development. AMH induces the regression of the Müllerian ducts, whose development lead to the formation of the uterus, tubes, and vagina. The regression of the Müllerian ducts allows the development of the ejaculatory ducts, epididymis, deferens ducts, and seminal vesicles from the Wolffian ducts [16]. Therefore, exposure to substances that can damage SCs in prenatal life may negatively impact the development and structure of the male reproductive apparatus.

Physiology of postnatal testicular composition

During childhood, SCs are the most representative component of the testis. During this phase, the testis is not quiescent, since several metabolic processes take place, such as the proliferation of immature SCs, and AMH secretion (for review: [15, 17]). These events seem to be highly important for future fertility, since, during puberty, the increase in intra-tubular testosterone concentrations makes the SCs switch from a proliferative and immature state, to a mature state, and therefore incapable of proliferation. In other words, SCs lose the ability to proliferate at puberty. This is very important since each SC is able to

support the differentiation of a definite number of germ cells. Therefore, a reduced SC proliferation in childhood can lead to irreversible oligozoospermia in adulthood (for review: [15–17]). Whether EDCs are able to impact SC proliferation in childhood is reviewed in section *Endocrine disruptors and male reproductive function*.

Physiology of spermatogenesis

The spermatogenetic process takes about 74 days and occurs inside the seminiferous tubules and continues within the epididymis, where spermatozoa acquire motility and fertilizing ability. Three main phases occur during spermatogenesis: the proliferation of spermatogonia, meiotic division of spermatocytes, and changes in shape and nuclear content of spermatids (spermiogenesis). The spermatogonial stem cells are undifferentiated spermatogonia with a maintained potential to self-renew. Based on the molecular signals of SCs, these cells differentiate into type A_{paired} and type $A_{aligned}$ spermatogonia, which have lost the ability to self-renewal. The $A_{aligned}$ spermatogonia, in turn, divide into type A_{1-4} and type B spermatogonia, in about 16 days. Another 16 days are required for the differentiation from type B spermatogonia into primary spermatocytes (for review: [18]. The latter undergo their first meiotic division in 16 days, thus differentiating into secondary spermatocytes. A number of complex molecular events occur during the first meiotic division, such as programmed double-strand breaks, the pairing of homolog chromosomes, and crossing over. Then, secondary spermatocytes undertake the second meiotic division, which takes a few hours, during which sister chromatids segregate. Later, a 26-day long process called spermiohistogenesis is required to allow the differentiation of round spermatids into mature spermatozoa (for review: [18]. Reviewing the development of testis pre- and post-natally, as well as the physiology of spermatogenesis, we can conclude that a proper hormonal balance in these processes plays a pivotal role.

Endocrine disruptors

Endocrine disruptors are chemicals or mixtures of chemicals that interfere with any aspect of hormone function [14]. With regard to male fertility, many of these chemicals have estrogen-like or anti-androgenic effects. These chemicals can be classified into two broad categories: natural and introduced with food, or synthetic and used in industrial solvents and by-products [19]. Most of the EDCs are present at low concentrations with negligible impact but it is the repeated exposure over time or the combination of one or more EDCs that can have a synergistic effect to impact male reproductive and sexual health [20]. Several EDCs can have an impact on male reproductive and sexual function including bisphenol A (BPA), phthalates, polychlorinated biphenyls (PCBs), polybrominated diphenyl esters (PBDEs), dichlorodiphenyl-dichloroethylene (DDT), pesticides, and herbicides, organophosphates (OPs), and heavy metals (Table 1).

Many EDCs have long half-lives, which allow them to persist in the environment for several years without breaking down. Even substances that were banned several years ago can be detected. Human exposure mainly occurs by ingestion, inhalation, or dermal uptake [21]. EDCs can easily contaminate fish, meat, dairy, and poultry, and finally are transferred to humans by ingestion. Most humans have detectable levels of EDCs in their tissues and blood, especially lipophilic EDCs and those that are in abundance in the environment, such as BPA [22]. Over time, there is a rising concentration of EDCs that are detected especially in more industrialized cities. However, even areas that are relatively pristine can become polluted based on the migratory patterns of humans and animals. Furthermore, certain climatic environments (e.g., windy) could also favor the spread of pollutants.

BPA is used in a variety of applications including manufacturing, packaging for canned or bottled food and beverages, various plastic goods, and toys. BPA resins can be found in food or beverages when exposed to high heat, physical manipulation, or repetitive use. BPA is a widespread chemical monomer that can easily be absorbed through dietary or transdermal routes. It is so common that ~93% of Americans have a measurable amount in their urine [22]. The US Environmental Protection Agency safety level of BPA is set at 50 µg/kg/day, whereas the European Food Safety Authority's temporary tolerable daily intake was lowered to 4 µg/kg/day [23]. BPA can have estrogenic, anti-estrogenic, and anti-androgenic effects [23].

