ISSN Online: 2349-7785

Effect of Endocrine Disruptors on Human Reproductive Health

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Received 19 November 2015; accepted in revised form 14 December 2015

Abstract: Endocrine disruptors (EDs) are naturally occurring compounds or man-made substances that interfere with the function of endocrine system of the body. EDs may be any estrogen-like and anti-androgenic chemicals, environmental agents [e.g., polychlorinated biphenyls (PCBs), dichlorodiphenyl-trichloroethane (DDT), dioxin, and some pesticides)] or biological stressors like oxidative stress or pharmacological agents like radiation and drugs. These molecules elicit their action by mimicking, blocking and triggering actions of hormones and disturb entire neuro-endocrine equilibrium. EDs may be blamed for functional abnormalities include decreased semen quality, reduced numbers of sperm, disrupted estrous or menstrual cycle and premature menopause, behavioral abnormalities include altered sexual behavior decreased libido and infertility. The present review describes various factors contributing bioaccumulation of EDs and their possible effect on human reproductive function.

Key words: Endocrine disruptors, Pesticides, Estrogen, Hormones, Neuro-endocrine, Infertility.

Introduction

Over recent decades, since the mid-20th century epidemiological studies have reported an increasing incidence of human reproductive diseases and a consequent decline in reproductive health worldwide. This leads to increase incidence of infertility problems affecting 10 % - 15 % of the sexually active population. Given the short time edge, genetic changes cannot explain it. Thus, environmental substances may be responsible for the observed trends [1]. Endocrine disruptors (EDs) are naturally occurring compounds or man-made substances that interfere with the function of endocrine system of the body (Fig. 1). Thus, create disturbances in the closed feedback loops of the hormonal and homeostatic systems. The endocrine system control many vital functions of human body like growth, reproduction and maintain interim balance of body by secreting autocrine, paracrine and endocrine signaling molecule (hormones) and peptides [2]. The term "endocrine disruptor (ED) was first used at the Wingspread Conference in Wisconsin, USA in 1991 for those endocrine active substances (EASs), which may lead to an adverse health effect [3].

The group of known EDs is extremely heterogeneous. These releases to environment as industrial effluents, fertilizers, pesticides, insecticides, herbicides, germicides, cosmetics, food and beverages, heavy metals, medicated accessories (steroids, excess consumption of antibiotics, plastic bags, blood transfusion bags, personal care products). Human being constantly exposed to EDs by occupation (working in radiation zone, industries that produce plastic based products, nuclear reactors, flame retardants, minerals extraction and mining areas) and also endogenously by stress, depression and injuries. By far, the greatest concerns for the potential adverse effects of EDs have concentrated on their deleterious impact on reproductive health. The present paper mainly focuses on status, compo-

