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Environmental contaminants and male infertility: Effects and mechanisms

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Abstract

The escalating prevalence of male infertility and decreasing trend in sperm quality have been correlated with rapid industrialisation and the associated discharge of an excess of synthetic substances into the environment. Humans are inevitably exposed to these ubiquitously distributed environmental contaminants, which possess the ability to intervene with the growth and function of male reproductive organs. Several epidemiological reports have correlated the blood and seminal levels of environmental contaminants with poor sperm quality. Numerous in vivo and in vitro studies have been conducted to investigate the effect of various environmental contaminants on spermatogenesis, steroidogenesis, Sertoli cells, blood–testis barrier, epididymis and sperm functions. The reported reprotoxic effects include alterations in the spermatogenic cycle, increased germ cell apoptosis, inhibition of steroidogenesis, decreased Leydig cell viability, impairment of Sertoli cell structure and function, altered expression of steroid receptors, increased permeability of blood–testis barrier, induction of peroxidative and epigenetic alterations in spermatozoa resulting in poor sperm quality and function. In light of recent scientific reports, this review discusses the effects of environmental contaminants on the male reproductive function and the possible mechanisms of action.

KEYWORDS

endocrine disruptors, environmental contaminants, male infertility, spermatogenesis, steroidogenesis

1 | INTRODUCTION

The global incidence of infertility has risen to 15% in contrast to 7%–8% in the early 1960s (Mascarenhas, Flaxman, Boerma, Vanderpoel, & Stevens, 2012). Over the past several decades, a significant deterioration in male reproductive health has been reported in association with increased industrialisation, which has contributed to a massive release of synthetic pollutants into the environment (Rim, 2017; Skakkebaek et al., 2016). The concerns over declining male reproductive health were elicited by one of the landmark publications by Carlsen et al., which revealed a worldwide reduction in the average sperm count to half between 1940 and 1990 (Carlsen, Giwercman, Keiding, & Skakkebaek, 1992). These findings prompted several scientists, mainly Swan et al. to re-evaluate the trend in semen quality over time in different regions throughout the world and eventually confirmed a significant decrease in sperm concentration in western countries (Swan, Elkin, & Fenster, 1997). Incidentally, a parallel increase in the occurrence of testicular cancer and congenital abnormalities (cryptorchidism and hypospadias) were reported in several countries (Ferguson & Agoulnik, 2013; Hutson, 2000). These observations prompted researchers to explore the potential role of common environmental factors in causing a decline in male reproductive health.

In 1993, it was hypothesised that the growing incidence of male reproductive anomalies could be due to exposure to chemicals possessing oestrogenic property (Sharpe & Skakkebaek, 1993).

Subsequently, numerous studies reported defects in the reproductive ability of wildlife species such as fish, birds, alligators, turtles, salamanders, frogs, toads and Florida panthers, which were exposed to specific industrial chemicals directly or indirectly during prenatal or post-natal period (Barakat, Seymore, Lin, Park, & Ko, 2019; Doyle, Bowman, Windell, McLean, & Kim, 2013; Fang et al., 2018; Unuvar & Buyukgebiz, 2012). The reported reproductive defects in wildlife included, but were not limited to, decreased hatching, gonadal morphological abnormalities, eggshell thinning, demasculinisation and feminisation of the male offspring, altered circulating hormone concentration, impaired viability of offspring and population decline (Anwer, Chaurasia, & Khan, 2016). In addition to several wildlife incidents, a substantial number of epidemiological reports on the declining trends in male reproductive health revealed a strong correlation between exposure to environmental contaminants and reduced semen quality and an increased incidence of cryptorchidism (Street et al., 2018; Woodruff, Carlson, Schwartz, & Giudice, 2008). Occupational exposure to hazardous chemicals has been reported to cause recurrent abortion, congenital defects, stillbirth, testicular dysfunction, sperm abnormalities and impaired male fertility (Kumar, 2018).

Environmental contaminants comprise a wide variety of chemicals such as pesticides, herbicides, fertilisers, plasticisers and surfactants, effluents released from the production units, polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbon (PAH) and heavy metals (Sprovieri et al., 2007). Approximately more than eighty thousand new chemicals have been released into the environment in the past hundred years. They are ubiquitously distributed in the ecosystem and find their way into human life through the food chain. Most of the environmental contaminants have been found in sediment, water, wastewaters as well as in human and wildlife food materials at either low or high levels (Ferrara, Ademollo, Delise, Fabietti, & Funari, 2008; Guenther et al., 2002; Di Nisio & Foresta, 2019; Rodriguez-Mozaz, Marco, Lopez de Alda, & Barceló, 2004; Tavares, Escada-Rebelo, Correia, Mota, & Ramalho-Santos, 2016). In fact, studies have revealed the presence of environmental contaminants in the Arctic region (known as a natural milieu due to its remoteness), which indicates the transport of environmental contaminants to the northern Arctic region by water currents (Carlsson et al., 2018).

The universal presence of environmental contaminants and their ability to intervene with male reproductive development and functions have been well documented (Jeng, 2014; La Rocca et al., 2015). Several animal studies have been conducted to examine the deleterious effects of various environmental toxicants on male fertility and decipher their possible mechanism(s) of action (Akarca-Dizakar et al., 2019; Albert, Nardelli, Lalancette, Hales, & Robaire, 2018; Aydin & Erkan, 2017; Campos et al., 2019; Kim, Cheon, Choi, & Lee, 2019; Kolatorova et al., 2018). The focus of this review is to shed light on the impact of environmental contaminants on male reproduction and the underlying mechanism of action based on the recent scientific data available.

