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Environmental toxicants and male fertility

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A B S T R A C T

Semen quality has declined especially among Western men. Experimental and epidemiological studies have shown potential links between exposure to environmental toxicants and poor male fertility. Some environmental exposures in utero can disrupt fetal testicular function and result in cryptorchidism, low semen quality, low serum testosterone levels, and low fertility. Environmental exposure in childhood and adulthood can also adversely affect germ cells, Sertoli cells, Leydig cells, or the hypothalamic-pituitary-testicular axis, resulting in impaired male fertility. In this review, we report the latest results from human studies that investigated the role of endocrine disrupting chemicals, heavy metals, tobacco smoking, alcohol drinking, and use of marijuana in low semen quality and impaired male fertility. Current evidence suggests the relationship between these environmental factors and low male fertility; however, some factors showed conflicting results which need further investigation.

Abbreviations: AhR, aryl hydrocarbon receptor; ART, assisted reproductive technologies; BPA, bisphenol A; CB, cannabinoid; DBCP, 1,2-dibromo-3-chloropropane; DBP, di-n-butyl phthalate; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; DEHP, di(2-ethylhexyl)phthalate; DEP, diethyl phthalate; DiNP, di-isononyl phthalate; EDC, endocrine disrupting chemical; HCB, hexachlorobenzene; MP, methylparaben; PBDEs, polybrominated diphenyl ethers; PCBs, polychlorinated biphenyls; PCDDs, polychlorinated dibenzo-p-dioxins; PCDFs, polychlorinated dibenzofurans; PFASs, poly- and per-fluoroalkyl substances; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; POPs, persistent organic pollutants; p,p'-DDE, p,p′-dichlorodiphenyldichloroethylene; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; TSC, total sperm count.

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Introduction

Current evidence suggests that semen quality has been declining. Carlsen et al. reported in 1992 that sperm concentration of men around the world had decreased over 50 years from 1938 to 1991 [1]. This finding was supported by subsequent meta-analyses [2,3]. The latest systematic review and meta-regression analysis by Levine et al., in 2017 demonstrated a significant decline in sperm concentration among men of Western origin and unselected by fertility by 52%, which equals 1.4% per year, from 1973 to 2011 [4]. Several factors have been proposed to be involved in this adverse trend, including dietary changes, increasing rates of obesity, chronic diseases, tobacco smoking, substance abuse, lifestyle changes, and environmental toxicants [5,6].

Male infertility is a public health concern. It is associated with the need for assisted reproductive technology, which is of high cost, causing psychological stress to couples. In addition, the female partner may have to undergo assisted reproductive technologies (ART), which can cause emotional and physical stress to her since the currently available infertility treatment focuses on females [7,8]. In addition, recent studies demonstrated that male fertility reflects a man's general health, and male infertility is related to an increased risk of cardiovascular disease [9,10].

We reviewed the role of environmental toxicants on male fertility, focusing on clinical research articles and meta-analyses, when available.

Mechanisms of environmental chemicals affecting male fertility

Endocrine disrupting chemical (EDC) is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations [11]. Exposure to environmental chemicals can affect male fertility in several ways. First, EDCs can interfere endocrine actions at one or more hormone receptors. Estrogenic or anti-androgenic actions can alter normal male physiology. Bisphenol A (BPA), parabens, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), phthalates, alkylphenols, ultraviolet (UV) filters, and some pesticides, for instance dichlorodiphenyltrichloroethane (DDT) and its metabolites, can act as xenoestrogens [12]. Chemicals with anti-androgenic properties are, for example, PBDEs, p,p′-dichlorodiphenyldichloroethylene (p,p'-DDE), phthalates, and poly- and per-fluoroalkyl substances (PFASs). Dioxins and polycyclic aromatic hydrocarbons can activate the aryl hydrocarbon receptor (AhR), which also has a role in the male reproductive system [13,14]. Some EDCs can disturb hypothalamic-pituitary-testicular axis function and androgen biosynthesis resulting in decreased testosterone levels and impaired spermatogenesis. For example, some pyrethroids can decrease testosterone biosynthesis, PCBs can inhibit estrogen sulfotransferase and aromatase enzymes, while PFASs have been related to decreased serum testosterone and increased estrogen levels [12,13,15,16].