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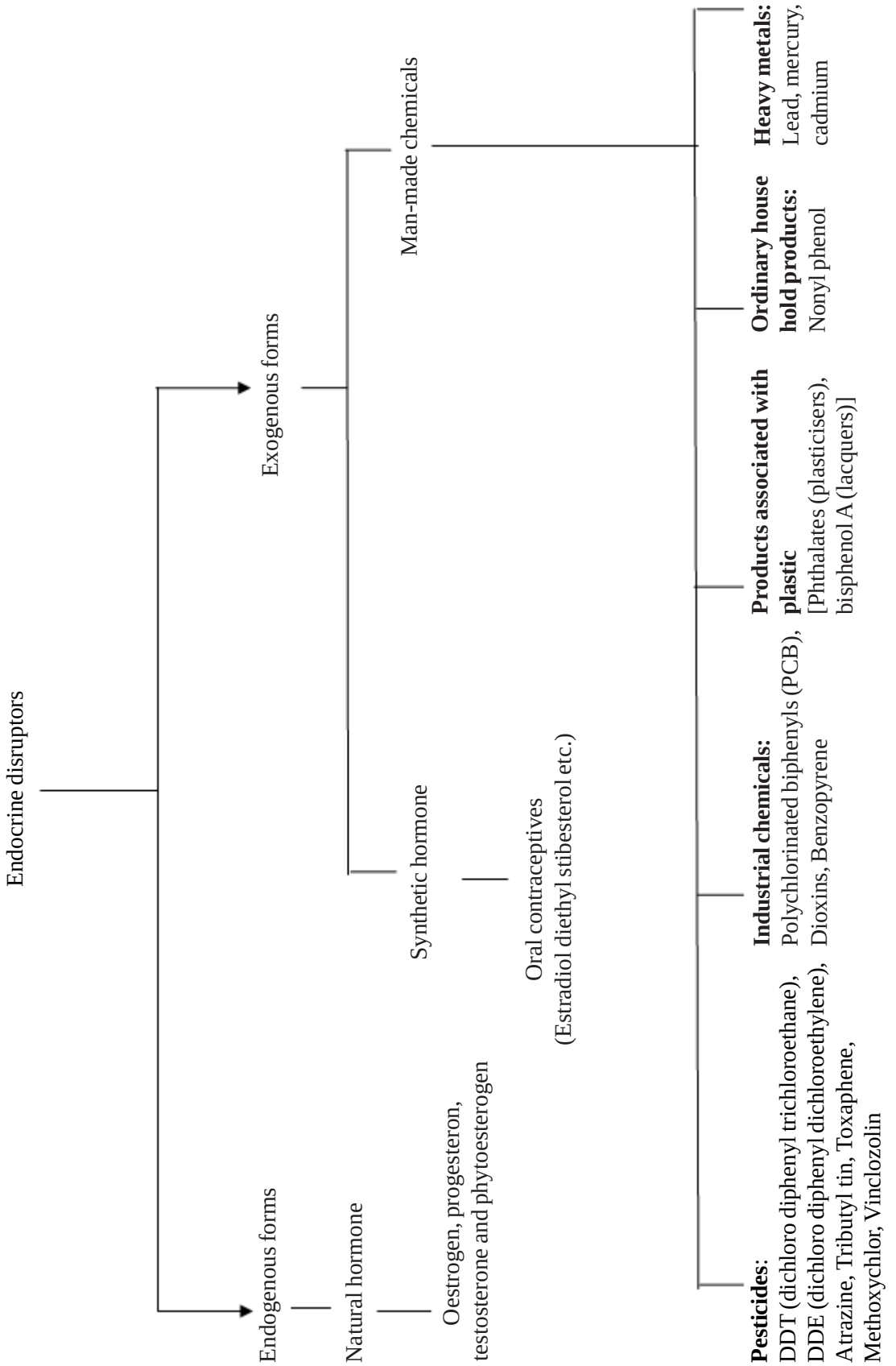

Fig. 1. Types of endocrine disruptors (EDs)

sition and diversified anthropogenic influence of EDs on human male and female reproductive physiology.

Significance of EDs

EDs (Figure 1) after released into the environment do not stay at same places but move by water and air current throughout the globe. Man-made EDs vary in potency and in the level of exposure required to produce a deleterious effect. EDs have longer half-life (t1/2) and are bio-accumulated in living organisms and generally resist biodegradation [4]. They show biologically magnification when go from one tropic level to next tropic level. Individually, they may not be released into the environment at levels that would pose substantial risks, but the effects of chronic low levels of exposure of EDs are of major concern. In addition, these substances occur in the environment not individually but in various combinations, and they may interact synergistically. In some experimental systems, a combination even of two weak compounds has proven to be more dangerous (1,000 times) than either individual compound. However, the dose at which they elicit irreversible damage is still controversial. The major route of human exposure is via aerosol through inhalation and skin contact or ground water or terrestrial route such as ingestion of food (e.g. meat, fish, dairy products and vegetables), as well as plain water and other beverages, EDs-contaminated food and water may contain environmental pollutants, such as pesticide residues and heavy metals, in addition to processing aids and anabolic steroids used in medicated therapies. Most individuals have traceable amounts of these substances in their serum or urine. EDs mainly accumulated in neuroendocrine and HPG (hypothalamus-pituatary-gonadal) axis and deregulated normal physiological functions and behavior, specifically affect human reproductive function, causing pathologies like cancers and urogenital malformations, alter hormone network of specific gender and often result trans-generational reproductive effects [5].

