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Role of endocrine disruptors in male infertility and impact of COVID-19 on male reproduction

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Introduction

The male reproductive system mainly includes a pair of testes, epididymis, vas deferens, ejaculatory duct, and accessory sex glands (such as seminal vesicles, prostate, and bulbourethral glands) and is regulated by hormones secreted from hypothalamus, pituitary, and gonads. All these organs are susceptible to environmental toxicants, drugs, hormonal disruptors, etc. (Sikka, 2018). These agents have effect on the male reproductive system during embryonic stage and/or throughout the life cycle. Under their influence, the reproductive potential of adult male is compromised affecting his fertility capacity. It may also result in mutagenesis and other developmental issues in their progeny. This updated chapter focuses on male reproductive tract as the target site of many such factors, endocrine disruptors (EDs), and their potential mechanisms of action. In addition, the impact of COVID-19-related

infection on the male reproduction is unknown and no scientific data is yet available. Since many healthy young men of reproductive age group are potential target of such infection, it is important to touch some base on this issue.

Development of male genital system

In the initial embryonic phase, male and female external genitalia look similar until 9 weeks. A pair of longitudinal ridges lies ventromedial to the mesonephric kidney. These are called genital or gonadal ridges. Germ cells appear in these ridges after the 5th week. Primordial germ cells appear in the endoderm of the yolk sac and they migrate by amoeboid movements, via dorsal mesentery, reaching and invading the genital ridges during the 5th to 6th weeks. If they fail to reach the ridges, the gonads do not develop. The primitive sex cords arise from the epithelium. Prior to the

onset of sexual differentiation, the human gonads are composed of proliferating coelomic/mesenchymal cells, primordial germ cells, and endothelial cells. The final form of gonads is usually not visible until week 12 (Table 59.1).

Development of the male reproductive system is controlled by the SRY sex-determining gene on the short arm of the Y-chromosome. SRY gene leads to the production of Mullerian-inhibiting substance (MIS), and testosterone. MIS is produced by the Sertoli cells and causes regression of paramesonephric ducts. Testosterone produced by the Leydig cells influences the differentiation of the mesonephric ducts into male genital ducts and modulates the differentiation of the male external genitalia. In females there is no MIS and testosterone and instead development of uterine tubes and uterus takes place from paramesonephric and mesonephric duct system regression.

Male reproductive tract as target site

The human male reproductive tract consists of a pair of gonads called testes, a series of ducts (epididymis, vas deferens, ejaculatory duct, and urethra that serve to transport spermatozoa to the female reproductive tract), and accessory sex glands (seminal vesicles, prostate, and bulbourethral glands). The development and function of these are under control of hormones from hypothalamus, pituitary, and gonads.

Testes

In humans each testis weighs about 25 g (0.875 ounce) and is 4–5 cm (1.6–2.0 inches) long and 2–3 cm (0.8–1.2 inches) in diameter. Each testis is covered by a fibrous capsule called the tunica albuginea and is divided by partitions of fibrous tissue from the tunica albuginea into 200–400 wedge-shaped sections, or lobes. Within each lobe are 3–10 coiled tubules, called seminiferous tubules, which produce the sperm cells. The partitions between the lobes and the seminiferous tubules both converge in one area near the anal side of each testis to form what is called the mediastinum testis. The testes originally develop in the abdomen and descend into the scrotum, a sac of skin and connective tissue positioned outside the pelvic cavity. This scrotal location is important for maintaining a testicular temperature to about 35°C, approximately 2°C below body temperature of 37°C. This cooler temperature is required for spermatogenesis, a process of multiple cell divisions (meiosis and mitosis) to form spermatozoa. Inside each testis there is a network of fine-diameter tubes called seminiferous tubules residing in association with Sertoli cells and Leydig cells. Sertoli cells nourish, support, and protect developing germ cells by forming a “blood–testis barrier” that keeps away the unwanted toxicants. Spermatogenesis begins near the wall of a seminiferous tubule, and after multiple divisions, the spermatozoa are shed into

TABLE 59.1 Embryonic development of male gonads.