In addition to the endocrine effects, some chemicals can cause direct toxic effects on accessory male sex organs and the testis, for example, 1,2-Dibromo-3-Chloropropane (DBCP) effects on germ cells [17,18]. In utero exposure to EDCs with antiandrogenic or estrogenic properties is associated with an increased risk of congenital cryptorchidism since testosterone is important for testicular descent in the fetus [19]. Patients with cryptorchidism have an increased risk of impaired spermatogenesis and testicular hormone production, which may cause infertility in adulthood [20]. Here we do not focus on the studies on cryptorchidism, since this topic has been reviewed previously [21]. EDCs can also induce epigenetic changes, particularly DNA methylation, which have a role in the transgenerational effects of EDC exposures [13].

EDC exposure in different periods of life

Prenatal and postnatal exposures to EDCs have different effects on the male reproductive system. Prenatal exposure may influence the development of the testis and the reproductive tract, resulting in subnormal testicular function, including decreased testosterone production [22]. Reduced androgen actions in fetus, particularly during 8–14 weeks of gestation, the so-called masculinization program-

ming window, can disturb male reproductive system development and are associated with congenital cryptorchidism and hypospadias in newborns, as well as low semen quality and low testosterone levels in adulthood [23,24]. Prenatal EDC exposure may also be associated with epigenetic changes in sperm, which may be transferred to the offspring [25]. Postnatal EDC exposure can affect the hypothalamic-pituitary-gonadal axis resulting in decreased testosterone production and impaired spermatogenesis [22]. Fig. 1 illustrates the possible impacts of EDC or environmental exposures in different periods of life.

EDC exposure and semen quality

Bisphenol A

Bisphenol A (BPA) is widely used in plastic material production and is detected in containers for food and beverages, kitchen utensils, microwave-cooking plastic containers, and packaged food [26,27]. It was also used in baby bottles until year 2011 [28,29]. Primary modes of BPA exposure are via contaminated food intake and skin contact [28–30]. BPA contamination increases when food has a long storage time in a container, is composed of fat, and is in high temperatures (>70 °C) [26]. BPA in the human body undergoes rapid metabolism and excretion through urine [26]. Therefore, studies on the associations between bisphenol A and semen quality use urinary BPA levels to estimate BPA exposure.

Even though the association between BPA exposure and low semen quality has been shown in experimental studies, clinical studies have shown conflicting results [21]. To date, only one study has investigated the link between in utero exposure to BPA and semen quality. The Western Australian Pregnancy Cohort (Raine) study showed that serum BPA levels of pregnant women were positively associated with sperm concentration and progressive sperm motility of the sons [31].

The relationship between concurrent BPA exposure in adulthood and semen quality was examined in several cross-sectional studies, some cohort studies, and one case-control study. Most studies showed an inverse association between urinary BPA levels and sperm concentration and/or total sperm count. Some studies showed a negative association with sperm motility [21]. However, sperm motility is the only semen parameter that had a significant negative association with urinary BPA levels in a meta-analytic study in 2021 and this association became non-significant when the data were adjusted for publication bias [32].

Phthalates

Phthalates are widely used as plasticizers and additives and are found in a variety of consumer products [33,34]. They can enter the human body by ingestion, inhalation, intravenous administration, and skin contact [33]. They are excreted into urine after a few hours of exposure; therefore, urinary levels of phthalates and their metabolites are the standard methods of evaluation of the level of exposure [36].

The roles of phthalates and their metabolites in low semen quality have been widely studied. Prenatal phthalate exposure was examined in two studies. Negative associations were found between maternal serum monoethyl phthalate (MEP) level and seminal volume, between mono(-carboxyisooctyl) phthalate (MCiOP) level and sperm motility in one study [35], and between mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), MCiOP levels and semen volume in another study [36]. However, both studies measured phthalates or phthalate metabolites from serum, not from urine.