Phthalates are a group of compounds used as liquid plasticizers found in plastics, coatings, cosmetics, and medical tubing. These compounds were first introduced as additives to plastics, which resulted in the widespread use of polyvinyl chloride (PVC) plastics. However, they are not chemically bound to plastic and can leach into the environment. Phthalates have been detected in human serum, urine, and breast milk samples [24]. Estimated daily exposure to phthalates ranges from 3 to 30 µg/kg/day [23].

PCBs are a class of industrial chemicals that were used as plasticizers in rubber and resins, carbonless copy paper, adhesives, and paints. PCB production was stopped in the 1970s and production of PBDEs began. These compounds act as xenoestrogens and are resistant to degradation thus they accumulate in water and the environment. They are also lipophilic and accumulate in fatty tissue and especially in obese individuals compared to lean individuals [25]. PBDEs have been detected in human adipose tissue, serum,

Table 1 Summary table of endocrine-disrupting chemicals (EDCs): main usage and effect on the human body

No	EDC	Main usage	Effect on the human body
1	Bisphenol A (BPA)	Manufacturing, packaging for canned or bottled food and beverages, various plastic goods, and toys	Estrogenic, anti-estrogenic, and anti-androgenic effects
2	Phthalates	Plastics, coatings, cosmetics, and medical tubing	Have been detected in human serum, urine, and breast milk samples
3	Polychlorinated biphenyls (PBDEs)	Plasticizers in rubber and resins, carbonless copy paper, adhesives, and paints	PBDEs have been detected in human adipose tissue, serum, and breast milk
4	DDT and Dichlorodipheyldichloroethylene (DDE)	Synthetic household insecticides with a long half-life that were mainly used for malaria vector control	Have anti-androgenic function exerting their effects by blocking the androgen receptor
5	Dioxins	Manufacturing processes including smelting, herbicides, and pesticides as well as natural processes such as forest fires or volcano eruption	Long-term exposure can impact reproductive function. Blood levels of dioxin in US residents are generally less than 20 parts of dioxin per trillion parts of lipid
6	Organophosphates (OPs)	Flame retardants, plasticizers, performance additives to engine oil as well as registered pesticides	Increase in sperm abnormality
7	Heavy metals	Lead, cadmium, arsenic, chromium, and mercury are widely used in many different industries and can be released into the environment	Directly bind estrogen receptors

and milk. PCB congeners have concentrations ranging from 38.4 to 161.7 ng/g in human adipose tissue samples in people of the Southern Spain [26]. The general United States (US) population has an average plasma concentration of PBDEs ranging from 4 to 366 ng/g of lipid with the average adult ingesting 1 ng/kg/day [27, 28].

DDT and DDE are synthetic household insecticides with a long half-life that were mainly used for malaria vector control. They are lipophilic in nature and this allows them to accumulate in the adipose tissue. Both have anti-androgenic properties and, therefore, block the androgen receptor [29]. In South Africa, houses were sprayed with DDT as part of an indoor spraying program. Levels were reported to be very high in breast milk and the mean blood concentration was around 239 ug/g [30].

Dioxins are environmental contaminants made of lipophilic chemicals. High-fat-containing foods (meat, milk, breast milk, cheese, etc.) are the most common route for exposure to dioxins in humans [31]. Dioxins are by-products of manufacturing processes including smelting, herbicides, and pesticides as well as natural processes such as forest fires or volcano eruptions. They are found throughout the environment, especially in soil, sediment, and some foods. Long-term exposure can impact reproductive function. Blood levels of dioxin in US residents are generally <20 parts of dioxin per trillion parts of lipid (https://www.cdc.gov/niosh/pgms/worknotify/dioxinmedstudy.html).

OPs are commonly utilized in various products, such as flame retardants, plasticizers, performance additives to engine oil as well as registered pesticides in Europe and the US. These compounds leak into the environment and have been found in air, water, soil, and sediment.

Heavy metals are generally compounds of high density. At higher concentrations, these naturally occurring elements can interfere with reproductive health and processes mediated by endogenous hormones. Lead, cadmium, arsenic, chromium, and mercury are widely used in many different industries and can be released into the environment. Some of them are also known as metalloestrogens as they can directly bind estrogen receptors [32, 33]. Exposures can occur via inhalation, ingestion, dermal, and parenteral routes.

