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REVIEW ARTICLE

Recent Updates on the Effect of Endocrine Disruptors on Male Reproductive Functions

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Abstract:

Endocrine disruptors are man-made or naturally occurring chemical substances, upon exposure, alter the male reproductive health by interfering with hormonal homeostasis and spermatogenesis. Several studies have supported the hypothesis that a decrease in sperm count over the past few decades is due to exposure to environmental contaminants possessing estrogenic or anti-androgenic properties. Bisphenol A, phthalates, alkylphenols, and polychlorinated biphenyls are some of the endocrine-disrupting chemicals commonly present in our day-to-day products that have been shown to pose a significant threat to reproductive health. Many chemicals directly or indirectly affect the endocrine systems, altering metabolism, sex differentiation, growth, stress response, gender behavior, and reproduction. The endocrine pathway disruption is possible *via* membrane receptors or nuclear receptors and inhibition of enzymatic pathways. The declining male reproductive health has been linked to an increased presence of chemical contaminants in our environment in the form of pesticides and plastics. The effect of endocrine disruptors on reproductive health remains a real issue considering public health. This review gives a recent update on environmental chemicals that have endocrine-disrupting potential and their effect on the male reproductive system.

Keywords: Endocrine disruptors, Pesticide, Sperm Testicular function, Pesticides, Public health, Growth.

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1. INTRODUCTION

In recent decades, several chemical and biological agents have been shown to interfere with various metabolic pathways, leading to development, growth, and reproduction alterations. Endocrine disruptors are exogenous agents that can interfere with the production, release, transportation, metabolism, binding, action, or elimination of natural hormones in the body needed to maintain homeostasis and regulate the developmental processes of an organism [1]. Endocrine-disrupting chemicals (EDC) are a heterogeneous group of substances that have been under consideration for the past three decades due to their possible harmful effects on wildlife and human [2]. Humans and animals are exposed to a wide range of chemical substances from the environment, contributing to a complex exposure situation in our day-to-day lives. Most of the reported effects on wildlife are based on the observation of aquatic organisms and have been linked to the concentration of pollutants along the food chain. In humans, there is increasing evidence that the birth sex ratio is altered in areas close to industry and exposed to environmental and industrial chemicals [3]. Epidemiological studies support the hypothesis that human male reproductive disorders have been increasing over the past few decades in relation to the increase in endocrine disruptors in our environment [4, 5].

Exposure to EDC has been linked to several reproductive disorders, including infertility, testicular germ cell cancer (TGCC), one of the most prevalent cancers in young men, and congenital developmental defects such as cryptorchidism and hypospadias [6]. Interestingly, exposure to endocrine disruptors during fetal, neonatal, and adult life plays a significant role in perturbing normal reproductive function and development. Increased exposure to these chemicals has decreased reproductive function and the average sperm counts [7, 8]. The existence of specific receptors in target cells allows the hormone-mimicking effect of endocrine disruptors. Even though some toxic substances, such as polychlorinated biphenyls and polybrominated diphenyl ether, are banned in many countries, many of these substances can still be detected in considerable amounts in our environment [9]. Multigenerational and transgenerational effects on reproduction have been reported in both male and female

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rodents following exposure to endocrine-disrupting chemicals [10 - 12]. This brief review investigates the possible effects of environmental chemicals that have endocrine-disrupting potential and their effect on the male reproductive system.

1.1. Endocrine Disruptors (EDs)

The endocrine disruptors are a group of chemicals either occurring naturally or released into our environment due to man-made activities. EDs mimic or interfere with the endocrine system, thereby altering normal development and causing abnormalities in reproductive health. EDs are present in several products, and some of them are potentially hazardous. Unknowingly, we are exposed to these chemicals every day. The term EDs has been used to describe a highly heterogeneous group of substances that could be either toxicants or toxins that can disrupt the action of endogenous hormones. Some include industrial solvents, by-products of industrial processes, plasticizers, pesticides, pharmaceutical agents, phytoestrogens, and heavy metals. EDs are detected in air, soil, drinking water, food, cosmetics, household products, electronic devices, and textiles. Some EDs are highly persistent and lipophilic, so they accumulate in the body and appear in bodily fluids.