Most studies investigating concurrent phthalate exposure were cross-sectional by design – most of which showed an association with lower sperm concentration, total sperm count, and sperm motility. A meta-analysis of 14 studies in 2015 by Cai et al. reported a negative association between urinary monobutyl phthalate (MBP) and monobenzyl phthalate (MBzP) levels and sperm concentration and negative association between MBP, mono(2-ethylhexyl) phthalate (MEHP) levels and straight line velocity. The increased MBzP and MEP levels were associated with an increased comet extent. Monomethylphthalate was not associated with any semen parameters [37]. A systematic review by Radke et al., in 2018 found moderate to strong evidence of an inverse association between urinary phthalates

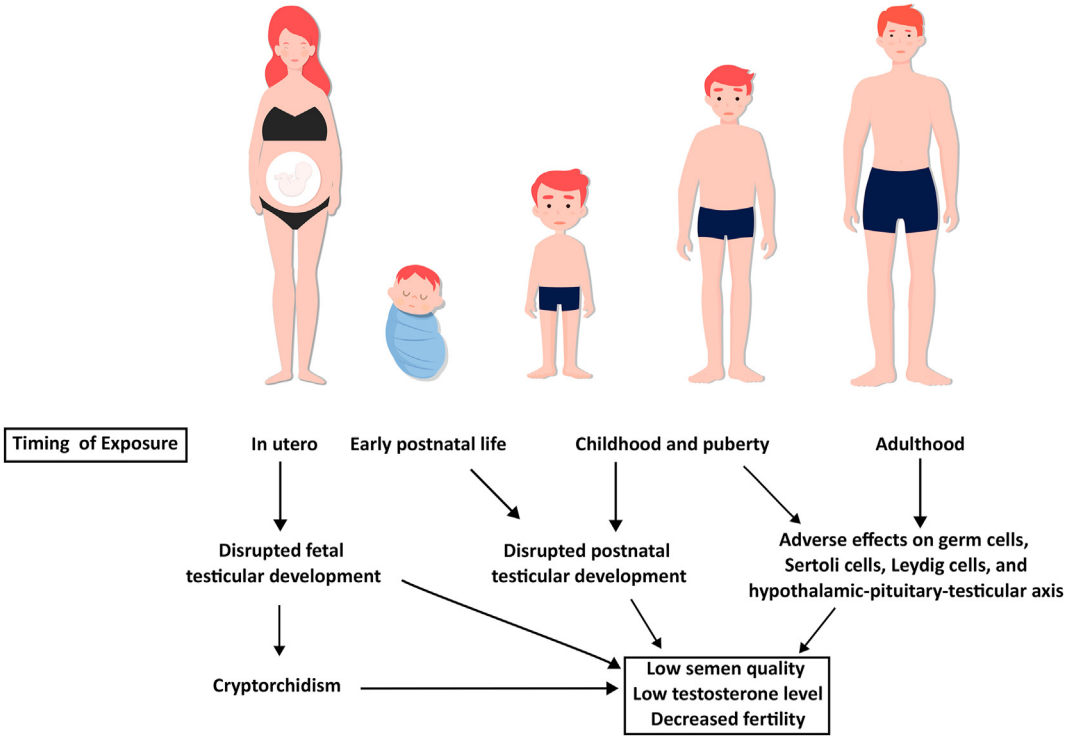

Fig. 1. Possible impact of endocrine disrupting chemical exposure at different periods of life – pregnancy, infancy, childhood, puberty and adulthood. Chemical and environmental exposure in utero may impair fetal testicular development resulting in decreased androgen synthesis. Androgens are crucial for differentiation of external genitalia into normal penis and scrotum, their further growth, and in the transinguinal phase of testicular descent. Decreased androgen level or action in fetus may cause congenital cryptorchidism, low serum testosterone level, poor semen quality, and low fertility in adulthood. Postnatal chemical or environmental exposure may disturb postnatal testicular development resulting in poor male reproductive health in adulthood. Some chemical or environmental exposures may disturb or cause damage to testicular cells or hypothalamic-pituitary-testicular axis and adversely affect male reproductive health.

and phthalate metabolites, including di(2-ethylhexyl)phthalate (DEHP), di-isononyl phthalate (DiNP) (measured by its metabolites, monoisononyl phthalate (MiNP) and mono(carboxy-isononyl) phthalate (MCiNP)), di-*n*-butyl phthalate (DBP) (measured by its metabolite, mono-*n*-butyl phthalate (MBP)), butyl benzyl phthalate (BBP) and semen quality, particularly sperm concentration and some also with sperm motility. There was little evidence of the negative association between DIBP exposure and semen parameters and studies on diethyl phthalate (DEP) showed mixed results [38].