Stage	Age from conception	CR length (mm)	Event
I: Indistinguishable phase	32 days	5	Gonadal primordia develop; growth of Wolffian ducts; primordial germ cell differentiation
	37 days	10	Primordial germ cells reach gonadal ridge; differentiation of Mullerian ducts
	42–50 days	15–20	Seminiferous cord differentiation
	55–60 days	30	Beginning of secretion of AMH; Leydig cell differentiation; cranial part of Müllerian ducts begins to regress
	9 weeks	40	Leydig cells produce testosterone; beginning of masculinization of urogenital sinus and external genitalia
	10 weeks	45–50	Meiotic entry of oocytes in the medulla; beginning of degeneration of female Wolffian ducts; male Müllerian ducts disappear; prostatic buds appear
	12 weeks	55–60	Seminal vesicles develop; testis at internal inguinal ring
II: External male genital organ development phase	14 weeks	70	Completion of male urethral organogenesis
	20 weeks	150	Testosterone serum level is low; formation of prostatic utricle
	24 weeks	200	Beginning of penile growth
	27–30 weeks	230–265	Inguinoscrotal descent of the testis

CR, crown-rump length and measurement establishes fetus age.

the inner lumen of the tubules. Proteins produced by Sertoli cells are required for spermatogenesis, as is the testosterone from Leydig cells.

Leydig cells

Leydig cells are located in the interstitium of the testis near the seminiferous tubules. These cells arise from interstitial mesenchymal tissue between the tubules during the 8th week of human embryonic development. The development and maturation of Leydig cells are dynamic processes involving interaction between hormones and numerous additional factors. In humans, fetal and adult populations of Leydig cells with distinct lineages have been described. The fetal population represents an essential element of male sex differentiation, as demonstrated by the observation that dysfunction or absence of these cells gives rise to disorders associated with incomplete masculinization of male fetuses (Caron et al., 1997; Geissler et al., 1994; Svechnikov et al., 2010). During the embryonic and fetal life, these cells secrete testosterone and other androgens, which regulate not only the masculinization of internal and external genitalia, but also neuroendocrine functions, thereby influencing behavioral and metabolic patterns.

Finally, following a prolonged childhood period of steroidogenic quiescence, the Leydig cells are stimulated by the pituitary gonadotropin luteinizing hormone (LH) to grow in number and cellular size, and, at the same time, mature and differentiate to initiate the pubertal surge of testosterone required for the start and maintenance of full spermatogenesis, development of the accessory sex glands, and appearance of the secondary sexual characteristics. The developmental transitions of the different types of Leydig cells are regulated by a complex cocktail of endocrine and paracrine factors, which trigger cascades of cellular events (e.g., the expression of steroidogenic enzymes and androgen receptor) that optimize cellular activity for each particular period of male development.

Sertoli cells

Sertoli cells are somatic cells that associate with germ cells and nurture their development into sperm. They are the first cell type known to differentiate within the gonad from bipotential precursors of the supporting cell lineage and are therefore the first indicator that the gonad has passed from the indifferent stage into testis development. These cells form a continuous and complete lining within the tubular wall and establish the blood–testis barrier by virtue of tight junctions. The luminal environment is both created and controlled by these Sertoli cells, also called “nurse cells.” These Sertoli cells have several functions including

providing structural support and nutrition to developing germ cells, phagocytosis of degenerating germ cells and residual bodies, release of spermatids at spermiation, and production of a host of proteins that regulate and/or respond to pituitary hormone release and that influence mitotic activity of spermatogonia.

Spermatogenesis and spermiation

Spermatogenesis is a chronological process spanning about 42 days in the rodent and 72 days in man. Spermatogenesis can be divided into three distinct phases: mitosis, meiosis, and spermiogenesis. The first phase is referred to as spermatogonial proliferation and renewal. During this period, relatively undifferentiated diploid spermatogonia, the immature germ cells, undergo several mitotic divisions to generate a large population of cells called primary spermatocytes. In the second phase the spermatocytes go through the process of two meiotic divisions leading to the formation of haploid germ cells, spermatids. In the third phase, the spermatids go through a complex series of cytological transformations and dedifferentiate to form stem cells that cyclically develop into highly specialized spermatozoa. Spermiogenesis is the transformation of spermatids into the elongated flagellar germ cells capable of motility. The release of mature germ cells is known as spermiation. The germ cells comprise the majority of testicular volume. A smaller than normal size indicates testicular damage. A significant characteristic of mitotic arrest is that the gonocyte becomes acutely sensitive to toxic agents that may completely eradicate germ cells. Hormonal control of spermatogenesis varies among species. The initiation of spermatogenesis occurs at the onset of puberty due to the interactions of the hypothalamus, pituitary gland, and Sertoli and Leydig cells. If the pituitary gland is removed, spermatogenesis can still be initiated by follicle-stimulating hormone (FSH) and testosterone.