Key points

- Environmental contaminants play a significant role in the growing incidence of male infertility.
- Various environmental contaminants impair testicular steroidogenesis via direct or receptor-mediated inhibition and/or inducing oxidative stress.
- Environmental contaminants disrupt spermatogenesis, Sertoli cell function and integrity of the blood–testis barrier.
- Epigenetic mechanisms are involved in the transgenerational inheritance of reproductive abnormalities induced by environmental contaminants.

Potential areas of research

- Epidemiological studies have correlated the concentrations of environmental contaminants with poor sperm quality, which warrants for establishing predictive biomarkers to identify human exposure to contaminants.
- Epigenetic and transgenerational epigenetic markers for environmental exposure can be deduced in the future by analysing the sperm samples of occupationally exposed subjects and their offspring.
- As we are exposed to a mixture of environmental contaminants in our day to day life, studies focusing on the synergistic effects of various contaminants would be of added value in the current scenario.

2 | IMPACT OF ENVIRONMENTAL CONTAMINANTS ON TESTICULAR FUNCTIONS

Some of the environmental contaminants are known as endocrine disruptors (EDs) due to their capability to mimic endogenous hormones and interrupt the endocrine systems (Rehman et al., 2018). They exhibit oestrogenic and/or antiandrogenic properties and thereby act as an agonist or antagonist of endogenous hormones in the body. Though environmental contaminants affect various organs, the testis is known to be one of the most vulnerable targets. The increased expression of oestrogen receptors (ER) in the testis and the regulatory influence of oestrogen on testicular spermatogenesis and steroidogenesis could be important contributing factors for the increased susceptibility of the testis to the detrimental effects of environmental contaminants.

2.1 | Environmental contaminants and spermatogenesis

Spermatogenesis is an intricate process stringently regulated by various factors and extremely infringed by environmental

contaminants due to its negative influence on germ cell proliferation and differentiation, resulting in male infertility (Smith & Walker, 2014). Exposure to environmental chemicals that mimic oestrogen has been reported to impair spermatogenesis in animals and humans (Jeng, 2014; McLachlan, 2016; Sweeney, Hasan, Soto, & Sonnenschein, 2015; Tavares et al., 2016). The oestrogenic effects of bisphenol A (BPA) measured in fertile and infertile Italian men from metropolitan, urban and rural areas showed an increased expression of ERα and ERβ with other nuclear receptors. In addition, the expression of ER showed a positive association with BPA levels in infertile men from the metropolitan area (La Rocca et al., 2015). On the other hand, maternal exposure of BPA significantly affects first filial generation (F1 generation) males' serum testosterone and oestrogen levels while increasing the expression levels of ERα and ERβ in testicular tissue at post-natal day (PND) 21 and 56 (Wei et al., 2019). Fenvalerate, a synthetic pyrethroid insecticide, has been reported to disturb the spermatogenic cycle in pubertal rats by increasing stage-specific (I-V) germ cell apoptosis (Zhang et al., 2018). Assessment of reproductive toxicity of a brominated organochlorine nematicide, 1,2 dibromo-3-chloropropane (DBCP) and 2-bromopropane (2-BP) using an in vitro human spermatogenic model demonstrated reduced germ cell viability through apoptosis and generation of reactive oxygen species (ROS) resulting in an oxidised cellular milieu (Easley et al., 2015). Governini et al. (2015) examined the presence of perfluorinated compounds (PFC), an organofluorine, in blood and semen samples in correlation with sperm quality, chromosomal segregation and DNA fragmentation (Governini et al., 2015). The study revealed alterations in sperm parameters along with an increased rate of sperm aneuploidy and DNA fragmentation index in PFC positive subjects. These findings suggested that PFC may have adverse consequences on spermatogenesis by disturbing both meiotic segregation and DNA integrity (Governini et al., 2015).

Within the testicular environment, Sertoli cells serve as the nurturing cells and support the developing germ cells through different stages of spermatogenesis. The Sertoli cell to germ cell ratio plays a vital role in the regulation of the spermatogenic energy metabolism and sustaining normal spermatogenesis (Rebourcet et al., 2017). The commonly reported histological changes in the testis of animal models exposed to various toxicants mainly include seminiferous epithelium sloughing (detachment and separation of germ cells from underlying epithelium) and Sertoli cell vacuolisation (Johnson, 2014). Cypermethrin, a synthetic insecticide, caused a substantial rise in epithelial height and dedifferentiation of Sertoli cells in the testis thereby, impairing the structural and functional integrity of Sertoli cells of the adult mouse (Rodríguez et al., 2017). Apart from these degenerative changes, environmental contaminants are also known to impair the molecular signalling pathways between Sertoli and germ cells (Gao, Mruk, & Cheng, 2015). The organochlorine pesticide, endosulfan, caused Sertoli–germ cell degeneration in exposed rats due to increased oxidative stress and associated activation of apoptotic pathway resulting in a decreased production of quality gametes (Rastogi, Narayan, Saxena, & Chowdhuri, 2014).