1.2. Human Exposure to Endocrine Disruptors

Some well-known examples of endocrine disruptors, similar to experimental rodents found in human bodily fluids, include bisphenol A, phthalates, PCBs, dioxins, alkylphenols, etc. Even though many chemicals possessing endocrine disrupting properties have been banned or restricted in some countries, they are still in use in other countries, and exposure occurs due to their presence in our environment at a considerable level. For example, even though the use of alkylphenols is restricted in the European Union and is still found in a considerable amount in our environment [13]. Several endocrine disruptors are detected in human urine, serum, amniotic fluid, breast milk, and semen [14 - 17]. Bisphenol A is one of the examples of endocrine-disrupting chemicals present in the bodily fluid of humans in several instances [18]. Men exposed to dioxins show a more significant number of morphologically abnormal sperm and low linear motility [19, 20]. Increased Exposure to polychlorinated biphenyls (PCBs) is associated with decreased sperm count, motility, and normal morphology [21, 22]. Exposure to organochlorine pesticides such as DDT has been shown to decrease normal sperm morphology, sperm count, volume, and motility [21, 23, 24], whereas organophosphate exposure has been shown to reduce the semen volume and increase pH [25, 26]. These findings in humans indicate that EDC exposure does affect human semen quality in a way that is similarly modeled by rodents in other studies.

1.3. Mechanism of Action of Endocrine Disruptors on the Male Reproductive System

EDs can modify the action of endogenous hormones and deregulate hormonal balance through multiple mechanisms. Phthalates, BPA, dioxins, and PCBs are some of the well-known EDs shown to decrease semen quality [19 - 21, 23 - 27]. They behave as imperfect ligands, activating or inhibiting the nuclear hormone receptors' functions, such as estrogen, androgen, progesterone, retinoid, and thyroid receptors. EDs can also act as transcriptional co-activators and inhibit enzymatic pathways of steroid biosynthesis. Monoethylhexyl phthalate (MEHP), the reactive metabolite of di (2-Ethylhexyl) phthalate (DEHP), activates the peroxisome proliferator-activated receptor (PPAR) α and PPARγ, leads to stimulation of retinoid x receptor (RXR) and PPAR to compete for binding sites on DNA and leads to inhibition of transcription of enzyme aromatase involved in sexual development. PPAR diminishes the steroidogenic proteins and leads to low sperm quality [28, 29]. Steroidogenic acute regulatory protein (StAR) is regulated by cAMP and mediates the rate-limiting step in steroidogenesis by the transportation of cholesterol into Leydig cells' mitochondria [30]. MEHP decreases the production of StAR protein and leads to a reduction in cholesterol transport. Apart from inducing oxidative stress in Leydig cells, exposure to a high level of MEHP inhibits the activities of steroidogenic enzymes such as 3β and 17β hydroxysteroid dehydrogenases, thereby altering testosterone biosynthesis [31, 32]. MEHP affects spermatogenesis by decreasing the number of Sertoli cells and its interaction with gonocytes and triggers testicular apoptosis by increasing Fas ligand expression [33 - 35]. The male reproductive system can be disturbed at different phases of a lifetime. Androgens are the essential hormones required for the normal development and differentiation of Wolffian ducts into the epididymis, vas deferens, and seminal vesicles. Dihydrotestosterone is produced from testosterone by 5α-reductase, an important hormone required for the masculinization of external genitalia and the prostate [36]. BPA affects sperm quality by the upregulation of the aryl hydrocarbon receptor mRNA level, which induces the expression of the CYP1 gene, which encodes the aromatase enzyme. Hence, a balanced hormonal environment is required for the normal development of the male reproductive system. Abnormal development of testes in fetal and neonatal life has long-term effects on sperm production [37]. Prepubertal exposure to endocrine-disrupting chemicals has negative consequences on reproductive function, as the blood-testis barrier in humans is developed just before puberty [38]. Thus, the effects of endocrine-disrupting chemicals mediated *via* activation or inhibition of androgen and estrogen receptors are the leading cause of adverse effects on male reproductive function. Estrogenic endocrine-disrupting chemicals exert more negative effects via the induction of oxidative stress. In addition, recently, possible negative actions on progeny through toxic epigenetic mechanisms have been found. Epigenetic modifications include heritable changes in gene expression without any change in DNA sequence. These changes include DNA methylation, histone modifications, and non-coding RNA expression. The early developmental period is susceptible to epigenetic mechanisms as the rate of DNA synthesis is maximum [39, 40]. The possible epigenetic action of EDs in humans is supported only by *in vitro* cell culture studies and more *in vivo* and human studies are needed to confirm it.