Endocrine disruptors and male reproductive function

Endocrine-disrupting mechanism of action

Several studies have shown a decline in semen quality in the last four decades [34, 35]. There might be many reasons, but it may be postulated that exposure to EDCs during

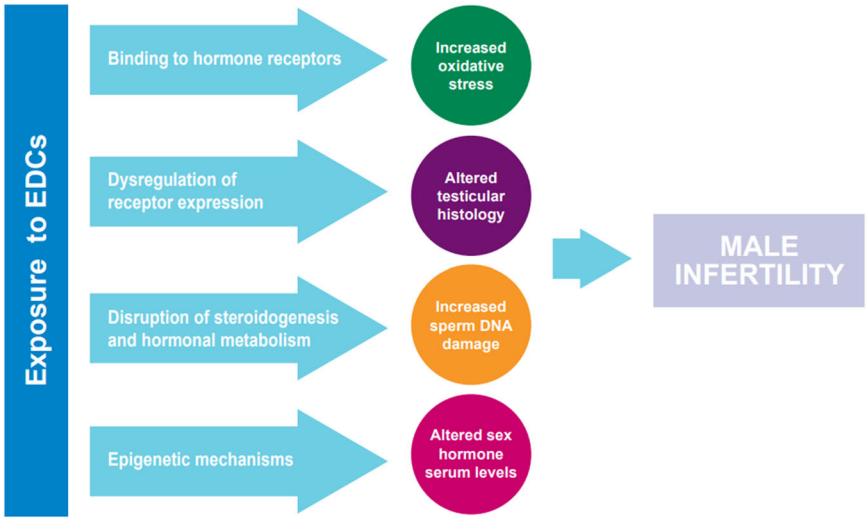

Fig. 1 Possible mechanisms through which EDCs can compromise male fertility

intrauterine life to adulthood may disrupt the male reproductive function.

The mechanisms by which EDCs act in the male reproductive system are not yet fully elucidated. Since EDCs are not natural ligands, they do not have the same specificity and affinity to the hormonal receptors. However, EDCs interfere with endocrine effects at the receptor or cell levels. They can bind the corresponding hormonal receptor and trigger a hormonal response in an agonistic or antagonistic way, especially for the androgen or estrogen receptor (receptor-mediated mechanisms). EDCs can also show multiple hormone-binding properties. For instance, while one of the metabolites of DDT exerts its toxicity with an anti-androgenic effect, DDT itself is an agonist for estrogen receptors [36].

Another deleterious effect of EDCs at the hormone receptor level is the dysregulation of receptor expression. A good example of this mechanism is the dysregulation of the steroid receptors in rat testes by BPA [37].

Along with the hormone-related receptor effects, EDCs can also interfere with enzymes that act in steroidogenesis and hormonal metabolism. For example, phthalates directly inhibit the CYP17 enzyme. This, in turn, results in a lower testosterone synthesis by Leydig cells. EDCs were also found to inhibit the action of the 5-α reductase enzyme, which metabolizes testosterone to dihydrotestosterone, a hormone that contributes to the development of male sex characteristics [38]. Tetrachlorodibenzo-p-dioxin (TCDD), an environmental polluting chemical, also exerts its anti-androgenic activity by inhibiting hormone synthesis [39].

EDCs can also bind to nuclear receptors and affect the expression of sex and steroid hormone-activated target genes, by inducing their transcription at the molecular level (enzyme-related mechanisms). Mono-(2-ethyl-hexyl) phthalate (MEHP), the reactive metabolite of di-(2-ethylhexyl) phthalate (DEHP), stimulates peroxisome proliferator-activated receptor (PPAR) α and PPARγ pathways. This in turn inhibits the transcription of aromatase and steroidogenic genes [40–42]. An additional example is endosulfan, an insecticide, which was associated with a decrease in some of the male reproductive system-associated genes (*wt1* and *Sox9a*) [43].

DNA methylation, histone acetylation, and non-coding RNAs are the leading epigenetic mechanisms that refer to heritable alterations in gene action [44]. Epigenetic mechanisms can be driven by EDCs during the course of life and result in negative consequences across generations, as supported by the Developmental Origins of Health and Disease theory [45]. EDCs may cause epigenetic effects on the germline and lead to a transgenerational consequence on male reproduction [46]. It has been demonstrated that a decreased spermatogenic capacity induced by vinclozolin (an anti-androgenic compound) or methoxychlor (an estrogenic compound) was transferred through the male germline to nearly all males of all offspring, which was correlated with DNA methylation patterns in the germline [46]. Figure 1 summarizes the possible mechanisms through which EDCs affect male infertility.