Steroidogenesis

Steroidogenesis is the multistep process for biosynthesis of steroid hormones from cholesterol. Primary organs for steroidogenesis in the male are the pair of testes and adrenal glands. In the testis, steroidogenesis is restricted to Leydig cells where conversion of cholesterol to testosterone (T) takes place with the help of cytochrome P450 enzymes predominantly in delta-5 pathway in human (Sikka et al., 1986; Miller and Auchus, 2011; Odermatt et al., 2016). Within the steroid hormone biosynthetic pathway, cytochrome P450–dependent steroidogenic regulatory proteins [17 α -hydroxylase/17,20-lyase/17,20-demolase,

3 β -hydroxysteroid dehydrogenase (3 β -HSD), and 17 β -HSD] are recognized as important targets for the actions of EDs leading to the reduction of androgens (Jeng, 2014).

Hormonal control

There are six major hormones involved in regulating the male reproductive system. Gonadotropin-releasing hormone (GnRH) is mainly present in the preoptic area of the hypothalamus and upon release travels to the pituitary gland where it stimulates the biosynthesis and secretion of the gonadotropins, FSH, and LH. Both LH and FSH are released by the anterior pituitary gland. In the testes, LH binds to receptors on Leydig cells, which stimulates the biosynthesis and secretion of T and other androgens. T stimulates the sex drive, and is the hormone that is associated with aggression. Inhibin is made by the Sertoli cells when they are low in nutrients and unable to nourish developing germ cells. Inhibin acts as a negative feedback, going to the brain to slow the release of GnRH and FSH (Fig. 59.1).

FSH stimulates both the production of androgen-binding protein by Sertoli cells and the formation of the blood–testis barrier. Androgen-binding protein is essential to concentrating T in levels high enough to initiate and maintain spermatogenesis, which can be 20–50 times higher than the concentration found in blood. Increasing the levels of FSH will increase the production of spermatozoa by preventing the apoptosis of type A spermatogonia. The hormone inhibin acts to decrease the levels of FSH. Both LH and FSH support the process of spermatogenesis by suppressing the proapoptotic signals and, therefore, promote spermatogenic cell survival. The Leydig cells and

Sertoli cells also mediate part of spermatogenesis through production of T, estradiol, and inhibin.

Endocrine disruptors

The term “endocrine-disrupting chemicals” (EDCs) was first coined in 1993 to describe a group of chemicals that could mimic the action of endogenous hormones, disrupting hormone homeostasis (Colborn et al., 1993). It was suggested that exposure to these chemicals was responsible for the increased incidences of lower fertility, intersexed animals, disrupted sexual development, obesity, diabetes, endometriosis, etc. According to the US Environmental Protection Agency, an EDC is defined as “an exogenous agent that can interfere with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes” (Kavlock et al., 1996). In the present scenario, these EDs are found in many industrial products including plastic bottles, metal cans, detergents, flame retardants, many food items, toys, cosmetics, and pesticides. According to the United Nations Environmental program, close to 800 chemicals are known or suspected to be capable of interfering with hormone receptors, hormone synthesis, or hormones conversion. However, only a small fraction of these chemicals has been investigated in tests capable of identifying overt endocrine effects in intact organisms. From the pharmacological perspective, modulation of hormonal signaling could have potentially therapeutic effects (Table 59.2).

It is estimated that a large proportion (up to 40%) of young men have low semen quality (Sinclair, 2000), high