Pesticides

Pesticides contain several chemicals classified by mechanisms of action and biological effects into organochlorines, organophosphates, carbamates, pyrethroids, phenylpyrazoles, and neonicotinoids [39]. Human can be exposed to pesticides via ingestion of contaminated food, inhalation and dermal contact, which can be from environmental or occupational exposure [39].

Organochlorine pesticides, including DDT and its most potent congener, dichlorodiphenyldichloroethylene (p,p'-DDE), hexachlorobenzene, and lindane, have been the most widely studied pesticides. One study showed that maternal serum p,p'-DDE levels were not associated with semen quality of the sons [40]. The studies on adult exposure to organochlorine pesticides and semen quality have shown mixed results; serum or plasma levels of these chemicals were negatively associated with semen volume in some studies and with sperm concentration and sperm motility in a few studies [21].

A limited number of studies investigated the role of chronic organophosphate or pyrethroid exposure on semen quality. Studies on organophosphates assess the level of exposure by measuring the levels of dialkyl phosphates or acetylcholinesterase or butyrylcholinesterase activity. A meta-analysis by Giulioni et al., in 2021 showed that organophosphate exposure was negatively associated with semen volume, sperm concentration, total sperm count, and total sperm motility. Pyrethroid exposure was inversely associated with the percentage of sperm with normal morphology [41].

Overall, the evidence suggests that pesticide exposure was associated with decreased semen quality with varied associations with each semen parameter [42].

Perfluorinated compounds

Poly- and perfluoroalkyl substances (PFASs) such as perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are used in fire-fighting foams, hydraulic fluids for aircraft, waterproof textiles, and non-stick household cookware [16]. Because of their long half-life and widespread use, their health effects are of concern. Maternal PFOA levels were negatively correlated with sperm concentration and total sperm count of the sons, while maternal PFOS levels were not significantly associated with any semen parameters [43]. Cross-sectional studies on associations between levels of perfluorinated compounds, mainly PFOA and PFOS, and semen quality showed mixed results. Some studies showed a lower percentage or number of morphologically normal spermatozoa, lower sperm concentration, total sperm count, or sperm motility in men who had higher serum PFOA or PFOS levels, while some studies did not show these findings [44,45].

Dioxins

Dioxins and dioxin-like chemicals consist of polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs). Of dioxins, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) has the highest toxicity [46]. Mocarelli et al. studied the semen quality of sons born to mothers with a history of TCDD exposure during an accident in Seveso, Italy. The study showed that breastfed sons had lower sperm concentration, total sperm count, progressive motility, and total motile count than breastfed sons of mothers without dioxin exposure. Formula-fed sons with and without maternal exposure had similar semen quality [47]. This study demonstrated the role of in utero and early postnatal dioxin exposure on poor semen quality. Another study found that men who were exposed to TCDD in infancy had lower sperm concentration, progressive sperm motility, and total number of motile sperms compared with men who were not exposed. In contrast, exposure during puberty was associated with higher total sperm count and total motile sperm counts. The exposure in adulthood was

not associated with low semen quality [48]. This study indicates a different influence of TCDD exposure in different periods of life. Also, Minguez-Alarcon et al. showed that serum TCDD levels and PCDD toxic equivalents measured from the boys at the age of 8–9 years were negatively associated with their sperm concentration, total sperm count, and total motile sperm count in adulthood [49].

Polychlorinated biphenyls

Polychlorinated biphenyls (PCBs) belong to a group of persistent organic pollutants (POPs). They were used in many industrial and commercial products, for example transformers, capacitors, electronic equipments, motor and hydraulic oil. Even though they were banned for use in 1970s, their levels can still be detected and may cause adverse health effects because of their lipophilicity and bioaccumulation in fat [50]. One study found that sons of mothers exposed to PCBs and polychlorinated dibenzofurans (PCDFs) during pregnancy had higher percentage of sperm with abnormal morphology, lower sperm motility and lower sperm capacity to penetrate hamster oocytes [51]. A larger study found no significant association between exposure to background PCB levels and semen quality [40]. Several cross-sectional studies investigated the associations between the man's PCB exposure and semen quality. Most of them showed an inverse association, particularly with sperm motility, even though some studies did not [21,52].