Animal studies

Bisphenol A

The effect of EDCs, including BPA, pesticides, parabens, dioxins, and combustion products, on reproductive health has been shown in various animal studies. BPA is one of the most commonly produced chemical compounds globally, mainly used in the plastic industry. It exerts its toxicity by compromising DNA integrity, which is associated with failure in embryogenesis, early miscarriage, and significant

Table 2 Summary of the effects of Bisphenol A observed in animal studies

Reference	Species	Exposure	Effects observed
Tainaka et al. [111]	Mice	Pregnant mice were treated with subcutaneous BPA	- Decreased sperm production (daily) - Decline in motility
Kalb et al. [112]	Mice	BPA exposure via breast milk during the lactation (early postnatal) period	- Decreased DNA and acrosome integrity - Testicular degeneration - Complete aplasia in some seminiferous tubules
Rahman et al. [113]	Mice	Pregnant mice were gavaged with BPA	- Decline in sperm motility - Disrupted membrane and acrosomal integrity - Decline in intracellular ATP and mitochondrial enzymes
Xie et al. [114]	Mice	Newborn male mice were subcutaneously injected with BPA	- Damaged seminiferous tubules - Mitotic arrest at spermatogonia stage - Increased apoptosis in germ cells per tubule - Increased chromosome fragments
Wang et al. [115]	Mice	In vivo and in vitro toxicity of BPA on mature mouse spermatozoa	- Transient inhibition of cation channels of sperm - Decreased acrosomal reaction and sperm motility.
Rezaee-Tazangi [116]	Mice	Epididymal spermatozoa obtained from mice and isolated mice testicular mitochondria with BPA	- Significantly elevated ROS, MDA and MMP SOD and GSH levels in isolated mitochondria
Rafiee et al. [117]	Mice	Mouse sperm and isolated mitochondria were exposed to BPA	- Enhanced ROS and MDA levels in isolated mitochondria - Markedly reduced SOD and GSH levels in isolated mitochondria
Liu et al. [118]	Rat s	Male Wistar rats to BPA by gavage	- Persistence of DNA strand breaks during pachytene - Increased spermatocyte apoptosis
Tiwari et al. [119]	Rats	Male rats were gavaged with BPA	- Decline in daily sperm production - Decline in motility - Decline in DNA integrity - Decline in acrosome integrity
Hulak et al. [120]	Fish (Sterlet Sturgeon)	Fish spermatozoa were exposed to concentrations of BPA possibly occurring in nature	- Decreased sperm motility - Atypical flagella - Intracellular ATP content of spermatozoa decreased - A dramatic increase in DNA fragmentation
Singh et al. [121]	Chicken (Leghorn males)	Sperm were exposed to concentrations of BPA	- Decreased sperm motility - Reduced fertilizing ability with high doses of BPA - Higher percentage of moribund sperm with higher doses of BPA
Zhang et al. [122]	Fish (Rare minnow)	Adult male rare minnows were exposed to BPA	- Increased apoptotic germ cells - Increased chromosome fragments - Dysregulation in RNA expression of meiosis regulation gene
Zhu et al. [123]	Fish (Rare minnow)	Adult male rare minnows were exposed to BPA	- Increased DNA/histone methylation levels - Decreased sperm quality
Zhu et al. [124]	Fish (Adult male rare minnow)	Chronic BPA exposure, adult male rare minnows	- Increased oxidative stress - Increased inhibiting activities of antioxidant related enzymes - Decreased genomic methylation level

GSH glutathione, *MDA* malondialdehyde, *MMP* mitochondrial membrane potential, *ROS* reactive oxygen species, *SOD* superoxide dismutase

birth defects. BPA was also linked with abnormal spermiogenesis, which can compromise fertility potential. The effects of BPA observed in animal studies are summarized in Table 2.

Pesticides

Pesticides produced to control pests are commonly used substance in the current world. Pesticide is an umbrella term

that includes all the following: insecticides, herbicides, fungicides, etc. In general, pesticides were associated with decreased testosterone levels and impaired fertility in animal studies. However, the exact mechanisms are not yet fully elucidated. Several studies found associations between insecticides and poor sperm parameters in animals. In rats, the effect of daily deltamethrin, a synthetic pyrethroid insecticide, was evaluated for 35 days on mice and their offspring. Mice exposed to deltamethrin had decreased testosterone and inhibin B levels as well as decreased libido. Also, deltamethrin use was found to be linked with deteriorated testicular histology, which exerted itself with alterations of the seminiferous tubules, sloughing of germ cells, vacuolization of the germ cell cytoplasm, and disruption of spermatogenic cells [47]. The negative effects (abnormal semen parameters, reduced testicular weight) of deltamethrin on the reproductive system in male mice were also shown in other studies [48, 49]. Glyphosate, an herbicide given to Wistar rats during pregnancy and lactation, exerted adverse reproductive effects on male offspring with a decline in daily sperm production and sperm abnormality [50]. Methoxychlor, another pesticide, shows reproductive toxicity with its estrogenic effect and is associated with decreased testosterone levels in animal models [51, 52]. After vinclozolin (a fungicide) exposure, a reduction of testosterone synthesis was also shown in a rat model due to its anti-androgenic effects [53, 54].