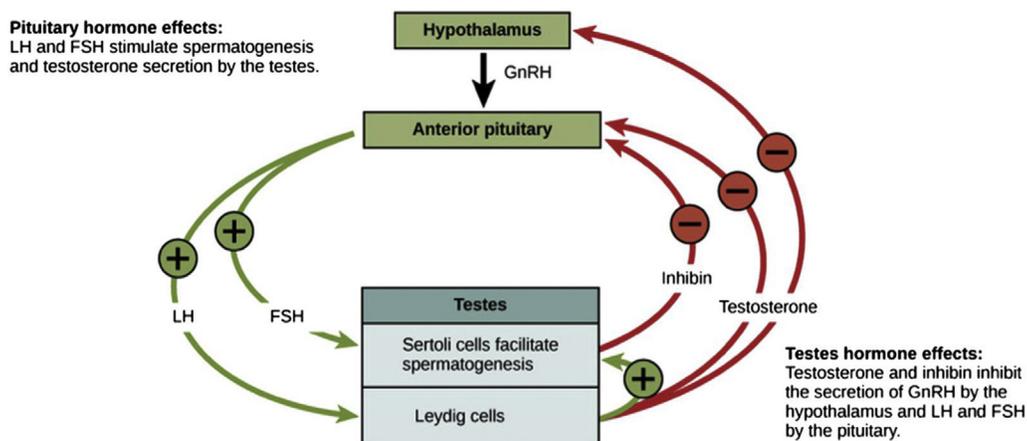


FIGURE 59.1 Hormonal regulation of the male reproductive system: gonadotropin-releasing hormone (GnRH) stimulates the production of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which act on the testes to begin spermatogenesis and develop secondary sex characteristics in the male. In turn, the testes production of testosterone and the hormone inhibin inhibit the release of GnRH, FSH, and LH via negative feedback loops.

TABLE 59.2 Hormones and antagonists—sites of action.

Classification	Drug/Antagonists	Sites of action
Corticosteroids	Prednisolone	Chronic illnesses such as colitis, multiple sclerosis, and arthritis
Estrogens	Ethinyl estradiol	Contraceptive pills
Selective estrogen-receptor modulator	Tamoxifen, raloxifene, tibolone, toremifene	Breast cancer, prostate cancer
Selective estrogen-receptor degrader	Fulvestrant	Breast cancer
Aromatase inhibitors	Letrozole, anastrozole, exemestane	Breast cancer
Progestins	Hydroxyprogesterone	Preterm birth, endometrial carcinoma
Antiandrogens	Flutamide, bicalutamide	Prostate cancer, hirsutism, and other androgen-dependent conditions
5- α Reductase inhibitors	Finasteride, dutasteride	Benign prostatic hyperplasia, male pattern baldness
GnRH analogs	Naferelin, goserelin, leuprolide, degarelix	Carcinoma breast, prostate

incidence of undescended testes (cryptorchidism), testicular cancer, and genital malformations (hypospadias) in baby boys (Giwercman and Bonde, 1998; McLachlan et al., 1998; Skakkebaek et al., 1998).

Exposure and regulation of EDs

Exposure to EDs could be through air, water, food, detergents, flame retardants, pesticides, and a variety of industrial products, including personal care items. The mixture of EDs that leach into the soil and waterbodies (e.g., pesticides, contraceptive pills, and other chemicals from the urban and agricultural waste) accumulates in the environment and thus into the food chain. Food is the major source of human ED exposure (e.g., meat, fish, dairy products, vegetables, and water). Schechter et al. (2004) reported a total of 32 food samples from three major supermarket chains in Dallas, Texas, were contaminated with polybrominated diphenyl esters. Plastic packaging is another important source of ED in average human diet. Repeated exposure of food-contact materials to heat or acidic/alkaline contents may cause breakdown of polymers into monomers as phthalates and bisphenol A (BPA), which then leaches into the food and beverages (Muncke, 2011). Among the natural EDs phytoestrogens have been reported in high concentrations in infants ingesting soy-based formulas. These infants may have a phytoestrogen serum concentration 13–22 thousand times higher than endogenous estrogen levels that may affect brain,

reproductive organs, and, ultimately, fertility (Dinsdale and Ward, 2010; Setchell et al., 1998).

Association between EDs and testicular dysgenesis syndrome

Cryptorchidism, hypospadias, testicular cancer, and poor semen quality may all be symptoms of the entity called testicular dysgenesis syndrome, which has its origin in fetal life (Skakkebaek et al., 2001). Testicular dysgenesis may be caused by genetic and environmental factors, lifestyle factors, or a combination of these (Fig. 59.2).

Cryptorchidism

Cryptorchidism is a common urogenital malformation affecting 2%–9% of boys at birth and 1%–3% boys at 3 months of age. Testicular descent occurs in two phases: (1) transabdominal phase, which is T independent and requires insulin-like factor 3 (Insl3), and (2) the transinguinal and inguinoscrotal phase, which depends on androgen and Insl3 signaling. With a vast majority of cryptorchidism cases not linked with genetic factors, an increase in the incidences of cryptorchidism in the last decade has been linked to environmental factors including EDs, mainly estrogenic compounds (diethylstilbestrol), antiandrogens (e.g., vinclozolin, flutamide, phthalate esters, and procymidone), pesticides, polychlorinated biphenyls (PCBs), biphenyls and polybrominated diphenyl ether, dioxins, flame retardants, and