Parabens

Parabens are used as preservatives in cosmetics, food, and medicines [53]. Commonly used parabens include methylparaben (MP), propylparaben, and butylparaben [54]. There are limited number of studies on the correlation between urinary paraben concentration and semen quality. They showed mixed results, with some studies showing no correlation [55–57], while some studies showed a negative correlation with sperm motility and sperm count or a positive correlation with percentage of sperms with abnormal morphology [58,59].

Flame retardants

Flame retardants are chemicals that are added to the materials to prevent the fire to start or delay its spread. Flame retardants that are widely used; therefore, most studied are polybrominated diphenyl ethers (PBDEs). Humans can be exposed to PBDEs via ingestion of contaminated food, mainly fish and seafood, inhalation of dust, and skin contact [60,61]. The associations between PBDE congener levels in serum, hair, or seminal fluid and semen quality are inconclusive. Some studies showed that PBDE congeners were associated with low sperm concentration, total sperm count, or sperm motility; however, some studies did not show significant associations with semen quality [21].

Tables 1 and 2 summarize the results of the studies on EDC exposure and semen quality. The table shows that the number of studies on prenatal exposure is limited. The conclusion from studies on postnatal exposure to some chemicals is difficult to draw, because of the limited number of studies and the heterogeneity of the results. BPA and phthalates have the highest amount of evidence, with phthalates having the least heterogeneous results of association with low semen quality.

Tobacco smoking and semen quality and fertility

Maternal smoking during pregnancy has been associated with reduced semen quality of the son in cross-sectional studies [64]. Also, some prospective cohort studies where data on maternal smoking were collected during pregnancy, have reported an association between fetal exposure to maternal smoking and reduced sperm concentration, reduced total number of motile sperm or total sperm count in young men [65,66]. In a large ($n = 984$) longitudinal cohort study, also having prospectively collected data on parental smoking, exposure to maternal light ($\leq$10 cigarettes per day) or heavy (>10 cigarettes per day) smoking during pregnancy were associated with 19% and 38% lower sperm concentration, respectively, and 24% and 33% lower total sperm count in the sons, respectively [67]. Maternal smoking during first trimester of pregnancy has been associated with dose-dependently reduced number of germ cells and somatic cells in the embryonic testes [68].

Table 1
Summary of clinical evidence of the association between prenatal environmental EDC exposure and semen quality.

Chemicals (reference)	Main evidenced associations between chemical exposure and semen quality	Number of studies	Heterogeneity of results
BPA [31]	Positive association with sperm concentration and motility	*	NA, limited number of studies
Dioxins [47]	In utero exposure: lower sperm concentration, TSC, progressive motility, and total motile sperm count	*	NA, limited number of studies
PCBs [40,51]	Negative association with normal morphology and motility in high exposure	*	NA, limited number of studies
p,p'-DDE [40]	NS	*	NA, limited number of studies
Perfluorinated compounds [43]	PFOA: negative association with sperm concentration and TSC PFOS: NS	*	NA, limited number of studies
Phthalates [36,62]	MEP, MEHHP, and MCiOP: negative association with semen volume MCiOP: negative association with sperm motility	*	NA, limited number of studies

Abbreviations: NA, not assessed; NS, no significant association; TSC, total sperm count.
Number of studies: *1–5, **6–10, ***11–20, ****>20 studies.
Heterogeneity of results is classified as *slight; **moderate, ***marked. Marked heterogeneity indicates that the results are mixed, including positive, negative and no association.
Data are summarized from the latest systematic reviews, meta-analyses, or narrative reviews.

Paternal smoking during pregnancy may also be a risk factor for sons reduced semen quality in adulthood. Cross-sectional studies have reported that paternal smoking during pregnancy is associated with up to 41% lower sperm concentration and up to 51% lower total sperm count in the adult sons when comparing with semen quality of adult men whose father did not smoke during pregnancy [69,70]. However, other studies have reported no significant associations [64], and also the above-mentioned large longitudinal cohort study observed only non-significant decrease in sperm concentration and total sperm count in men with a history of paternal smoking during pregnancy [71].