A study on the effects of 2,2-bis(4-chlorophenyl)-1,1-dichloroethylene (DDE), an organochlorine pesticide and an ethylene metabolite of DDT, on the bioenergetics parameters of testicular mitochondria, revealed a significant reduction in mitochondrial function and its possible implication on the bioenergetics of spermatogenesis and male fertility (Mota et al., 2011). Mice exposed to a low dose of cadmium chloride ($CdCl_2$) significantly altered the immunological microenvironment in the testis as evidenced by increased expression of interleukin (IL)-6, tumour necrosis factor-α (TNF-α) and IL-1β resulting in increased vulnerability to testicular autoimmunity (Ogawa et al., 2013). Geoffroy-Siraudin et al. used a rat seminiferous tubule culture model to demonstrate the dose-dependent toxic effects of hexavalent chromium on meiotic cells (Geoffroy-Siraudin et al., 2010). Among their prominent observations were a decreased number of late spermatocytes and round spermatids along with an increased percentage of synaptonemal complex abnormalities (Geoffroy-Siraudin et al., 2010). More evidence on the deleterious effects of environmental contaminants on spermatogenesis is presented in Table 1.

2.2 | Environmental contaminants and steroidogenesis

Leydig cells present in the interstitial space are the primary cells involved in the biosynthesis of testosterone under the influence of luteinising hormone (LH) (Odermatt, Strajhar, & Engeli, 2016; Tremblay, 2015). Testosterone plays a vital role in the initiation and maintenance of spermatogenesis, differentiation of male genital organs and development of secondary sexual characteristics. Any factor that affects Leydig cell viability and/or interferes with testicular steroidogenesis can lead to the disruption of endocrine regulation of spermatogenesis and impairs fertility. Environmental contaminants are known to impair steroidogenesis by exerting an inhibitory effect on one or more steps in the steroidogenic pathways (Aydin & Erkan, 2017; Maske, Dighe, Mote, & Vanage, 2020; Singh & Singh, 2019) (Table 2).

Studies reveal that exposure to BPA and triclosan results in decreased expression of LH receptor with an associated reduction in adenylate cyclase activity, leading to decreased synthesis of cAMP (Kumar, Balomajumder, & Roy, 2008; Wisniewski et al., 2015). Exposure of preimplantation embryos to BPA has been reported to reduce the levels of steroidogenic acute regulatory protein (StAR) and $P450_{scc}$ leading to reduced testosterone synthesis and resulting in retardation of testicular development in mice (Hong et al., 2016). A similar kind of effect on StAR and $P450_{ssc}$ mRNA expression has been noted in guinea pigs treated with fluoride and aluminium (Dong et al., 2016). Mouse Leydig cells exposed to Aroclor 1,242, a commercial mixture of PCBs, resulted in reduced Leydig cell viability and impaired testosterone biosynthesis by inhibiting two steroidogenic enzymes (3β-hydroxysteroid dehydrogenase [HSD] and 17β-HSD) (Aydin & Erkan, 2017). In adult male rats, organochlorines, namely lindane and methoxychlor, have been reported to alter the testicular levels of StAR protein, androgen-binding

TABLE 1 Effect of environmental contaminants on spermatogenesis

Toxicant (s)	Observed effects	Study model	Reference
Agriculture products			
Pesticides			
2,2-bis(4-chlorophenyl)-1,1-dichloroethylene (DDE)	Inhibition of the oxidative phosphorylation system of testicular mitochondria.	Rat in vivo	(Mota et al., 2011)
Endosulfan	Increased cell death in Sertoli–germ cells due to oxidative stress, depolarisation of mitochondrial membrane and activation of the intrinsic apoptosis pathway.	Rat in vivo	(Rastogi et al., 2014)
Insecticide			
Cypermethrin	Increased epithelial height and the dedifferentiation of Sertoli cells	Mice in vivo	(Rodríguez et al., 2017)
Fenvalerate	Significantly reduced sperm concentration and sperm motility, increased inner diameter of seminiferous tubules, disturbed array of spermatogenic cells and increased germ cells apoptosis.	Rat in vivo	(Zhang et al., 2018)
Fungicide			
Chlorothalonil	Decreased boar sperm motility in vitro, inhibited spermatogenesis in mice via disruption of oestrogen receptor signalling.	Boar sperm in vitro, Mice in vivo	(Zhang et al., 2019)
Plasticisers			
Bisphenol A (BPA)	Seminiferous tubules deformation at varying degrees, testicular apoptosis and reduced spermatozoa in offspring.	Mice in vivo	(Wei et al., 2019)
	Decreased semen quality, antioxidant levels with multiple semen profile defects.	Human semen samples	(Omran, Gaber, Mostafa, Abdel-Gaber, & Salah, 2018)
Bisphenol S	Increased sperm DNA damage, adversely affected sperm quality, function and morphology,	Mice in vivo	(Ikhlas & Ahmad, 2020)
Polybrominated diphenyl ethers (PBDEs)	Decreased sperm concentration and motility.	Human semen analysis	(Albert et al., 2018)
Diethylhexyl phthalate (DEHP)	Disturbed sperm viability, motility and DNA integrity.	Dog in vivo	(Lea et al., 2016)
Industrial influence			
Perfluorinated (PFC)	Altered mitotic segregation via increased alteration in sperm parameters, sperm aneuploidy and increased sperm DNA fragmentation in PFC-contaminated subjects.	Human participants' sperm in vitro	(Governini et al., 2015)
Polychlorinated biphenyl 153 (PCB 153)	Disturbed sperm viability, motility and DNA	Dog in vivo	(Lea et al., 2016)
Air pollution			
$PM_{2.5}$	Decreased sperm concentration, motility and morphology.	Mice in vivo	(Yang et al., 2019)
Non-endocrine disrupting chemicals			
Nematicide			
1,2-Dibromo-3-chloropropane (DBCP)	Induced ROS, reduced germ cell viability through apoptosis, reduced spermatogonia viability, reduced percentage of haploid spermatids.	Human in vitro	(Easley et al., 2015)
Cleaning agent			
2-Bromopropane (2-BP)	Increased ROS, germ cell apoptosis, reduced spermatocyte viability, reduced percentage of haploid spermatids.	Human in vitro	(Easley et al., 2015)
Heavy metal			
Chromium	Decreased late spermatocytes and round spermatids, and increased synaptonemal complex abnormalities.	Rat in vitro	(Geoffroy-Siraudin et al., 2010)