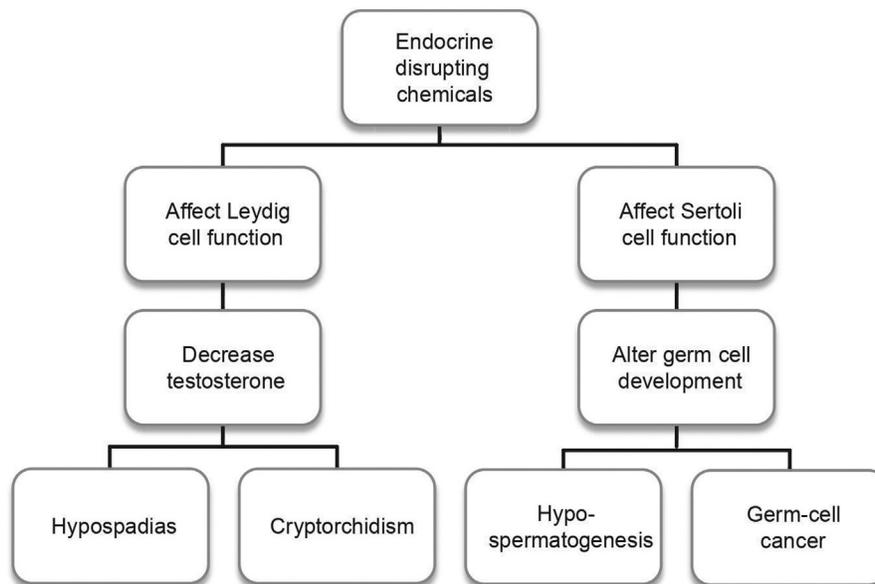


FIGURE 59.2 Schematic representation of endocrine-disrupting chemicals affecting both Leydig cell and Sertoli cell functions, leading to downstream abnormalities.

phthalates (Martin et al., 2008; Palmer et al., 2009; Toppari et al., 1996; Virtanen and Adamsson, 2012) (Fig. 59.3).

TGCT in men exposed to DDE and PCB (Purdue et al., 2009).

Testicular cancer

Testicular cancer is a common malignancy in young men (aged 15–34 years) worldwide (Wu et al., 2005). About 95% of all testicular cancers are germ cell tumors (GCTs), with an approximately equal division between seminomas and nonseminomatous GCTs. Epidemiological studies show both geographical variability and dramatic upward trends in the incidence of testicular GCTs (TGCTs) (Adami et al., 1994; Diamanti-Kandarakis et al., 2009; Huyghe et al., 2003; McGlynn et al., 2003). Such a temporal rise over a relatively short period suggests nongenetic factors pointing to environmental and lifestyle factors may be playing a significant role. Increased exposure to p,p'-dichloro diphenyl ethylene (DDE) and PCB has been reported to associate with the risk of both seminomatous and nonseminomatous TGCTs (McGlynn et al., 2008). Subjects in the highest serum p,p'-DDE quartile ($>0.39 \mu\text{g/g}$ lipid) compared to those in the first serum p,p'-DDE quartile ($0.157 \mu\text{g/g}$ lipid) supported such an increased risk of

Effect of various endocrine disruptors on male fertility

Listed below are some of the key EDs that have been found to affect male fertility.

Bisphenol A

BPA (2,2-bis(4-hydroxyphenyl)propane), a monomer of polycarbonate plastics, is one of the most common EDCs. It was first developed as synthetic estrogen (also called xenoestrogen, from the Greek xeno = foreign) in the 1890s. Thereafter, BPA has been used in numerous consumer products, including polycarbonate plastics and epoxy resins, such as food and drink containers, plastic water bottles, dental sealants, and a variety of household products. BPA is widespread in the environment and every year 2.2–4.7 million tons of BPA are released into the environment (Knez, 2013; Liu et al., 2013). Human body is exposed to 10 μg of BPA per day, which can be detected in

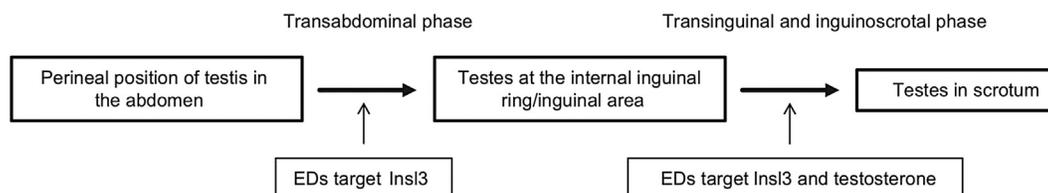


FIGURE 59.3 Schematic representation of possible targets of endocrine disruptors (EDs) in testicular descent.