Table 1. Endocrine-disrupting chemicals and their impact on the male reproductive system.

Endocrine Disruptors	Sources	Effect on Male Reproduction
Bisphenol A	Polycarbonate plastics and epoxy resins	Reduced sperm concentration, motility, and normal morphology and arrest spermatogenesis at meiosis [83 - 86].
Phthalates	Plasticizers, vinyl flooring, lubricating oils, and personal-care products (soaps, shampoos, hair sprays)	Reduced fertility and semen quality parameters and reduced anogenital distance, reproductive abnormalities [33, 87 - 89]
Dioxins	Incomplete combustion of organic material by forest fires or volcanic activity, emissions from municipal solid waste and industrial incinerators, chlorine bleaching process used by pulp and paper mills	Reduced normal sperm morphology, lowered testosterone level, and limits prostate gland growth [90 - 93].
Pesticides	Occupational Exposure as well as Exposure from gardens and lawns, agriculture, drift from spraying, and pesticide residues on certain fruits and vegetables	Reduced sperm concentration, motility, and normal morphology alters Sertoli cell function and damages spermatozoa [94 - 97]
Triclosan	a widely-used antimicrobial in personal care products	Alters the morphology of sperm, and further research is necessary to conclude [98, 99]
Heavy metals like cadmium, lead	Cigarette smoke, release from phosphate fertilizer, waste incineration process, paints, etc.	Structural damage to seminiferous tubule hinders Leydig cell development and function, low sperm count, and motility [100 - 103].
Phytoestrogen	Mainly from food	Androgen insufficiency with under masculinization of the male urogenital tract and lowers sperm count [104 - 106]
Polychlorinated biphenyls	Cutting oils, lubricants, and electrical insulators in transformers and capacitors	Damages Sertoli cells, affects sperm motility and sperm count [107 - 109]
Alkylphenol	Used as precursors to detergents, additives for fuels and lubricants, polymers, and as components in phenolic resins, emulsifiers	Low sperm count, motility and reduced testosterone biosynthesis [110, 111].

2. IMPACT OF ENDOCRINE-DISRUPTING CHEMICALS ON MALE REPRODUCTIVE HEALTH

Several endocrine-disrupting chemicals have been shown to alter male reproductive functions, either directly or indirectly competing for the same hormone receptors. Furthermore, they also inhibit the enzymes involved in steroidogenesis and the synthesis of other factors required for normal spermatogenesis. This review discusses some of the most common endocrine disruptors and their effects on male reproductive functions (Table **1**).