TABLE 2 Effect of environmental contaminants on steroidogenesis

Toxicant (s)	Observed effects	Study model	Reference
Agriculture products			
Herbicide			
Atrazine	Decreased serum testosterone, increased foetal Leydig cell aggregation, down-regulated expression of *Scarb1*, *Cyp17a1* and *Hsd17b3* in Leydig cells	Rat *in utero*	(Fang et al., 2018)
Biocide			
Tributyltin chloride (TBT)	Blocked Leydig cells developmental regeneration by down-regulating steroidogenic gene expression (*Lhcgr*, *Cyp11a1*, *Hsd3b1*, *Cyp17a1*, and *Hsd17b3)*, inhibited proliferation of Leydig cells	Rat in vitro	(Wu et al., 2017)
Fungicide			
Triphenyltin chloride (TPT)	In vivo treatment reduced the testosterone level and lowered *StAR*, *Hsd3b1*, and *Hsd17b3* mRNA levels.	Rat in vivo, in vitro	(Li et al., 2018)
In vitro exposure to TPT increased ROS and rat Leydig cell apoptosis.	Decreased serum testosterone levels, induced foetal Leydig cell aggregation, disrupted foetal Leydig cell and Sertoli cell development	Rat foetal testis, *in utero*	(Ge et al., 2018)
Plasticisers			
Bisphenol A (BPA)	Reduced Leydig cell capacity and decreased sperm count	Human serum samples in vivo	(Adoamnei et al., 2018)
Phthalate mixtures	Prenatal exposure down-regulated the expression of testicular steroidogenic genes	Mice in vivo	(Barakat et al., 2019)
Di-(2-ethylhexyl) phthalate (DEHP) and diethyl phthalate (DEP)	Affected foetal Leydig cell (aggregation and cell size) and StAR expression	Rat in vivo	(Hu et al., 2018)
Industrial influence			
Aroclor 1,242 (Polychlorinated biphenyl)	Reduced Leydig cell viability, increased ROS, inhibited steroidogenic enzymes 3β-hydroxysteroid dehydrogenase [HSD] and 17 β-HSD	Leydig cells in vitro	(Aydin & Erkan, 2017)
n-Butylparaben	Disrupted testicular expression of steroid receptors (ERα and β, AR) and StAR genes	Rats in vivo	(Maske et al., 2020)
Perfluorooctane sulphonate	Lowered testosterone without decreasing LH and FSH, down-regulated Hsd17b3 mRNA level, induced Leydig cell apoptosis.	Rats in vivo	(Li et al., 2018)
Perfluoroalkyl acids (PFAAs)	Reduced intra-testicular and serum testosterone levels accompanied with a decrease in testicular expression of StAR, 3β- and 17β-HSD.	Mice in vivo	(Singh & Singh, 2019)
Air pollution			
$PM_{2.5}$	Decreased levels of testosterone biosynthesis-related genes, StAR, P450scc, P450arom, ER and FSHR.	Mice in vivo	(Yang et al., 2019)

protein (ABP) and activities of 3β-HSD and 17β-HSD with associated increase in the levels of H_2O_2 (Saradha, Vaithinathan, & Mathur, 2008; Vaithinathan, Saradha, & Mathur, 2008). The inhibitory effects of these organochlorines on steroidogenesis was reported to be due to impaired Sertoli cell function and increased generation of ROS associated with oxidative stress (Saradha et al., 2008; Vaithinathan et al., 2008). Chronic exposure to arsenite, a natural environmental contaminant, has been reported to activate the immunological responses of macrophages in the testis, which affects testosterone metabolism and inhibits steroidogenesis (de Araujo Ramos, Diamante, de Almeida Lamas, Dolder, & de Souza Predes, 2017).

Numerous studies have demonstrated the deleterious effects of phthalates, the most commonly used plasticiser, on Leydig cell steroidogenesis using a rodent model (Rehman et al., 2018; Svechnikov et al., 2016; Wang, Ni, et al., 2019). The study conducted with human organo-culture adult testis revealed the inhibitory effect of di-(2-ethylhexyl) phthalate (DEHP) and mono-(2-ethylhexyl) phthalate (MEHP), on steroidogenesis, notably androgen synthesis in testicular tissue (Desdoits-Lethimonier et al., 2012). In fact, epidemiological studies have demonstrated an inverse correlation between serum testosterone concentration and urinary levels of MEHP (Svechnikov et al., 2016).