Effects of EDs on animal reproductive function can be multi-faceted and pleiotropic. Given the complexity of the endocrine system, the mechanisms of action of EDs are difficult to unravel. Most EDs are supposed to act through several mechanisms, which may have synergistic or antagonistic outcomes. EDs blocks the synthesis of hormone at the site of origin or at any place of transport route by interacting with single or multiple hormone pathways or even by forming single ED-receptor or EDs-multireceptors complexes making the expected effects are even more complex and miserable [6, 7]. They suppose to elicit their response by acting as imperfect ligands (either agonists or antagonists) to nuclear and membrane receptors (for both steroidal and non-steroidal hormones, and also for orphan receptors), thus interfering with hormone-regulated cell signaling pathways and gene expression.

Kiss1, a principal regulator of the secretion of gonadotrophins, and its role is critical for onset of puberty, the regulation of sex steroid-mediated feedback and controlling adult fertility. Recently, it was reported that, Kisspeptin the functional product of Kiss1 gene is affected by EDs like bisphenol A, dichlorodiphenyltrichloroethane (DDT), vinclozolin and certain polychlorinated biphenils (PCBs) as well as complex mixtures of EDs. Kisspeptins act via the receptor, GPR54, are neuropeptides produced at discrete neuronal populations within the hypothalamus with key roles in brain sex differentiation, puberty onset and fertility. Sex steroid hormones, most notably estradiol, play a pivotal role in the sex-specific organization and function of the kisspeptin system [8]. A subset of Kiss1 neurons has been recently shown to co-express neurokinin B (NKB), another neuropeptide with important reproductive roles. Kisspeptins also stimulate luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion. Although GnRH neurons are critical component of the reproductive axis, kisspeptin (Kp) peptides have been identified recently as vital upstream regu-lators that integrate central and peripheral signals with GnRH release, thereby playing a pivotal role in the control of reproduction [9]. EDs interact with steroid hormone signaling. Thus, these compounds (EDs) have the potential to disrupt the sexually dimorphic ontogeny and function of kisspeptin signaling pathways and have adverse effects on neuroendocrine physiology [10].

Reproductive health of human solely relies on

proper functioning of human reproductive system, that include primary reproductive organs, secondary reproductive organs and other accessory parts, Germ cells are biological unit of gonads. These cells constitute a very different cell population from other somatic lineage, as they can differentiate into gametes those carry genetic information. The details of gametogenesis and the accumulating knowledge of the mechanisms underlying it have been described elsewhere in a number of excellent articles. Toxics exposure may affect critical events in the development of the reproductive system, ranging from early primordial germ cell determination to gonadal differentiation, timing of pubertal onset, estrous cycles, gametogenesis, external genitalia, or signaling events regulating sexual behavior of human. EDs affect male reproductive function by affecting testicular development and functions (*i.e.*, steroidogenesis and spermatogenesis) and female reproductive cycle by creating disturbance in any of these phenomenons such as (i) gametogenesis, (ii) embryogenesis, (iii) menstruation, (iv) ovulation, (v) possible pregnancy, (vi) endometrial and (vii) mammary gland changes.

Development of the female reproductive system during fetal life determines reproductive success [11]. Although, number of EDs are numerous, that causes severe reprotoxicity to human but all are not well docu-mented. Scanty reports are available from human hence, data collected from experimental analysis of laboratory animals like rodents, porcine and mice are use to draw conclusion about the effects of EDs on reproductive function of human.