Phthalates

Phthalates are also commonly studied EDCs in the literature. In mice, DEHP was associated with a 30% decrease in daily sperm production, a 70% decrease in sperm count from the epididymis, and a 20% decrease in sperm vitality [55]. In other studies, DHEP was linked with decreased testosterone levels, reduced sperm count, down-regulation of FSH and LH receptors, and seminiferous tubule atrophy [56, 57]. Although the exact mechanism of action of phthalates is not known, reduced gonadotropin signaling may be the main factor responsible for decreased steroidogenesis [58].

Dioxins

The main characteristic of dioxins is their ability to bind and activate the aryl hydrocarbon receptor. TCDD is counted as the most toxic environmental pollutant in animal studies among the dioxins [59]. In male rats, reduced sperm counts, demasculinization, and feminized morphology were associated with the gestational administration of TCDD [60, 61]. Decreased sperm viability and abnormal morphology were also linked with TCDD use [62]. Furthermore, in rats, high concentrations of TCDD were associated with impaired steroidogenesis causing decreased circulating levels of testosterone and dihydrotestosterone [63]. Also, significant alterations in testicular histology, including necrotic degeneration were shown in dioxin-exposed mice [60]. Evidence around the use of TCDD in animals supports both endocrine and direct toxic effect of dioxins on the testis.

Alongside the commonly studied EDCs, the toxic effect of several other EDCs on male reproductive health was shown in animal studies, including paraben [64], combustion products [65, 66], tributyltin chloride [67], nonylphenol metabolites [68], Microcystin-LR [69], and silver nanoparticles [70]. From the animal studies, it is evident that EDCs are associated with abnormal semen parameters, reduced circulating testosterone and dihydrotestosterone levels, and abnormal testicular histology and that a single EDC can disturb a variety of different mechanisms.

Human studies

Bisphenol A

Several observational studies have evaluated the link between BPA exposure and male reproductive function, but the findings are inconsistent [71].

In a study on 191 men with different degrees of fertility, seminal BPA levels were negatively correlated with sperm concentration ($p = 0.009$), sperm count ($p = 0.018$), and morphology ($p = 0.044$) [72]. In a case-control study, short- to intermediate-term BPA exposure was associated with reduced concentrations of circulating serum sex hormones, suggesting BPA could be an element for disturbed fertility [73]. Interestingly, obesity was found a factor that boosts BPA toxicity on spermatogenesis, most likely due to the critical roles of BPA metabolites in fatty acid oxidation [74]. However, this study did not show any relationship between BPA levels and sperm parameters, including sperm concentration, total count, motility, or semen volume [74]. Another cross-sectional study that included 215 healthy young men (18–23 years) investigated the associations between urinary BPA levels with semen parameters and sex hormone levels [75]. While LH levels showed positive significant correlation ($\beta = 0.07$, 95% CI: 0.02; 0.12, p value < 0.01), sperm concentration ($\beta = -0.04$, 95% CI: -0.07; -0.02, p value < 0.01) and total sperm count ($\beta = -0.05$, 95% CI: -0.08; -0.02, p value < 0.01) showed significantly inverse correlation with urinary BPA concentrations. No significant associations were observed with other semen parameters or sex hormone levels [75].

Another study with a cross-sectional design including 984 men from an infertility clinic evaluated the effect of both BPA and its substitutes bisphenol F (BPS) and bisphenol S (BPS) on sperm parameters [76]. It was observed that higher BPA and BPS exposures were

associated with deteriorated semen quality. Also, a decline in semen parameters was observed in higher exposures to mixtures of BPA, BPF, and BFS. A recent MA investigated the association between urinary BPA levels and semen quality. Studies only assessing the relationship between urinary BPA concentrations and conventional semen parameters with multivariable linear regression analyses were included in this MA [77]. Accordingly, a total of nine studies were included involving 2399 men and only the sperm motility parameter was found to be statistically negatively associated with urinary BPA levels (pooled β-coefficient = −0.82; 95% CI: −1.51 to −0.12, $p = 0.02$; $P_{\text{for heterogeneity}} = 0.1$, $I2 = 42.9\%$). However, this significance was lost after data adjustment for publication bias [77]. In general, from the current evidence point, data on the effect of BPA on male reproductive health in humans is limited due to the heterogeneity in population types, enrollment designs, and the extent of BPA exposure.