several human body fluids including serum, urine, breast milk, and semen (Vandenberg et al., 2010). BPA has weak affinity to bind to the estrogen α and β receptor and has been reported to interfere with both androgen production and function (Akingbemi et al., 2004; Knez, 2013; Lee et al., 2003; Welshons et al., 2003). It has also been reported to impair Sertoli cell function by interfering with expression and localization of tight junction protein (Fiorini et al., 2004; Li et al., 2009; Salian et al., 2009). Furthermore, BPA has been shown to have epigenetic effects, including DNA hypomethylation (Doshi et al., 2011; Singh and Li, 2012). A study from Komarowska et al. (2015) indicated that high serum BPA was associated with cryptorchidism. Many studies have shown that increased urinary BPA levels are associated with poor semen quality, decreased sperm concentrations, and decreased and increased single-strand breaks causing sperm DNA damage (Li et al., 2011; Meeker et al., 2010). However, such data have not provided sound evidence to reveal that detrimental environmental BPA exposure affects male reproductive capacity and impairs fertility.

Phthalate

The diesters of 1,2-benzenedicarboxylic acid (phthalic acid), commonly known as phthalates, are a group of man-made chemicals widely used in hundreds of products in our homes, hospitals, cars, and businesses (Johnson et al., 2012; Knez, 2013). They are primarily used to make flexible polyvinyl chloride plastic because of their strong durability and stability. Phthalates are categorized as high and low, depending on their molecular weight. High phthalates are those with 7–13 carbon atoms in their backbone and include diisononyl phthalates, diisodecyl phthalates, and dipropylheptyl phthalates. High phthalates are primarily used for wires, cables, flooring, wall covering, self-adhesive films, synthetic leather, coating fabrics, roofing, and automobile applications. On the other hand, low phthalates are those with three to six carbon atoms in their chemical backbone and include di(2-ethylhexyl) phthalates (DEHP) and dibutyl phthalates (DBPs). These are primarily used in medical devices, adhesives, ink, perfumes, and hair fixative spray. Since phthalates are not covalently bound to the polymer, they can leach from plastic into foods, beverages, and body fluids with product age, use, and ultraviolet light exposure, making them more hazardous for health. Ingestion, inhalation, skin absorption, and through intravenous injection tubing are potential modes of phthalate exposure. Typically, phthalate intake in humans is estimated at 1.7–52.1 $\mu\text{g}/\text{kg}$ per day, whereas exposure of children is two- to fourfold higher than that of adults (Doull et al., 1999; Koch et al., 2005; Martinez-Arguelles et al., 2013; Moody et al., 2013). Several studies have demonstrated a link between phthalate

exposure and disorders of male reproduction. Phthalates are considered to be one of the major groups of antiandrogenic substances which have possible adverse effect on Leydig cells or the hypothalamic–pituitary–gonadal (HPG) axis (Main et al., 2006). Phthalate exposure has been linked with presence of multinucleated germ cells and adult pathologies such as Leydig cell aggregation, Sertoli cell–only tubules, poor spermatogenesis, TGCTs, increased sperm DNA damage, and reduced semen quality (Hoei-Hansen et al., 2003; Jeng, 2014; Knez, 2013; Nistal et al., 2006). Studies showed that mono-butyl phthalate and phthalate metabolites were significantly associated with decreased sperm motility (Hauser et al., 2006; Jeng, 2014; Jurewicz et al., 2013).

Alkylphenols and their derivatives

Alkylphenols are organic industrial chemicals used in the production of lubricating oil additives, laundry and dish detergents, emulsifiers, and solubilizers (Soares et al., 2008). They are also found in personal care products, especially hair products, as an active component of many spermicides (nonoxynol-9), various laboratory detergents (including Triton X-100), and some pesticide formulations. The exposure to these compounds is via skin, air, and water. Unlike most of the exogenous chemicals, which usually become less toxic with degradation, alkylphenols actually increase their toxicity with time. During biodegradation, alkylphenol polyethoxylates lose ethoxy groups to become alkylphenols (typically nonylphenol), which are more stable, persistent, and hydrophobic, leading to their accumulation in sewerages and rivers and their volatilization into ambient air (Davis et al., 1994; Rudel et al., 2003). Many alkylphenols are toxic to aquatic organisms, and the most toxic are those with a large alkyl chain, i.e., octyl-, nonyl-, and dodecyl-phenol. Alkylphenols have attracted attention due to their prevalence in the environment and potential roles as EDs and xenoestrogen. Exposure of nonylphenol and octylphenol has been shown to cause testicular damage, decreased testicular size, decreased sperm production/quality, and dysfunction of male reproduction system (De Jager et al., 1999; Falco et al., 2015; Lee et al., 1999; Ponzio and Silvia, 2013).