Effect of EDs on male reproductive health

Most epidemiological, clinical and experimental data suggest that at least one cause of impairment of male reproductive function such as decline sperm counts and increase incidence of testicular cancer, hypospadias, cryptorchidism and abnormal spermatogenesis are exposure to EDs [12]. Fetal testis performs two major functions: gametogenesis and steroidogenesis. EDs may disrupt spermatogenesis by interfering functions of germ cells and spermatogenesis-supporting cells like Leydig cells and Sertoli cells (Table 1). Fetal testis is major target of EDs. EDs affect male fertility either temporary or permanent manner results disruption of proper intrauterine testicular development and function. These disorders have been regrouped as the testicular dysgenesis syndrome (TDS). Impaired Leydig cells function is the main cellular trait of TDS. The anthropogenic EDs that create reproductive problems in male are estrogenic pollutants including agricultural products (phytoestrogens), industrial chemicals and heavy metals and many pharmacological and biological agents.

Environmental agents (Chemicals)

At present, India is the largest producer of pesticides in Asia and ranks twelfth in the world for the use of pesticides with an annual production of 90,000 tonnes [17]. Over 700 active ingredients are in use worldwide as pesticides, each with distinct chemical and toxicological properties. Accumulated data suggest pesticides able to induce reproductive toxicity by interfering with the endocrine regulation and cause decline semen quality and increased risks of subfertility and infertility

Table 1. Cytopathic effects of EDs on the testicle

No.	EDs	Cellular effects	References
1	Phthalates, diethylstilbestrol, ethinyl oestradiol	Alter the development of the germ cell lineage, decreased gonocyte number, induce germ cell apoptosis.	13,14
2	PCBs (polychlorinated biphenyls), phthalates, cypermethrin, dieldrin and cadmium	Reduce steroidogenesis in Leydig cells.	1,15
3	Life style factors (e.g. smoking and alcohol)	Sertoli cell-only syndrome	4,16

in men. Pesticides may directly damage spermatozoa, alter Sertoli cell or Leydig cell function and may disrupt the endocrine function in any stage of hormonal regulation (hormone synthesis, release, storage, transport, and clearance; receptor recognition and binding; thyroid function; and the central nervous system). The commonly used pesticides are organochlorine, organophosphate, carbamate, and pyrethroid insecticides. The pesticides severely disrupt male reproductive function are beta-HCH, carbaryl, chlordane, dicofol, dieldrin, DDT (dichlorodiphenyl-trichloroethane) and its metabolites, endosulfan, heptachloro and H-epoxide, lindane (gamma-HCH), malathion, mathomyl, methoxychlor, mirex, oxychlordane, parathion, synthetic pyrethroids, toxaphene and transnonachlor. DDT is the major pesticide used for mosquito control. DDT was broadly used to control malaria in many countries of the world. Mexico used DDT in malaria fight until 1999, due to low cost and lack of acute toxicity to expose populations [18,19]. It is still popular in developing counties for killing the adult mosquito and larvae. At high concentrations DDT and isomers of DDT can delay maturity of male child. DDT after metabolized in liver produced DDE (dichloro-diphenyl-dichloroethylene). DDE has anti-androgenic action and can also disturb estrogen metabolism [20, 21]. However, in the 1970s and 1980s many developed countries banned its use because of its extensive persistence in the environment which affects human health severely [22].

Pesticides show poisonous activities in *in vitro* and *in vivo* condition. However, results from more recent studies are very inconsistent and no uniform conclusion can be drawn about the effects of pesticides on male reproductive function [23]. 1, 2-dibromo-3-chloropropane (DBCP) is a pesticide used against nematodes (roundworms or threadworms) that damage pineapples, bananas and other tropical fruits. It was introduced into US agriculture in 1955 and approved for use as a fumigant in 1964. DBCP is the chemical responsible for causing sterility in the workers at the California chemical plant. The data of medical examinations provided compelling evidence that out of 25 non-vasectomised men 14 were suffering from deficient or absent sperm with elevated follicle-stimulating hormone (FSH) and luteinising hormone (LH) serum levels. No other major abnormalities were detected and testosterone levels were normal. While conducting this study, a quantitative estimation of exposure could not be obtained, the observed effects appeared to be related to duration of exposure to DBCP [24]. The spermatogenic effects of DBCP are usually irreversible and this chemical is also toxic to female reproductive system [25].