Man's own cigarette smoking has been associated with reduced semen quality in several meta-analyses. A meta-analysis based on 46 studies on semen quality reported that smoking was a risk factor for semen volume, sperm density, total sperm count, the percentage of sperm with progressive motility and the percentage of normal sperm, both among healthy men and infertile men [72]. However, heterogeneity and regional differences in the risk were observed [72]. Among healthy men, the pooled mean differences between smokers and non-smokers were 5.9 million/mL in sperm concentration and 36.9 million in total sperm count [72]. Also, another meta-analysis including only studies published year 2010 onwards and including 5,865 men showed that smoking was overall associated with reduction in sperm concentration, motility and morphology [73]. In general, the negative effect of smoking was more pronounced among infertile men than in the general population, and among heavy/moderate smokers than among mild smokers [73]. A more recent meta-analysis included only studies on infertile men (in total 10,823 infertile men), and also in this analysis tobacco smoking was observed to be associated with increased risk of low sperm concentration (risk ratio 1.29 for oligozoospermia, i.e., sperm concentration above zero but below normal limit) and morphological abnormalities of sperm head, neck, and tail [74]. Another recent meta-analysis evaluated association between exposure to pollution and semen quality, and high exposure to smoking was negatively associated with semen volume, sperm count and concentration, and sperm motility [75]. In conclusion, several meta-analyses have found man's own smoking as a risk factor for impaired semen quality, especially for reduced sperm concentration, motility and percentage of sperm with normal morphology.

Cigarette smoke includes thousands of chemicals, like nicotine, carbon monoxide, and polycyclic aromatic hydrocarbons, and it also includes toxic heavy metals, like lead and cadmium [76]. Cigarette smoke may cause increased levels of oxidative stress (increased seminal levels of reactive oxygen species ROS),

Table 2
Summary of clinical evidence of the association between postnatal environmental EDC exposure and semen quality.

Chemicals (reference)	Main evidenced associations between chemical exposure and semen quality	Number of studies	Heterogeneity of results
BPA [21,32]	Negative association with sperm concentration, TSC, and sperm motility	***	**
Dioxins [48,49]	Exposure in infancy: lower sperm concentration, progressive motility, and total motile sperm count Exposure in peripuberty: lower sperm concentration, TSC, and total motile sperm count [49] Exposure in puberty: higher total sperm count and total motile sperm counts [48] Exposure in adulthood: NS	*	NA, limited number of studies
PBDEs [63]	Negative association with sperm concentration, TSC and sperm motility	**	***
Parabens [55–59]	Negative association with sperm concentration and motility	*	***
PCBs [21,52]	Negative association with sperm motility	**	***
Perfluorinated compounds PFASs [45]	NS	**	***
Pesticides [42]			
Organochlorines [21]			
p,p'-DDE	Negative association with semen volume, motility	**	**
HCB	Negative association with semen volume and sperm motility	*	*
Organophosphates [41]	Negative association with semen volume, sperm concentration, TSC, and total motility	**	**
Pyrethroids [41]	Negative association with percentage of sperm with normal morphology	*	**
Phthalates [37,38]	Negative association with sperm concentration and motility	***	*

Abbreviations: NA, not assessed; NS, no significant association; TSC, total sperm count.
Number of studies: *1–5, **6–10, ***11–20, ****>20 studies.
Heterogeneity of results are classified as *slight; **moderate, ***marked. Marked heterogeneity indicates that the results are mixed, including positive, negative and no association.
Data are summarized from the latest systematic reviews, meta-analyses, or narrative reviews.

increased apoptosis, and alterations in genome and epigenome of the germ cells [76,77]. Smoking may also affect spermatogenesis via affecting reproductive hormone levels [78]. In addition, smoking has been associated with impaired sperm maturation, impaired function of spermatozoa, and reduced fertilization capacity of spermatozoa [77,78]. Studies on pregnancy planners have shown mixed results on the association between male smoking and reduced fecundability [79–81]. In a recent study on couples planning pregnancy, smoking was associated with advanced sperm epigenetic aging, which in turn was associated with increased time to pregnancy [82]. Further studies are needed in order to understand the underlying mechanisms via which smoking causes impaired semen quality and possibly reduced fertility [76,78].