Molecular mechanism of endocrine-disrupting chemicals

DNA integrity

The structure of the sperm chromatin is unique compared to other cell types. Histones in sperm head are replaced by protamines during spermatogenesis, resulting in an extremely condensed DNA (Dadoune, 1995). Alteration in chromatin modeling, apoptosis, and oxidative stress can

result in abnormalities of the sperm chromatin structure and DNA damage affecting fertility, abnormal pronuclear formation, or early embryo quality and pregnancy outcome. There are a number of studies showing sperm DNA damage as a result of EDs, although with contradictory epidemiological data. The reasons for this inconsistency might be different methodologies used to detect sperm DNA damage, variation of exposure of EDs and their mixtures, and different inclusion criteria for the studies (Bungum et al., 2007; Hauser et al., 2003; Rignell-Hydbom et al., 2005). Nevertheless, EDCs have been associated with sperm DNA fragmentation (Bonde et al., 2008; Hauser et al., 2007; Jurewicz et al., 2013) and impaired sperm chromatin condensation (De Jager et al., 2006; Rignell-Hydbom et al., 2005; Spano et al., 2005), and induce point mutation, single- and double-strand DNA breaks, and aneuploidy (Iso et al., 2006; Meeker et al., 2010; Takahashi et al., 2001).

Induction of oxidative stress

Oxidative stress is a collective term that includes highly reactive oxygen species (ROS) such as hydroxyl ions, superoxide anion, hydrogen peroxides, and many antioxidant enzymes (Wright et al., 2014). In spermatozoa, ROS are also required for a number of specific and essential functions (e.g., sperm capacitation, acrosome reaction). Due to the short half-life of ROS produced by spermatozoa, they are relatively harmless under normal circumstances. In addition, antioxidant mechanisms help maintain the key balance that is required for these ROS-related physiological functions (Sikka, 2001). However, increased concentration of ROS in the seminal plasma can attack DNA, lipids, and proteins of sperm; alter enzymatic systems; produce irreparable alterations; and cause cell death leading to a decline in the semen parameters associated with male infertility (Agarwal et al., 2014). Oxidative stress is identified as a common mechanism of action for EDs in affecting cellular structures and functions (Braconi et al., 2011). BPA and phthalates induce testicular toxicity via increasing oxidative stress by downregulating the production of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase (Asghari et al., 2015; Dhanabalan and Mathur, 2009). Studies on testis have shown that EDs induce oxidative stress causing disruption of tight junctions between Sertoli–Sertoli cells and Sertoli–germ cells (Cheng et al., 2010; Wong and Cheng, 2009). This disruption of cell junction is mediated by the activation of phosphatidylinositol-3-kinase/c-Src/focal adhesion kinase and MAPK signaling pathways affecting polarity proteins.

Thus disruption of such cell junctions ultimately leads to reduced sperm count, sperm quality, and reproductive dysfunction in men.

COVID-19 impact on male reproductive hormones

Coronavirus infection discovered in 2019 (COVID-19) is likely to have potential impact on the physiological function of male gonads (Khalili et al., 2020; Patel et al., 2021; Tian and Zhou 2021). Male infertility is linked with testicular pathology via dysregulation of HPG axis (Selvaraj et al., 2021, Sengupta and Dutta, 2021). Recent studies indicate abnormal levels of reproductive hormones in men infected with COVID-19. The FSH/LH ratio was altered due to increased levels of LH and decreased levels of testosterone in subjects with COVID-19 (Ma et al., 2020). Moreover, LH and FSH levels increased based on the severity of the disease (Cayan et al., 2020). In addition, low testosterone levels were reported in COVID-19 patients (Ma et al., 2020, Rastrelli et al. 2021; Kadihasanoglu et al., 2020) and it was correlated with increased levels of proinflammatory factors such as IFN- γ and IL-2 (Schroeder et al., 2020). The levels of these hormones were in normal range in patients recovered from COVID-19 infection (Temiz et al., 2021). In addition to imbalances in the reproductive hormones, Sansone et al. (2021) highlighted the possible damage to the vascular integrity due to COVID-19 infection that may result in erectile dysfunction. COVID-19 infection has no age barrier and is affecting many young men of reproductive age.