Pesticide linuron demonstrates anti-androgenic activity and elevates the degree of occurrence of testicular tumors in rodent [26]. Vinclozolin is a fungicide and antiandrogenic agent, exposure during embryogenesis decreases the sperm motility and concentration of offspring at adulthood. This effect is transferred to several generations of male offsprings and is associated with alterations in the sperm methylation profile and may cause developmental defect like cryptorchidism and hypospadias [27]. A study conducted in rat concluded that prenatal administration with vinclozolin causes intrauterine defects like testicular maldescent, happen due to induction of an aberrant migration of the gubernaculum associated with an abnormal extension of the processus vaginalis [28]. Another compound that impairs rat spermatogenesis is the organochlorine pesticide lindane (γ-hexachlorocyclohexane) [29].

Exposure to pesticide lindane damages the germinal epithelium and the number of spermatids and Sertoli cells in humans testis causing formation dysfunctional male gametes [30]. The severity of this organochlorine lindane is markedly notice as it disturbs oxidative balance of animals by inducing oxidative stress as it decreases the activities of antioxidant enzymes and sialic acid, superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase along with increase in hydrogen peroxide generation and lipid pathways [31].

Synthetic plastics are polymers of organic modules have become an imperative part in our day to day lives. Global Plastics Consumption to Reach 297.5 Million Tons by 2015, according to New Report by Global Industry Analysts, Inc. However, these plastics are non-biodegradable and accumulate at the rate of 25 million tons per year. The thermoplastic and thermosetting raw materials use to produce plastics and plastics based product

are strong reprotoxic agents such as phthalates, polyethylene, polyvinyl chloride (PVC), polyethylene terephthalate (PET) and polyster. Phthalates used as raw material in the industries like manufacturing of automobiles, medical supplies, plastics, beverage containers and coating of metal cans. The principal forms of Di (2-ethylhexyl) phthalate (DEHP) are a priority pollutant in several countries with annual production amounts to 3-4 million tonnes. DEHP is emitted to the environment during the production of plastics and plastic products, during their use and after disposal. In the environment, physicochemical degradation of DEHP is practically non-existent. Biodegradation occurs readily under aerobic conditions (t1/2 = 2-4 weeks), but not under anaerobic conditions. The acute toxicity of DEHP to mammals is low. Animal studies consistently demonstrated that phthalate esters are male reproductive toxicants produce testicular atrophy, spermatogenetic cell loss, and damage to the Sertoli cell population [32]. Phthalate monoesters target Sertoli cell functions. A study conducted in rats, demonstrated that phthalates affects male reproductive physiology by impeding testicular function, producing malfunctioned androgen-dependent tissues [33]. Phthalates after binding to androgen or estrogen receptors inhibit synthesis and secretion of testosterone by Leydig cells thus affects steroidogenesis of HPG hormone center. Thus, results lower level of androgenic hormonal secretion. The male reproductive tract influence by lower level of androgenic hormone in an anti-androgenic way, causing ill developed male reproductive organs and also demolish other development of secondary sexual characters. Many sub-chronic and chronic effects have, however, been identified. Emissions of DEHP can be reduced by the biological treatment of wastewater and waste gas, the use of alternative plasticizers in PVC or the substitution of other plastics for PVC. The evidence suggests that polyethylene terephthalate (PET) is the main ingredient in most plastic containers used for beverages and condiments worldwide may yield endocrine disruptors under conditions of common use, particularly with prolonged storage and elevated temperature [34].