2.3 | Environmental contaminants and blood–testis barrier

The blood–testis barrier (BTB) is comprised of tight junctions (TJ), gap junctions and adherent junctions (AJ) between the Sertoli cells (Mruk & Cheng, 2015). The BTB segregates the seminiferous epithelium into two

sections, namely the basal and the apical compartments. Post-meiotic germ cell development takes place in the apical compartment, while spermatogonial renewal and differentiation up to pre-leptotene spermatocytes occur in the basal compartment of the epithelium (Cheng & Mruk, 2011; Xiao, Mruk, Wong, & Cheng, 2014). Furthermore, the BTB creates an ideal milieu for meiosis and development of post-meiotic germ cells in isolation from the systemic circulation, which would otherwise result in the development of anti-sperm antibodies (Islam et al., 2017). The presence of multiple junction types has been attributed to the inherent tightness of the BTB. Ironically, the BTB is one of the primary targets for various environmental toxicants (Chianese et al., 2018; de Freitas et al., 2016; Qiu et al., 2016; Zhou et al., 2020). Exposure to the commercial PCB mixture, Aroclor 1,254 resulted in disruption of the BTB in treated rats and cultured Sertoli cells by promoting endocytosis and degradation of junctional proteins via the p38 mitogen-activated protein kinase (MAPK) pathway (Jia et al., 2017). Also, $CdCl_2$ has been reported to disrupt the BTB via the p38 MAPK signal transduction pathway (Siu, Mruk, Porto, & Cheng, 2009). In another study, in vivo and in vitro models were used to demonstrate the effect of perfluorooctane sulphonate (PFOS), a ubiquitous pollutant, on the BTB. Exposure to PFOS resulted in increased BTB permeability, p38/activating transcription factor 2 (ATF2) phosphorylation and matrix metalloproteinase 9 expressions with a parallel decrease in the expression of BTB proteins (occludin and connexin 43) highlighting the role of p38/ATF2/MMP9 signalling pathway in PFOS-mediated BTB disruption (Qiu et al., 2016). Effects of BPA and $CdCl_2$ on cultured human Sertoli cell revealed perturbation of Sertoli cell adhesive function by inducing alterations in the F-actin network (Xiao et al., 2014). Exposure of human Sertoli cells to monobutyl phthalate (MBP), an endocrine disruptor, resulted in reduced expression of junctional proteins occludin, ZO-1, β-catenin and androgen receptor (AR) (de Freitas et al., 2016). The study revealed that MBP alters the structural and functional integrity of BTB via the AR-dependent pathway (de Freitas et al., 2016). This report points to the increased susceptibility of the junctional proteins to the detrimental effects of various environmental toxicants.

Dankers et al. reported that some of the endocrine disruptors such as BPA, tetrabromobisphenol A (TBBPA), DEHP, MEHP, perfluorooctanoic acid (PFOA) and PFOS interfere with ATP-binding cassette transporters in the BTB resulting in decreased testosterone secretion in murine Leydig cells (MA-10) (Dankers et al., 2013). A recent report shows chronic exposure of BPA in rats via the placenta, over lactation and at weaning increased the body weight in the male offspring at PND 45 and affected the first round of spermatogenesis by damaging BTB, DNA and decreasing the expression of protein sirtuin 1(SIRT1) (Chianese et al., 2018).

3 | IMPACT OF ENVIRONMENTAL CONTAMINANTS ON EPIDIDYMAL FUNCTIONS

The spermatozoa exiting the testis are immotile and lack the ability to fertilise an egg. The epididymis provides an ideal milieu for sperm maturation and storage (in the distal cauda). Spermatozoa acquire forward motility as well as fertilising ability during their transit through the epididymis (Sullivan & Mieusset, 2016). The epithelium of the epididymis is characterised by a unique set of tight junctions that contribute to the formation of a blood–epididymis barrier, which is responsible for the maintenance of a distinct intraluminal microenvironment. In fact, the proteins and enzymatic composition of the intraluminal fluid continuously change along the epididymis from caput to cauda, which facilitates the essential morphological and biochemical changes associated with sperm maturation. Therefore, any factor that disrupts the structure and/function of the epididymis can result in the impairment of sperm maturation and hence, affect male fertility.

The most commonly reported effects of environmental contaminants on the epididymis include a reduction in the epididymal weight, degenerative changes in the epithelium and decreased epididymal sperm count (Li et al., 2019). Exposure of adult rats to a mixture of heavy metal cadmium and pesticide diazinon resulted in significant structural changes in epididymal tissue such as epithelial thickening, necrosis of epithelial cells, constriction of blood vessels, interstitial oedema and infiltration of the mononuclear cell (Adamkovicova et al., 2014). A recent study investigated the juvenile toxicity of inorganic arsenic in prepubertal rats following exposure to dose levels (0.01 and 10 mg/L) that reflect realistic environmental concentrations. The study demonstrated disruption of testicular and epididymal histoarchitecture and inflammatory infiltration, reduced epididymal sperm concentration in the lumen and alterations in the expression of androgen receptor in the epididymis (da Cunha de Medeiros et al., 2019).

Maternal exposure to EDs such as BPA has been reported to disrupt reproductive functions in the offspring by increasing sperm reserves and transit time in cauda epididymis leading to sperm abnormalities (Campos et al., 2019). Altered expression of tight junctional proteins, occluding and ZO-1 has been reported in mice exposed to PCB (Cai, Wang, Huang, Chen, & Zuo, 2013). Similar effects have been documented in rodents exposed to BPA along with significant damage to epididymal tissue and abnormalities in the sperm head and tail (Akarca-Dizakar et al., 2019).