2.1. Bisphenol A (BPA)

BPA is commonly used in the manufacturing of polycarbonate plastics and epoxy resins and is found in a variety of food containers such as hard, rigid plastics and the epoxy-based inner coating of canned foods. Exposure to BPA mainly *via* consuming contaminated food and drinking water, while exposure from the environment, domestic supplies, medical equipment, and occupational sources can also occur [41, 42]. BPA is one of the most extensively studied endocrine-disrupting chemicals that mimic natural estrogen. Estrogen plays a critical role in the development of the brain, mammary gland, and testis, interference of BPA with estrogen activity, especially during early development, results in permanent changes that affect reproductive functions later in life [43]. Even though they have a weak affinity to estrogen receptors (ERs), they can bind to and stimulate them. BPA acts primarily by mimicking the effect of estrogen, modifying DNA methylation [44] and modulating the activities of several enzymes, and subsequently induces metabolic diseases, spermatogenesis defects, and/or infertility in males [45]. It has also been observed that frequently exposed males to epoxy resins have higher urinary BPA concentrations and are associated with slightly lower FSH concentrations [46]. Increased BPA concentration is associated with lower sperm concentration, motility, morphology and higher levels of DNA damage [47]. BPA is a nonsteroidal estrogen that impedes nuclear estrogen receptors in different targets in the body [48]. Androgen level is inversely associated with urinary BPA concentration in men of proven fertility and has no association with semen quality [46]. BPA impairs Sertoli cell function by impeding the expression and localization of tight junction proteins [49 - 51] as well as indirect actions through the induction of epigenetic mechanisms and DNA hypermethylation. Exposure to BPA during prenatal, perinatal, and adult either through oral route or subcutaneous injections cause developmental abnormalities such as genitourinary anomalies, decreased epididymal weight, daily sperm production, or increased prostate weight [52 - 54]. Prenatal exposures to BPA increase the size of the preputial glands, reduce the size of the epididymides, and decrease the efficiency of sperm production in mice [54]. Perinatal exposure also causes infertility, daily sperm production and count reduction, and motility [55, 56]. Exposure to BPA prevents the action of anti-Müllerian hormone on Müllerian ducts of the developing fetus [57], leading to cause the failure of testicular descending [58]. The activities of steroidogenic enzymes such as 3β- and 17β-hydroxysteroid dehydrogenase decrease following BPA exposure, in both rat and human testicular microsomes, together with inhibition of 17α-hydroxylase/17, 20-lyase [59]. BPA induces Sertoli cell apoptosis [60] *via* induction of caspase-3 [61]. Sertoli cell plays a pivotal role in spermatogenesis under the influence of FSH; therefore, modulation of the Sertoli cells by BPA directly or indirectly *via* inhibition of FSH synthesis [46] may impair reproductive function in exposed males. Occupational exposure to high levels of BPA causes sexual dysfunction, characterized by

reduced sexual desire and more significant erectile and ejaculatory difficulties [62]. A cross-sectional pilot study [63] has shown that workers exposed to BPA show altered sperm density and have a negative correlation between BPA concentration in blood and the percentage of normal sperm, suggesting the negative influence of BPA on semen quality. Male partners of subfertile couples seeking treatment from the Vincent Andrology Lab at Massachusetts General Hospital have shown a correlation between BPA exposure, increased DNA damage in spermatozoa, and reduced semen quality [47].