From the results of epidemiological studies and experimental analysis conducted in sexually mature laboratory animals it is noteworthy that chronic exposure and over accumulation of certain chemicals [for e.g. dioxin and its isomer 2, 3, 7, 8-Tetrachlorodibenzo-p-dioxin (TCDD), polychlorinated biphenyls (PCBs)] result low level sperms production, decreased testicular weight and formation of abnormal testes with reduced fertility. These chemicals also alter structural and morphological characteristics of primary and secondary sex organs [7]. Humans are exposed to dioxins through pulp and paper industry emissions, use of contaminated herbicides (now reduced in industrialized countries), and waste incineration emissions. Dioxins are lipophilic, slowly metabolized and thus are not easily eliminated leading to bioaccumulation in various tissues [35.] Dioxins are most toxic anthropogenic agents and TCDD show anti-androgenic and anti-estrogenic properties. Human working in industries like electrical appliances, hydraulic and heat transfer systems, lubricants, gasket sealers, paints, fluorescent lights, plasticizers, adhesives, carbonless copying paper, flame retardants and brake linings are constantly come to contact PCBs another antiandrogenic agents. PCBs affect synthesis and secretion of estrogen, androgen, thyroid, pituitary, corticosteroid and other hormones, thus severally impair male and female reproductive health [36].

Higher is the concentration of related analogs of PCBs in blood, low is the semen quality and less is the sperm motility is observed in human [37] Moreover, sperm with abnormal head shapes were observed in men occupationally exposed to carbaryl (1-naphthyl methyl carbamate) in a production plant for durations less than 6 years. However, it was observed that increases in sperm shape abnormalities were not related to exposure dose (estimated by number of years on the job or job classification during the year prior to semen collection) [38]. Recent work by Sadawarthe *et al* [39] has also confirmed that sustained exposure to pesticides can leads to deterioration of sperm concentration, morphology and impaired motility which may be the cause of infertility among farmers of central India.

Endosulfan ($C_9H_6C_{l6}O_3S$) a toxic organochlorine compound is a wide range insecticide. In 1954

registered for use in the United States, to manage agricultural insect and mite pests on a variety of field, and vegetable, fruit crops. Endosulfan is composed of two stereo isomers: α-endosulfan and β-endosulfanup to 70 % and 30 % correspondingly. Exposure of endosulfan to male mice with the dose of 3 mg/Kg body weight (BW) for 35 days seems to alter sperm morphology greatly revealed by marked loss of sperm tail, degenerated acrosome and coiled tail. Declination in the level of Testosterone and inclination in the level of LH were also observed which signify the testicular dysfunctions and finally causes infertility [40].

Gasoline is common contamination in all industrialized countries. The principal contaminations of gasoline are: aromatic hydrocarbons benzene and its derivatives like benzene, phenol, toluene, ethylbenzene, xylenes (BTEX), and more recently, methyl tert-butyl ether (MTBE). All are carcinogen. Ethylene dibromide (EDB) was used extensively as a scavenger for removal of lead traces from gasoline. Accumulation of EDB in workers of gasoline and its by-products industries show adverse effect on male fertility. It impairs testicular and post-testicular function. However, dysfunction of male reproductive health is proportional to time of exposure to all such contaminants. Longer the duration more is the severity. Long term EDB exposure decreases in sperm motility, viability and causes cell death where the short term exposure may slow sperm velocity. EDB result abnormal sperms production (tapered heads, absent heads, and abnormal tails). The accessory sex glands may be affected by EDB exposure [41].