4 | IMPACT OF ENVIRONMENTAL CONTAMINANTS ON PROSTATE AND SEMINAL VESICLES

Seminal vesicle and prostate are the two main accessory sex glands that contribute 90% of the seminal plasma content, with the remaining 10% coming from the epididymis and testis (Verze, Cai, & Lorenzetti, 2016). Seminal plasma serves as a medium to protect, nourish and carry spermatozoa after ejaculation up to fertilisation and contains essential modulators of sperm function. Seminal levels of environmental contaminants correlate negatively with sperm quality and biochemical markers of accessory sex glands in infertile men (Pant et al., 2003; Pant, Mathur, Banerjee, Srivastava, &

Saxena, 2004; Vitku et al., 2016). Pant et al. (2004) reported higher concentrations of chlorinated pesticides [isomers of hexachlorocyclohexane (HCH) and metabolites of dichlorodiphenyltrichloroethane (DDT)] in the semen of infertile men when compared to fertile subjects (Pant et al., 2004). Furthermore, the study revealed a direct correlation between seminal concentrations of chlorinated pesticides and fructose in infertile subjects. Fructose is crucial for sperm metabolism and motility, while seminal levels of fructose are suggestive of decreased utilisation by spermatozoa resulting in diminished motility. Pant et al. (2004) also reported a negative association between seminal concentration of chlorinated pesticides (α-HCH, β-HCH and *pp*'-DDE, a metabolite of DDT) and prostatic markers, namely acid phosphatase and γ-glutamyl transpeptidase, which indicated decreased prostatic function (Pant et al., 2004). A similar association has been shown between seminal plasma levels of heavy metals (lead and cadmium), and seminal vesicle and prostatic markers in infertile men (Pant et al., 2003).

Several contaminants have been shown to reduce the weight of seminal vesicles and prostate by either directly inducing degenerative histoarchitectural changes or indirectly via inhibition of the testicular production of testosterone, the major growth factor of accessory sex glands (Hou et al., 2020; Riad, Abd-Rabo, Abd El Aziz, El Behairy, & Badawy, 2018; Sugantha Priya et al., 2017). In a rodent model, exposure to BPA and octylphenol (OP) resulted in atrophic tubules and intraepithelial neoplasia of the prostate gland (Ahbab, Barlas, & Karabulut, 2017), while cadmium-induced vasoconstriction and degenerative cellular changes in the seminal vesicles and prostate (Sayed, Hassanein, & Senosy, 2014). Prenatal exposure to a mixture of phthalate, equivalent to human exposure levels, resulted in smaller gonads, prostates and seminal vesicles in F1 male mice with drastically decreased expression of steroidogenic genes and serum testosterone levels (Barakat et al., 2019).

5 | EFFECT OF ENVIRONMENTAL CONTAMINANTS ON SPERM FUNCTION

Male infertility is evaluated based on semen quality such as sperm density, motility, vitality and morphology. During the past few decades, the decrease in human semen quality and increasing prevalence of cryptorchidism in infants has been correlated with exposure to environmental contaminants. Lea et al. (2016) observed a decline in sperm quality in breeding dogs for the past 26 years (1988–2014) and increased number of cryptorchidism in male offspring from 1995 to 2014 (Lea et al., 2016). Furthermore, the study revealed the presence of phthalate (DEHP) and organochlorine (PCB 153) in adult dogs' testes and commercial dog foods at a disturbing level (Lea et al., 2016). In vitro exposure of human and dog spermatozoa to PCB153, and DEHP at different concentrations resulted in increased DNA fragmentation and decreased motility (Sumner, Tomlinson, Craigon, England, & Lea, 2019). Numerous epidemiological studies have demonstrated the negative correlation between seminal or urinary level of environmental contaminants (such as PCB, triclosan, BPA, lead) and low semen quality in men exhibiting alterations in sperm concentration, total sperm count, motility, viability and morphology (Albert et al., 2018; Mantzouki et al., 2019; Nassan et al., 2019; Paul et al., 2017; Ren et al., 2019). Wang et al. reported elevated urinary phthalates associated in men with poor sperm quality caused by metabolic disorders of seminal plasma mostly linked to PUFA and acylcarnitine (Wang, Wu, et al., 2019).

In vitro exposure of rodent spermatozoa to different concentrations of BPA inhibited sperm motility and motion kinematics through a significant reduction in ATP levels in spermatozoa (Rahman et al., 2015). Furthermore, higher concentrations of BPA increased the tyrosine phosphorylation of sperm proteins by regulating protein-dependent kinase (PKA) activity, which mediates acrosome reaction. BPA-mediated changes in fertility-related proteins induced premature acrosome reaction, resulting in poor fertilisation, and compromised embryonic development (Rahman et al., 2015). In vivo exposure to BPA has also been reported to adversely affect sperm quality, functions and morphology of exposed mice by inducing oxidative stress and DNA damage in spermatozoa (Ikhlas & Ahmad, 2020). In vitro treatment of human spermatozoa with two different phthalates, di-butyl phthalate (DBP) and mono-n-butyl phthalate (MBP), showed a detrimental effect on sperm motility, penetration capability and capacitation along with suppressed sperm tyrosine phosphorylation, which is involved in the regulation of sperm functions (Xie et al., 2019). In vivo exposure of DBP from medications of inflammatory bowel disease (IBD) resulted in differential expression of numerous sperm RNA elements as well as activation of oxidative stress and DNA damage pathways in spermatozoa of patients with IBD (Estill, Hauser, Nassan, Moss, & Krawetz, 2019). Chlorothalonil, a broad-spectrum fungicide, decreased boar spermatozoa motility and increased apoptosis by altering mitochondrial membrane potential (Zhang et al., 2019).