2.2. Phthalates

Phthalates are used as plasticizers, and are present in hundreds of products, including vinyl flooring, lubricating oil, and personal care products. Due to endocrine-disrupting properties, phthalates are well-known to cause reproductive and developmental abnormalities [64]. They exert their anti-androgenic action by hindering testosterone synthesis in Leydig cells, resulting from cytochrome CYP17 dysfunction [65]. Exposure to di (n-butyl) phthalate alters gene expression patterns that regulate cholesterol and lipid homeostasis or insulin signaling, which is responsible for lower testosterone synthesis in fetal rat testis (Barlow *et al*., 2003). In a rodent study, prenatal exposure to phthalates induces specific developmental and reproductive abnormalities such as hypospadias, undescended testes, malformations of the epididymis, vas deferens, seminal vesicles, and prostate, reduced sperm counts and testicular cancer that have been identified as a 'testicular dysgenesis syndrome' or 'phthalate syndrome' [65, 66]. Dibutyl phthalate administered during pregnancy and lactation shows the reduced anogenital distance in male rodents [67]. Oral administration of di-(2-ethylhexyl) phthalate in pre-pubertal rats has been shown to increase testicular apoptosis and loss of seminiferous epithelium [34]. There is a strong correlation between anogenital distance and maternal urinary concentrations of phthalate metabolites, and prenatal exposure to phthalates has been shown to alter the anogenital distance in boys [67]. However, a Danish cohort (2010-2012) study has shown that there are no consistent associations between any prenatal phthalate exposure to anogenital distance or penile width in the infant [68]. A prospective Danish-Finnish cohort study on cryptorchidism from 1997 to 2001 has shown that the reproductive hormone profiles and phthalate exposures in newborn boys are in accordance with rodent data and suggests that the development of human Leydig cells and their function may also be susceptible to perinatal exposure to some phthalates [17]. Exposure to phthalates decreases male fertility [38], a short-term *in vitro* incubation of spermatozoa with the phthalates has been shown to decrease sperm motility, while extended incubation of 96 hr, causes sperm cytotoxicity [7]. An inverse association has been reported between increasing concentration of urinary mono (2-Ethylhexyl) phthalate (MEHP) and circulating levels of testosterone, estradiol, and free androgen index [69]. In the body, phthalates are rapidly hydrolyzed by the enzyme esterase in the gut and other tissues into monoesters, the active molecules. For example, DEHP metabolizes to its monoester metabolite, mono-(2-Ethylhexyl) phthalate (MEHP), and DBP is converted into mono-butyl phthalate, with a high concentration of phthalates reducing motility, whereas it is cytotoxic in long-term cultures [7]. DBP could repress steroidogenesis in testes of mice and rats; no effects have been displayed in human xenografts for a range of DBP concentrations [70, 71] shows significant individual variations. The concentration of phthalates in biological fluids in human phthalate exposure has also been positively correlated with reactive oxygen species (ROS) production and increased DNA sperm damage [72]. A few epidemiological studies examined the detection of phthalate metabolites and their association with human testicular function [73], and have shown that there is a weak correlation between urinary metabolites of phthalate and lower sperm concentration, motility, and morphology [73]. However, sperm DNA damage increases in accordance with the urinary levels of phthalate monoester and oxidative metabolites [74]. *In utero* exposure to phthalates has been shown to induce 'testicular dysgenesis syndrome' [75 - 77] and abnormal aggregation of the fetal Leydig cells [78], an occurrence of intratubular Leydig cells, a reduction of fetal testosterone production [75, 79] and Leydig cell Insl3 gene expression [80]. Furthermore, *in utero* exposure to phthalates induces increased Sertoli cell proliferation by altering the ubiquitination pathway [81]. In vitro exposure to metabolites of phthalates, MEHP significantly inhibits the proliferation and differentiation of stem Leydig cells [82]. Increased concentrations of phthalates and their metabolites alter sperm concentration, motility, and morphology by various mechanisms; however, further studies are warranted to correlate exposure to phthalates and male reproductive health.

2.3. Alkylphenols (AP)

Alkylphenols (AP) are present in our environment in the form of isomers, and it becomes challenging when identifying and quantifying each isomer. The consequences of endocrine disruption by AP have been studied substantially in laboratory rodents by subjecting them to 4-n-nonylphenol (NP) for up to the third generation [112]. Sub-acute exposure of juvenile rats to NP causes testicular damage and depletion in spermatogenesis [113], and a notable increase in the rate of Sertoli cell apoptosis has also been observed *in vitro* studies with NP [114]. Several isomers of NP have also hindered testosterone biosynthesis by inhibiting testicular steroidogenesis in rats [115]. Gestational Exposure to NP has been shown to alter the epididymal weight [116].

2.4. Persistent Organochlorine Pollutants (POPs)

POPs are a large group of chemicals that include polychlorinated biphenyls (PCB), polychlorinated dibenzofurans (PCDFs), and polychlorinated dibenzo-dioxins (PCDDs), and the pesticide dichlorodiphenyltrichloroethane (DDT). PCBs are very stable mixtures of organochlorine chemicals that are resistant to extreme temperature and pressure; therefore, they are used widely in electrical equipment like capacitors and transformers as well as in hydraulic fluids, heat transfer fluids, lubricants, and plasticizers. Upon Exposure, PCBs are generally metabolized to phenols along with the formation of intermediates such as arene oxide *via* the P_{450} microsomal monooxygenase system. Due to its electrophilic nature, arene oxide covalently binds to