Pesticides

The potentially toxic effects of pesticides on male reproductive health have always gained attraction in the literature. Several systematic reviews documented the deleterious effect of pesticide exposure on sperm parameters [78, 79]. The possible ways that pesticides may exert their toxicity are inhalation of air or dust, dermal contact to pesticide-exposure areas, and ingestion of residues from diets. The key studies documenting the effects of pesticides on men's fertility are summarized in Table 3. In a recent MA, the toxic effect of OPs and pyrethroids (insectide) on human semen parameters were sought. While pyrethroid exposure only affected sperm morphology (WMD-7.61%, 95% CI −11.92 to −3.30; $p = 0,0,005$), OPs were associated with significant reduction of semen parameter, such as ejaculate volume (WMD −0.47 ml, 95% CI −0.69 to −0.25; $p < 0.0001$), sperm concentration (WMD-13.69×10^6/mL, 95% CI −23, 27 to −4.12; $p = 0005$), total count (WMD-40,03, 95% CI −66.81 to −13. 25; $p = 0003$), and motility (WMD −5.70%, 95% CI −12.89–1.50; $p = 0.12$) [80].

Phthalates

Phthalates are commonly used as plasticizers for PVC and other plastics. Some other areas where they are used in are lubricants, cosmetics, and paints. There are also several studies evaluating the toxicity of phthalates on human male fertility. In a recent MA [81], where five studies with phthalate esters were included, phthalates might be associated with increased sperm DNA damage [82, 83] and decreased sperm parameters, including concentration [84, 85], motility [84–86], and morphology [87]. This MA highlights the need for epidemiological studies in a large variety of geographic locations [81].

Dioxins

In a study, three age groups of adult men (1–9 years, 10–17 years, and 18–26 years) exposed to TCDD were compared with 184 healthy men. Especially in the infancy/prepuberty group, 71 men (mean age at exposure was 6.2 years), whose semen and blood samples were collected at 22–31 years of age, showed a significant reduction in sperm concentration (53.6 vs. 72.5 million/mL; $p = 0.025$), total motile sperm count (44.2 vs. 77.5×10^6; $p = 0.018$), and progressive motility (33.2% vs. 40.8%; $p < 0.001$) [31]. In contrast, 44 men exposed to TCCD in puberty (mean age at exposure, 13.2 years) showed a significant increase in total sperm count (272 vs. 191.9×10^6; $p = 0.042$) and total motile sperm count (105 vs. 64.9×10^6; $p = 0.036$). No significant differences were found in men who were exposed to TCC during the adulthood period compared to controls. This study is important as it suggests a critical window for dioxin to exert its toxicity on humans [88].

Heavy metals

A large body of literature have evaluated the impact of heavy metals on male infertility. A recent MA including 11 studies, for a total of 1093 infertile patients and 614 controls, found a significantly higher content of cadmium in the semen of patients vs. controls [0.50, 95% CI 0.39–0.61), $p < 0.05$], suggesting a role for the increased cadmium concentration in the pathogenesis of infertility [89]. To the best of our knowledge, no other MA are available on other heavy metals. A cross-sectional study analyzed the semen and the blood samples of men living in rural and in industrial areas. They were analyzed for the semen conventional parameters and concentration of lead, cadmium, mercury, arsenic, nickel, vanadium and selenium levels. The authors reported a positive association between cadmium levels in the seminal plasma and lower total sperm count. Seminal lead and cadmium concentration were associated with low progressive motility, suggesting the detrimental effect of these heavy metals on sperm conventional parameters [33].

Structural abnormalities of the male reproductive tract following exposure to environmental toxins

There has been a rising prevalence of male reproductive tract abnormalities, such as hypospadias, cryptorchidism, and poor semen quality known as testicular dysgenesis syndrome (TDS). The cause of this increased prevalence is of intense debate but is likely to be due to a combination of

Table 3 Summary of the key studies evaluating the toxicity of pesticides on male fertility