6 | EPIGENETIC EFFECTS OF ENVIRONMENTAL CONTAMINANTS ON MALE REPRODUCTION

Growing evidence indicates that epigenetic alterations can be an essential mechanism in mediating the impact of environmental contaminants on male reproduction (Donkin & Barres, 2018). The epigenetic mechanism includes DNA methylation, modification of histones and miRNAs gene expression (Dada et al., 2012; Muratori & De Geyter, 2019). Pubertal exposure to zearalenone (ZEA), an ED, has been reported to disturb the meiosis process and signalling pathways in spermatogenesis, leading to diminished semen quality in mice (Gao et al., 2015). Furthermore, DNA methylation markers 5mC and 5hmC were decreased, and histone methylation marker H3K27 was increased along with the decreased expression of testicular ERα in mice exposed to ZEA (Gao et al., 2015; Men et al., 2019). These studies revealed the crucial role of interactions between the oestrogen signalling pathway and genetic and epigenetic pathways in mediating the adverse effects of ZEA on spermatogenesis (Gao

et al., 2015; Men et al., 2019). Kim et al. reported nonylphenol induced pathophysiological abnormalities in testis and epididymis of F2 mice, which were suggested to be a result of epigenetic reprogramming by nonylphenol exposure (Kim et al., 2019).

Developmental exposure to environmental contaminants can lead to the transmission of epigenetic alterations across the generations known as transgenerational epigenetics (Rothstein, Harrell, & Marchant, 2017). Yuan et al. (2017) showed that embryonic exposure to DBP disturbs testicular function in F1 and F3 generations by modulating Sertoli cells and spermatogenesis. The exposure to DBP modified the global DNA hypomethylation in the offspring with a decrease in *follistatin like 3* (*Fstl3*) promoter hypomethylation (Yuan et al., 2017). Similarly, transient gestational exposure to atrazine induced differential DNA methylation regions in the F1-F3 generation spermatozoa (McBirney et al., 2017). Several recent studies have demonstrated the transgenerational inheritance of epigenetic alterations induced by embryonic exposure to environmental contaminants such as chlordecone, DDT, vinclozolin and DEHP leading to the deterioration of testicular architecture and sperm quality in F1 to F3 offspring (Ben Maamar et al., 2019; Doyle et al., 2013; Gely-Pernot et al., 2018; Skinner et al., 2019).

7 | MECHANISM OF ACTION OF ENVIRONMENTAL CONTAMINANTS

Environmental contaminants can disrupt the male reproductive system via various mechanisms (Figure 1). Numerous studies have reported that environmental contaminants exert their reprotoxic effects by targeting the endocrine system (Buck Louis et al., 2018; Dankers et al., 2013; Jeng, 2014; McLachlan, 2016). Specifically, these contaminants are known to possess oestrogenic or antiandrogenic properties and thereby affect the hypothalamic–pituitary–gonadal (HPG) axis resulting in impairment of reproductive function. The process of gonadotropin-releasing hormone (GnRH) release, gonadotropin secretion and subsequent downstream signalling are all potentially affected by environmental contaminants (Adoamnei et al., 2018; Rehman et al., 2018; Ren et al., 2019; Wisniewski et al., 2015). For instance, BPA, due to its antiandrogenic or antioestrogenic effect, has been reported to disturb the HPG axis through competitive inhibition at the receptor level resulting in hormonal imbalances and poor semen quality in men with higher urinary concentrations of BPA (Lassen et al., 2014). Disturbances in the HPG axis induced by environmental contaminants lead to changes in the levels of gonadotropins resulting in reduced serum LH, FSH and testosterone levels (Adamkovicova et al., 2014; Rehman et al., 2018; Ren et al., 2019; Wisniewski et al., 2015).

Environmental contaminants are known to affect LH receptors (LHR) expression on Leydig cells resulting in the inhibition of testicular steroidogenesis (Wang, Chen, Ye, Zirkin, & Chen, 2017). For instance, PFOS and PFOA have been reported to bind with LHR and inhibit testosterone synthesis (Foresta, Tescari, & Di Nisio, 2018). Reduction in the LHRs and impairment of downstream signalling (decreased adenylate cyclase and cAMP), as well as inhibition of steroidogenic enzymes, are commonly reported following exposure to various environmental contaminants (Pogrmic-Majkic et al., 2016; Wang, Chen, Ye, Zirkin, & Chen, 2017). Furthermore, decreased expression of StAR and inhibition of $P450_{scc}$, the rate-limiting steps of steroidogenesis, have been repeatedly reported as one of the mechanisms involved in the anti-steroidogenic effect of environmental contaminants (Hong et al., 2016; Kariyazono et al., 2015; Paul et al., 2017). Apart from the direct inhibitory effect on