nucleophilic cellular macromolecules such as DNA, RNA, and proteins and induces DNA strand breaks. Most of the toxic effects caused by PCDDs and PCDFs are mediated by the aryl hydrocarbon receptor (AHR), a ligand-activated transcription factor. Dioxins are a class of chemicals (polychlorinated dibenzo-*p*-dioxins) formed as by-products of incomplete combustion of chlorinated waste and in contact with plastics with hot surfaces. TCDD is structurally similar to polychlorinated aromatic hydrocarbons that act through the Ah receptor mechanism [117, 118]. After binding with the cytosolic receptor, the dioxin-receptor complex undergoes dimerization with the AHR nuclear translocator protein.

Consequently, this complex binds to dioxin response elements (DREs) on DNA, resulting in the induction of target genes such as CYP1A1 transcription [119]. Apart from inducing general toxicity, TCDD is well known to cause reproductive toxicity [90]. Following maternal exposure, the fetal pituitary gonadotrophin is the initial target of dioxins and indirectly impacts testicular steroidogenesis [120]. Interestingly, exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in infancy has been shown to reduce sperm concentration and motility, but an opposite effect has been reported during puberty [121]. NIOSH cohort studies have shown that workers exposed to high concentrations of TCDD result in decreased testosterone and increased gonadotrophin concentrations [122], suggesting that persistent organochlorine pollutants negatively impact male reproductive health.

2.5. Perfluorinated Compounds (PFCs)

Perfluorinated compounds (PFCs), such as perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA), are synthetic chemical substances with endocrine-disrupting properties. These substances are widely used as lubricants and surfactants in the industry and products like clothes, household utensils, and food wrapping. PFC has long half-lives, ranging from 3.5 to 7.3 years [123], and has been shown to bioaccumulate in animal tissues [124]. Epidemiological studies have confirmed the effects of PFCs exposure on testicular function [125]. High PFOS and PFOA serum levels have been shown to lower sperm concentration and also, *in utero* exposure of men to PFOA led to lower sperm numbers and higher levels of LH and FSH. PFCs also cause Leydig cell hyperplasia [126] and inhibits spermatogenesis in rats following pubertal exposure [127].

2.6. Pesticides

Despite its benefits in controlling agricultural pests, pesticide persists in soils and water bodies, moves up to the trophic chains, and affects predators. Several reproductive disorders have been connected to pesticide exposure, and more than one hundred of them have been listed as reproductive toxicants. Pesticides may act as endocrine disruptors by various mechanisms, including agonist receptors such as estrogen receptor, androgen receptor, estrogen-related receptor, pregnane X receptor, aryl-hydrocarbon receptor, and antagonist receptor by interfering with the synthesis, transport, metabolism, and excretion of natural hormones. The negative effect of pesticides includes abnormalities in reproductive and sexual development, gametogenesis, and early development of the fetus. Dichlorodiphenyltrichloroethane (DDT), a persistent organochlorine compound, was heavily used in the 1940s as a broad-spectrum insecticide. It was banned in the 1970s due to its estrogenic properties that have been shown to interfere with pubertal development [128]. Similar to DDT, organochlorine insecticides such as endosulfan and lindane have altered the testicular function in animal models [129 - 135]. Methoxychlor, an organochlorine pesticide introduced as an alternative to DDT, was also banned in the United States due to its endocrine-disrupting properties. It was detected in human adipose tissue and has impaired male reproduction [96, 97, 136]. We have also shown that methoxychlor induces apoptosis via mitochondria-and FasL medicated pathways in adult rat testis [137].