Biological agents

Effect such as chronic disease states, aging, toxin exposure, or genitourinary infection/inflammation, the cellular antioxidant mechanisms downplay and stimulate the production of estrogenic, anti-oestrogenic and antiandrogenic-like chemicals secretion which disturb our endocrine balance and create a situation called oxidative stress (OS). The disruption of balance between pro-oxidants and antioxidants caused OS. This imbalance is result by increased levels of reactive oxygen species (ROS) and/or reactive nitrogen species (RNS), or a decrease in antioxidant defense mechanisms. OS has been identified as one of the many mediators of male infertility. While small amounts of ROS are required for normal sperm functioning, disproportionate levels can negatively impact the quality of spermatozoa and impair their overall fertilizing capacity. ROS and their metabolites can attack DNA, lipids, and proteins and alter enzymatic systems, produce irreparable alterations, cause cell death; and ultimately, lead to a decline in the semen parameters associated with male infertility [42]. In addition, the generation of nitric oxide (NO) radicals and reactive nitrogen species (RNS) mediator of many cytotoxic and pathological effects. Hormonal imbalance cause due to EDs enhance NO generation that contribute to poor sperm motility and function, leads to male infertility [43].

Heavy metals

"Heavy metals" is imprecise term; it is widely used in scientific literature and commonly defined as a group of elements with a specific density of more than 5 g/cm ^{3} [44]. These elements are natural constituents of the earth's crust and it is beyond any doubt that indiscriminate human activities have drastically altered their geochemical cycles and biochemical balance. The main global sources of anthropogenic contamination by heavy metals include different branches of industry, the power industry, transport and municipal waste management. Are these heavy metals really a burden for human reproductive health? Accumulating evidences suggest, particularly when the studies are performed with low micromolar concentrations of heavy metals, they can act as endocrine-disrupting substances through specific, high-affinity pathways. Heavy metals (e.g., arsenic (As), lead (Pb), boron (B), mercury (Hg), cadmium (Cd), antimony (Sb), aluminum (Al), cobalt (Co), chromium (Cr), lithium (Li) have been found to exert reproductive toxicity, adverse reproductive effect on the testes and the hypothalamic-pituitary axis in human and experimental animals. Thus far, heavy metals primarily have been described to interact with the estrogen receptor giving rise to the term metalloestrogens. Historically, the fall of the Roman Empire has been attributed to lead poisoning. Among metals the nature of mercury is

versatile. There are three main chemical forms of mercury such as (1) organic mercury: used as fungicides, herbicides and wood preservatives, (2) inorganic mercury: used in the antiseptic and dermatological preparations and (3) elemental mercury. All these heavy metals man encounter in daily life through routes of ingestion of food such as fish and seafood, dermal absorption, and inhalation and occupational exposure. In addition, amalgam tooth fillings were identified as the major source of mercury contributing to the body burden in humans. Recently, the sale of Maggi noodles (Nestle) has been banned in India due to presence of lead in the product, than that of the maximum permissible level of 2.5 ppm [45]. The possible effects of some heavy metals on male reproductive health are given in Table 2.

Table 2. Effect of some heavy metals on male reproductive system

No.	Heavy metals	Industry	Adverse effect	References
1	Lead (Pb)	Battery plants and emissions from petrol, individuals inhabiting industrialized areas, who smoke and consume alcohol	A direct testicular toxicant induce reduce reproductive capacity, dose-dependentsuppression of serum testosterone level and spermatogenesis	46
2	Mercury (Hg)	Batteries, thermometers, thermostat and fluorescent tubes.	Impotence and decreased libido, abnormal sperm morphology and abnormal sperm motility. tubular atrophy and Sertoli-cell-only syndrome	47,48
3	Boron (B)	Glass, Cements, soaps, carpets, crockery, and leather products	Oligospermia and decreased libido	4
4	Cadmium (Cd)	electroplating, battery electrode production, galvanizing,plastics, alloys, paint pigments and cigarette smoking	Testicular necrosis	49