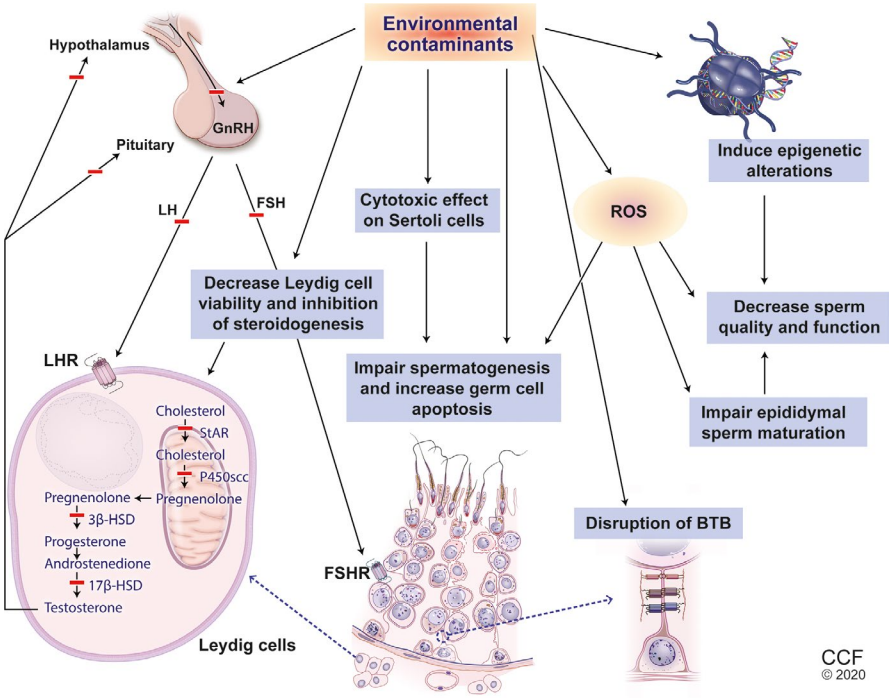

FIGURE 1 Mechanisms of action of environmental contaminants. Symbol (=) indicates inference by environmental contaminants; GnRH, gonadotropin-releasing hormone; LH, luteinising hormone; FSH, follicle-stimulating hormone; LHR, luteinising hormone receptor; StAR, steroidogenic acute regulatory protein; $P450_{scc}$, P450 side-chain cleavage enzyme; 3β-HSD, 3β-hydroxysteroid dehydrogenase; 17β-HSD, 17β-hydroxysteroid dehydrogenase; FSHR, follicle-stimulating hormone receptor; ROS, reactive oxygen species; BTB, blood–testis barrier

multiple steroidogenic enzymes, environmental contaminants are also known to inhibit the activities of these enzymes indirectly by inducing oxidative stress (Saradha et al., 2008; Sheweita, Al-Shora, & Hassan, 2016; Vaithinathan et al., 2008).

In addition to the steroidogenic pathway, the hormonal action of FSH, testosterone, oestradiol and their regulation by Leydig and Sertoli cells are essential for the maintenance of normal spermatogenesis. Environmental contaminants are reported to alter the spermatogenic cycle in rodent models resulting in increased germ cell apoptosis and decreased production of spermatozoa (McBirney et al., 2017; Zhang et al., 2018). In rodent models, environmental contaminants have been reported to induce germ cell apoptosis via Fas-FasL and mitochondrial-dependent cell death pathway (Vaithinathan et al., 2008; Wang & Su, 2018). Germ cells are dependent on Sertoli cells for functional and nutritional support. Exposure to environmental contaminants leads to the destruction of germ cells by impairing the structure and function of Sertoli cells (Johnson, 2014; Rodríguez et al., 2017). Compounds with hormonal activity such as BPA and phthalates exert their effect on Sertoli cells by modulating the expression of steroid hormone receptors (Gao et al., 2015; Rehman et al., 2018). Studies have reported that BPA acts as an ER modulator and thus, affects the reproductive system by targeting ERα in Leydig cells or ERβ in Sertoli cells (Cariati et al., 2019; Wei et al., 2019). In fact, the expression of nuclear receptors was directly associated with BPA levels in infertile Italian men (La Rocca et al., 2015). These endocrine disruptors affect spermatogenesis by reducing Sertoli cell numbers, proliferation and interaction with spermatogonia, thereby increasing testicular cell apoptosis (Gao et al., 2015; Quan, Wang, Duan, Huang, & Yang, 2017; Rehman et al., 2018). Aggregation of actin filaments in Sertoli cell and associated cytoskeletal disruption has been reported as one of the mechanisms in mediating the cytotoxic effect of BPA on Sertoli cell (Gao et al., 2015).

The gap and tight junctional proteins associated with BTB are one of the primary targets of contaminants (Gao et al., 2015). EDs such as MBP and BPA has been reported to reduce the expression of junctional proteins resulting in disruption of BTB via the AR-dependent pathway (de Freitas et al., 2016). Environmental contaminants such as PFOS and Aroclor 1,254 altered the levels of junctional proteins and increased the permeability of BTB via the p38-MAPK pathway (Jia et al., 2017; Qiu et al., 2016). Impairment in the structural and functional integrity of BTB compromises the immune- privileged status of the testis.

Oxidative stress is one of the main mechanisms involved in mediating the deleterious effects of environmental contaminants on male reproduction (Darbandi et al., 2018; Rehman, Jahan, Ullah, & Winberg, 2019) as increased levels of ROS inhibit the activity of steroidogenic enzymes and activate apoptotic pathways in testis resulting in impairment of steroidogenesis and spermatogenesis, respectively (Quan et al., 2017; Sheweita et al., 2016; Shi, Sekulovski, MacLean, & Hayashi, 2018). Furthermore, alterations in the antioxidant milieu of the epididymis induced by environmental contaminants negatively affect the sperm maturation process resulting in poor sperm quality (Adewoyin et al., 2017; Rahman et al., 2019). Elevated levels of ROS cause deleterious effects on spermatozoa by inducing lipid peroxidation and sperm DNA damage resulting in poor sperm motility, morphology and function (Ikhlas & Ahmad, 2020; Rahman et al., 2015; Xie et al., 2019). Exposure to environmental contaminants impairs testicular and epididymal functions by inducing oxidative stress resulting in deterioration of sperm quality.

8 | CONCLUSION

Environmental contaminants consist of chemicals that cause deleterious effects on male reproduction. These chemicals affect male reproduction by interfering with the HPG axis, testicular spermatogenesis and steroidogenesis, epididymal maturation, steroid receptor mediating signalling, pro-oxidant/antioxidant balance and epigenetic regulation of testis and spermatozoa. Consequently, sperm production, quality, function and morphology are compromised, leading to male infertility. Modulation of steroid receptors, induction of oxidative stress and epigenetic alterations are the key mechanisms involved in mediating the deleterious effects of various environmental contaminants.

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