Concluding remarks and future directions

Several epidemiological studies have found an association of increased urinary and serum levels of EDs with poor semen quality (Abdelouahab et al., 2011; Hauser et al., 2006; Meeker et al., 2010). Men with >240 ng/g lipid PCBs in serum have shown an inability to conceive which is associated with low sperm concentration (Hauser et al., 2002). Exposure to high dichloro diphenyl trichloroethane (DDT) concentration has been linked to low serum T and poor semen quality. DDT stimulates estrogen production by acting as estrogen receptor agonist and potent androgen receptor antagonist (Bulayeva and Watson, 2004; Lemaire et al., 2004; Tessier and Matsumura, 2001). Phthalates, another group of EDs, have shown to alter reproductive tract structure, seminiferous tubule degeneration, and impaired spermatogenesis (Campion et al., 2012). BPA, a

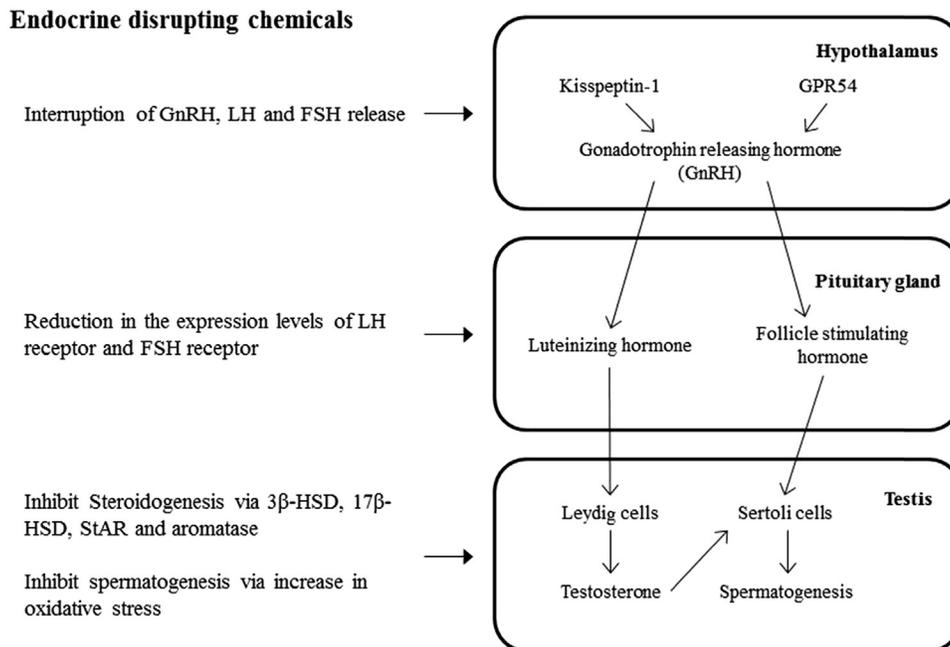


FIGURE 59.4 Scheme showing the potential sites of action of endocrine disruptors on the hypothalamus–pituitary–gonadal axis. *FSH*, follicle-stimulating hormone; *HSD*, hydroxysteroid dehydrogenase; *LH*, luteinizing hormone.

strong exogenous estrogen with antiandrogen effect, reduces LH, and decreases development of seminiferous tubules and spermatogenesis (Al-Hiyasat and Darmani, 2006; Furuya et al., 2006). Summarized below are other highlights of such reproductive toxicity in men:

- Urinary phthalate metabolites and BPA levels were negatively associated with FSH, LH, and T levels (Duty et al., 2005; Jonsson et al., 2005; Pan et al., 2006).
- DEHPs can exert their antiandrogenic action by directly inhibiting T synthesis via cytochrome P450 dysfunction (Diamanti-Kandarakis et al., 2009; Foster, 2005).
- Phthalates have been shown to disrupt the patterns of gene expression that regulate cholesterol and lipid homeostasis resulting in low T and interfere with the ability of Sertoli cells to respond to their normal endogenous ligand of FSH (Barlow et al., 2003; Heindel and Powell, 1992) (Fig. 59.4).
- BPA-induced inhibitory effect on the activity of ATP-binding cassette transporters of the cellular membrane of testicular tissues results in lower T (Dankers et al., 2013).
- The impact of COVID-19-related infection on the male reproduction is unknown. Since many healthy young men of reproductive age group are potential target of such infection, it is important to understand the mechanisms and further impact on their fertility potential.

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