Pesticides	Reference	Substrate	Cohort	Results
Pesticides that are on the fruit and the vegetables	Chiu et al. [125]	Semen	189 healthy young men	- Semen quality was not associated with the total intake of fruit and vegetables - Intake with low-to-moderate pesticide residues was associated with a higher total sperm count and sperm concentration
Unspecified pesticides	Daoud et al. [126]	Semen	2122 men who underwent andrological investigation for couple infertility	- Exposure to pesticides was associated with a significantly higher risk of asthenozoospermia and necrozoospermia
Chronic exposure to modern pesticides	Cremonese et al. [127]	Semen and Serum	36 urban and 99 rural men	- Urban men had higher sperm morphology, lower sperm count, and higher LH levels than urban men.
OPs and carbamate	Miranda-Contreras et al. [128]	Semen	Thirty-five healthy men (unexposed group) and 64 male agricultural workers (exposed group)	- Significant increments were observed in sperm DFI with significant decreases in semen quality in farmers. - DFI was negatively correlated with sperm concentration, morphology, and vitality in farmers. - FSH and LH were found to be increased in the farmers
Chronic exposure to pesticides	Miranda-Contreras et al. [129]	Semen	64 farmers and 64 male controls (aged 18–60 years)	- Sperm concentration, slow progressive motility, and sperm membrane integrity were found to be decreased in the exposed group - Eosin Y positive and sperm DNA fragmentation index were found to be increased in the exposed group
Methyl parathion, methamidophos, dimethoate and diazinon	Recio-Vega [130]	Semen and urine	A total of 139 semen samples from 52 volunteers	- Poorest semen quality was found among the subjects with the highest OP exposure and the highest urinary OP levels
Exposure to a mixture of OPs OPs 49%, fungicides 19%, herbicides 6.3%, carbamates 5%, piretroides 5%, biological pesticides 3.8%, organochlorine pesticides 1.3%, and others 10.6%	Sánchez-Peña et al. [131]	Semen and urine	227 agricultural workers (18–50 years)	- About 75% of semen samples were having >30% of DFI, whereas individuals without OP occupational exposure showed average DFI% values of 9.9%. - Most parameters of conventional semen analysis were within normality except for the presence of IGCs, in which 82% of the samples were above reference values
Occupational exposure of OPs (Phenylacetate and paraoxon)	Pérez-Herrera et al. [132]	Semen and blood	54 agricultural workers (18–55 years)	- Lack of association between conventional semen quality parameters and OP exposure - Dose–effect relationships between sperm motility and viability and OP exposure were found only in subjects featuring the 192RR genotype

Table 3 (continued)

Pesticides	Reference	Substrate	Cohort	Results
Unspecified OPs	Ghafouri-Khosrowshahi, et al. [133]	Semen and blood	30 rural men 30 urban men (20–40 years)	- The number of sperm, motility, and progressive status in rural farmers were significantly lower than in the urban population - A remarkable increase was found in testosterone levels in the serum of rural farmers compared to the urban population
Unspecified OPs	Multigner et al. [134]	Semen and blood	42 banana plantation workers, 45 controls (mean age 35 vs. 38)	- No significant difference was observed in the sperm parameters and hormones
Methyl parathion, ethyl parathion and methamidophos	Padungtod et al. [135]	Semen and urine	32 OP manufacture workers, 43 non-exposed (mean age 31 vs. 30)	- Significant decline in sperm concentration and sperm motility - No significant change in sperm morphology
Unspecified OPs	Yucra et al. [136]	Semen and blood	31 pesticide applicators, 80 non-exposed subjects (Mean age 30 vs. 33 years)	- Significant reduction in semen volume, seminal pH, rapid and progressive sperm motility, normal sperm morphology and higher leucocytes - Significant reduction in serum luteinizing hormone, serum testosterone levels, and seminal zinc concentration

DFI DNA fragmentation index, *FSH* follicle stimulating hormone, *IGC* immature germ cells, *LH* luteinizing hormone, *OPs* Organopohosphates

genetic, environmental, and lifestyle factors. Environmental factors such as EDCs have been suggested by various epidemiological studies and clinical observations as a risk factor for the development of TDS. While there is evidence to support the role of EDCs in animal studies, human studies show contradictory findings. In this section, we will examine the evidence of EDCs leading to an increased risk of cryptorchidism and hypospadias.

Cryptorchidism is thought to be dependent on androgen-mediated pathways and it was previously proposed that in-utero exposure to estrogens may disrupt this process [90]. This theory has been supported by studies showing a twofold risk of cryptorchidism after in-utero exposure to diethylstilbesterol (DES), especially when the exposure was before the 11th week of pregnancy [91]. However, a study by Storgaard et al. examined the effects between prenatal estrogen exposure and cryptorchidism and did not find enough evidence to support a link between the two [92]. Studies have not found a consistent relationship between cryptorchidism and exposure to phthalates, PBBs and PBDEs, dioxins, or PCBs [24]. When examining the effects of pesticides on cryptorchidism risk, studies have shown a slightly increased risk but these were not statistically significant [93, 94]. A recent MA identified six studies evaluating the risk of cryptorchidism and found that the OR was 1.03 after exposure to EDCs [95].