Alcohol and semen quality

In a longitudinal follow-up study of a pregnancy cohort, maternal alcohol consumption during pregnancy was not associated with adult son's semen quality [83]. However, in a larger study based on another pregnancy cohort, maternal alcohol consumption during pregnancy was negatively associated with son's semen quality (sperm concentration) [84]. It has been suggested that alcohol exposure may have a negative effect on development of Sertoli cells [84]. Further clinical studies are needed to evaluate the effects of prenatal exposure to alcohol on semen quality [85].

A large cross-sectional study found no consistent association between semen quality and man's alcohol intake [86]. However, in a meta-analysis based on 15 cross-sectional studies, alcohol was suggested to have effect on semen quality i.e., men with no or low (occasional) alcohol intake had higher semen volume and percentage of sperm with normal morphology than men who reported high (daily) consumption of alcohol [87]. Similar result was obtained in a subanalysis including only studies on men unselected for semen quality and alcohol intake [87]. A previous meta-analysis based on four studies reported also that alcohol is a risk factor for reduced semen volume [72]. It has been suggested that alcohol may affect semen quality via direct effect on spermatogenesis and via affecting testosterone levels [87].

Heavy metals and semen quality or fertility

Cadmium is a non-essential toxic heavy metal, and studies have suggested a negative association between cadmium levels and semen quality, especially sperm motility [88]. According to a meta-analysis of 20 studies, men with low fertility have higher seminal levels of environmental toxicants lead and cadmium when compared with men with normal fertility [89]. Zinc and copper are essential for human body and men with low fertility had lower levels of zinc and no difference in seminal levels of copper was found [89]. Also, a more recent meta-analysis of 11 studies reported significantly higher seminal levels of cadmium among infertile than normal men [90].

In a meta-analysis, men with occupational exposure to lead had significantly higher blood lead levels, lower sperm counts, and poorer sperm motility as compared to men without occupational exposure to lead [91]. Also, among men from infertile couples and without occupational exposure to lead, seminal lead levels have been negatively associated with sperm counts [92]. In the above-mentioned meta-analysis on the association between pollution and semen quality, lead exposure was associated with reduced sperm motility and sperm morphology [75].

Marijuana and male fertility

Marijuana has been widely used as a recreation drug and has also been recently used as medicine for some medical conditions in some regions [93]. The two main active substances in cannabis are tetrahydrocannabinol (THC) and cannabidiol (CBD), which can act on cannabinoid (CB) 1 and 2 receptors as well as transient receptor potential vanilloid 1 (TRPV1), which are expressed in male reproductive organs, including testicular cells. Even though the efficacy and safety of cannabis and cannabinoid agents as medicine are controversial, they are used in some regions for some neurological conditions, neuropathic pain, fibromyalgia, rheumatoid arthritis, chemotherapy-induced nausea and vomiting [94]. Marijuana use has been related to lower sperm concentration, total sperm count, percentage of sperm with normal morphology, and decreased motility in some studies [95–97]. In contrast, one study showed higher sperm concentration and total sperm count among marijuana ever smokers than never smokers [98]. A systematic review and meta-analysis in 2020 did not find any statistically significant association between marijuana use and low semen quality [99]; however, only four original studies were eligible and included. More studies are needed to further investigate the link between marijuana use and low semen quality.

Endocrine-disrupting chemicals - perinatal exposure, epigenetics

Animal studies have shown multi-generational effects and transgenerational effects of EDC exposures [100]. In rodents, some maternal or paternal EDC exposures, including exposure to DDT, DDE, DBP, DEHP, TCDD, and vinclozolin, have been shown to have effects on the offsprings in the next generations and decreased sperm concentration, sperm morphology, total sperm number or fertility were observed in the next generations [100]. The process is believed to occur via epigenetic mechanisms – DNA methylation, histone modification, or non-coding RNA. However, these effects have not been studied in human, because this would need a birth cohort study with a multi-generation follow-up and, and to our knowledge, no such study has been published.

Practice point

Physicians taking care of infertile couples should consider environmental toxicants in the evaluation of male fertility.

Research agenda

More knowledge on the effects of fetal environmental exposures and adult reproductive health is necessary. Birth cohort studies are needed to analyze these effects. Another important topic that needs further research is the mixture effects of the chemicals since humans are exposed to more than one chemical concomitantly.

Declaration of Competing Interest

None.

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