2.7. Phytoestrogens

Phytoestrogens are plant-derived substances possessing endocrine-disrupting effects; due to their consumption of foods and food products, it has been widely detected in human urine and blood samples across several countries [138, 139]. Perinatal exposure of rats to a dietarily relevant mixture of phytoestrogens has been shown to lower sperm quality by disrupting the hypothalamic-pituitary-gonadal axis and hormonal balance [140]. A higher soy food intake and isoflavone are associated with lower sperm concentration [141]. A case-control study has shown higher risks of male infertility following increasing exposure to phytoestrogens such as daidzein, genistein, and secoisolariciresinol [142]. Genistein is another well-studied phytoestrogen that acts as a tyrosine kinase inhibitor [143] and an antioxidant [144]. Phytoestrogen exposure interferes with the androgen receptor pathway and affects spermatogenesis's late steps [145]. *In utero* and neonatal exposure to genistein shows delayed spermatogenesis and a reduced number of epididymal sperm [146]. Since phytoestrogens are nonsteroidal compounds that mimic estrogen and act *via* estrogen receptors, once bound, they not only act as estrogen agonists but also behave as selective estrogen receptor modulators. Exposure to phytoestrogens shows detrimental effects on male reproductive health [104].

2.8. Cigarette Smoke and Endocrine Disruptors

Cigarette smoke contains numerous endocrine-disrupting chemicals that are noxious and toxic to the human body. Several studies have shown that exposure to nicotine decreases sperm motility and count and increases the percentage of sperm abnormality [147, 148] as well as decreases testosterone levels in rats [149 - 151]. Constituents in cigarette smoke such as benzo (a) pyrene and cadmium (Cd) are some of the well-known endocrine disruptors shown to alter male reproductive health. Smoking habits significantly correlate with Cd level in bodily fluids [152]. Further studies with an animal also confirm that Cd causes reproductive toxicity, including reducing sperm cell numbers and sperm motility with increases in DNA fragmentation and sperm abnormality [153]. Cd also interferes with steroidogenesis and may act as an estrogen-like factor by binding to ER. Benzo(a)pyrene alters sperm functional competence, evidenced by a reduced percentage of acrosome halo formation and sperm hyperactivation [154]. Prepubertal

exposure to Benzo(a)pyrene alters the male reproductive parameters [155]. Even though the relationship between tobacco smoking and semen quality has remained controversial for the past several decades, most studies have reported significant changes in the conventional semen parameters, including semen volume, sperm density, motility, viability, and normal morphology in the smoking population and suggesting that smoking harms the male reproductive health [155, 156].

CONCLUSION

Exposure to endocrine-disrupting chemicals may lead to adverse health effects at different stages of life-based on the time and duration of exposure. The role of endocrine disruptors as genotoxic/ epigenotoxic agents raises the issue of epigenome altering that may influence the health of the actual and future population. The influence of EDCs on reproduction, development, growth, metabolic rate, and gender behavior converts into present health hazards. Also, a change in dietary intake is responsible for increasing consequences. Furthermore, there is an increasing amount of research to describe that male children are more likely to develop reproductive disorders in response to neonatal and especially prenatal exposure; such exposures are even more likely to occur now with the increasing Exposure to EDCs from general consumers goods. Reproductive health is decreasing, as evidenced by the increased number of infertility cases that correlate with environmental exposure to endocrine-disrupting chemicals and lifestyle changes. Several *in vivo* studies for a few decades with rats and mice strongly support exposure to chemicals having endocrine-disrupting chemicals adversely affecting both male and female reproductive systems and fertility. However, no direct study correlates human exposure to endocrine disruptors and reproductive health, but based on animal studies, these chemicals can pose a significant threat to human reproduction. Several endocrine disruptors have been found in the bodily fluid of humans, suggesting that further studies are needed to elucidate their reproductive and non-reproductive effects. Even though, many known endocrine-disrupting chemicals present in our environment, either alone or in combination, pose a great threat to organisms. Apart from known environmental contaminants having endocrine-disrupting properties, several unknown chemicals are also present in our environment, and their effect needs to be studied in the future to understand their effect on reproductive and non-reproductive health.

LIST OF ABBREVIATIONS

ED	=	Endocrine Disruptor
BPA	=	Bisphenol A
DDT	=	Dichlorodiphenyltrichloroethane
FSH	=	Follicle Stimulating Hormone
LH	=	Leutinizing Hormone
ER	=	Estrogen Receptor
EDC	=	Endocrine Disrupting Chemical

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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