Hypospadias is a birth defect in boys in whom the opening of the urethra is not at the tip of the penis. The development of the male external genitalia is a hormone-sensitive process that is triggered by a surge of androgens from the fetal testis after sex determination. Exposure to EDCs is thought to be an underlying cause of this developmental defect. Despite this theoretical risk of hypospadias with prenatal exposure to EDCs, human studies are conflicting. Longnecker et al. studied maternal DDE levels during pregnancy and found an adjusted odds ratio of 1.32 for hypospadias development when compared to controls [96]. However, another study by Bhatia and colleagues did not find any association between DDE exposure and hypospadias [97]. The Collaborative Perinatal Project did not identify any association with PCB exposure and the risk of hypospadias [98]. A MA by Bonde et al. in 2016 identified an OR of 1.13 when evaluating 7 studies examining the risk of EDCs on development of hypospadias [95].

Overall, there appears to be a small increased risk of structural abnormalities of the male genital tract such as cryptorchidism and hypospadias after exposure to a combination of EDCs, which may act simultaneously and with different mechanisms of action. Future epidemiological studies need to elucidate which compounds in particular are responsible for this risk.

Endocrine disruptors and testicular tumor

Testicular tumor is the most common neoplasia diagnosed in men between the ages of 15 and 44 and is derived from germ cell neoplasia in situ [99]. Its prevalence has increased significantly during the 20th century and the cause for this cannot solely be attributed to known risk factors, such as age, carcinoma in situ, cryptorchidism, family history, or Caucasian ethnicity [99]. It has been speculated that EDCs can contribute increasing the risk of testicular tumor and TDS [100]. Further evidence stems from the observational studies on the offsprings of immigrants moving from low-risk countries to Denmark. The fathers maintained a low risk of testicular tumor like the men from their native country, while their offspring developed a higher risk of testicular tumor which becomes similar to the male population of their new country [101, 102]. EDCs are hypothesized to limit the fetal testis to sufficient androgen exposure which is thought to increase the risk of neoplastic transformation.

Many studies have evaluated mothers of men who have developed testicular tumor to identify if they have increased concentrations of EDCs. These are largely based on studies of sons of mothers exposed to DES during pregnancy who may be at an increased risk of developing male reproductive anomalies [103]. Hardell et al. identified 61 cases whose sons developed testicular tumor and compared them to 58 age-matched controls. They identified that cases had significantly higher concentrations of PCBs, HCB, and chlordane compared to controls [104]. Another study identified that maternal serum DDT-related compounds concentration in the early postpartum period corresponded to an increased risk of testicular tumor in their sons 30 years later when compared to controls [105]. These results suggest that in-utero exposure to EDCs can potentially impact the offspring's future risk of testicular tumor. A MA of 10 studies found that maternal exposure to EDCs was associated with a higher risk of testicular tumor in male offspring with a risk ratio of 2.16 (95% CI 1.78–2.62) [106].

Other studies have evaluated if exposure to EDCs directly leads to increased rate of testicular tumor. An Italian case-control study identified that exposure to organochlorine pesticides was associated with an adjusted OR of 3.34 for developing testicular tumor in cases compared to controls [107]. Analysis of the Servicemen's Testicular Tumor Environmental and Endocrine Determinants study showed that exposure to higher concentrations of DDE and chlordane compounds but not PCBs was associated with an increased risk of testicular germ cell tumors. [108, 109]. The Norwegian Janus Serum Bank cohort study identified that men who developed testicular germ cell tumors had elevated concentrations of DDE and total chlordane when compared to controls who did not develop testicular tumor [110]. A MA evaluating 8 studies relating to testicular tumor risk after EDC exposure found an OR of 1.2 (95% CI 0.78–1.89) [95].

There appears to be a slightly increased risk of testicular tumor with exposure to EDCs. The exact mechanisms responsible for this as well as risk stratification for in-utero exposure compared to direct exposure need to be elucidated. Future high-quality epidemiological studies are needed to further investigate this as well as identify which EDCs in particular pose the highest risk.

Conclusion

In conclusion, EDCs negatively impact testicular function, as showed by evidence in animals and humans. This effect is exerted by binding to hormone receptors, dysregulating the expression of receptors, disrupting steroidogenesis and hormonal metabolism, and by epigenetic mechanisms. In humans, exposure to EDCs has been associated with poor semen quality, a decrease in sperm DNA fragmentation, increased gonadotropins, a slightly increased risk of structural abnormalities of the genital apparatus, such as cryptorchidism and hypospadias, and testicular tumor. Also, maternal exposure to EDCs seems to predispose to the risk of developing testicular tumor. The increase in the exposure to EDCs prenatally and postnatally compared to the past may likely represent one of the factors leading to the temporal decline in sperm counts.

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Compliance with ethical standards

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