Pharma agents

A myriad of other factors such as radiation, therapeutic agents may show functional dissolution of male gonadal system that affect semen parameters. Gonadal tissues are most sensitive to radiation. Irradiation may have an intense effect on reproductive function. Irradiation therapy and many pharmacological drugs and chemotherapeutic agents are adversely affect germ cells of male reproductive system. Exposure to chronic radiation by occupation means (the personal dosimeters worn by workers of radiology department to measure the ionizing radiation), direct radiation to treat cancer affect the function of HPG axis. However, the damage due to irradiation highly depends: types of radiation (X-ray, neutron or radioactive materials). Doses of radiation (the doses >0.35 Gy) results reversible aspermia, but the dose >2 Gy cause irreversible aspermia, Moreover, the drugs used in chemotherapy can directly damage spermatogenesis either permanently or temporarily. Many pharmaceutical drugs likes depressants, calcium channel blockers (CCBs), alpha-adrenergic blockers, anti-epilepsy, anti-retroviral and some antibiotics may cause sperm DNA fragmentation, trigger premature acrosome reaction in sperms, decrease in ejaculate semen volume, abnormal sperm morphology, reduced motility, lower sperm count, and reduced testicular volume.

Role of EDs on female reproductive health

Female germ cells are a fixed population, present in ovary are mainly responsible for oocyte production. Female reproductive system constitutes of ovary, follipian tube, uterous, cervia, vagina, assessory glands and mammary glands are targets of EDs. Fertility in sexually mature women depends largely on the maintenance of healthy follicles, and their steady production ensures that an adequate number of follicles reach the antral stage. The stage of development at which the follicles are destroyed determines the influence of these factors on the fertility of women. Complete depletion of the follicle reserve results in irreversible infertility and partial depletion of the follicle reserve results in moderate effects on periodicity. Therefore, exposure of hormone-responsive, primordial and preantral follicles to EDs may impair folliculogenesis, inducing meiotic aberrations (e.g. aneuploidy and multiple oocyte follicles) or even follicular atresia. Ultimately, EDs can alter female reproductive development, fertility and onset of menopause results premature ovarian failure. The cytopathic role of man-made chemicals (EDs) on female reproductive cells and other accessory cells are diverse, they not only increase the incidence of reproductive anomalies and but also infertility which become epidemic (Table 4). While not as clearly defined the effect of EDs as in the male, evidence is accumulating that, EDs have been shown to affect trophoblast and placental function, the female hypothalamo-pituitary-gonadal axis, onset of puberty and adult ovarian function. The effects of EDs are complex, not least because it is emerging that low-level, 'real-life' mixtures of EDs may carry significant biological potency (Table 3). In addition, there is evidence that ECs/EDCs can alter the epigenome in a sexually dimorphic manner, which may lead to changes in the germ line and perhaps induce transgenerational effects [50].

What is remarkable about these EDs? These substances can cross placental barrier and enter into the embryological circulation. There is strong correlation between exposure of mother to these EDs and reproductive birth defects developing fetus. After the birth, neonates are susceptible to EDs mediated reprotoxicity via lactation [51].

Table 3. Cytopathological effects of EDs on the ovarian cells

No.	EDs	Adverse cellular effects	Consequences
1	PCB, phthalates, genistein, atrazine and MXC	Impaired folliculogenesis women leads to infertility.	Scanty oocyte production, if occurred in mid-aged.
2	BPA	Follicular atresia	Premature ovarian failure and polycystic ovary syndrome.
3	BPA, diethylstilbestrol (DES) and genistein	Meiosis disruption	Developmental defects, especially aneuplody.
4	TCDD, DDT and MXC	Reduced steroidogenesis ingranulosa/theca cells	Adrenal and.gonadal agenesis, impaired expression of pituitary gonadotropins. Less Androgen secretion by theca cells (TCs) can delay follicle development and ovulation and may not able to provide precursor materials for estrogen synthesis.

Table 4. Effect of heavy metals on female reproductive health

No.	Heavy metals	Effects	References
1	Cd (metalloestrogen)	Potential causative agent of oestrogen-dependent diseases, such as breast and endometrial cancer, endometriosis and spontaneous abortions, endometrial dysfunctions, implantation failure, premature delivery, subfertility, spontaneous abortions and preeclampsia.	72,73
2	Pb (abortifacient)	Spontaneous abortion through its potential teratogenic action and pregnancy related complications.	70
3	Hg (slow poison)	Reproductive disturbances, such as stillbirth or spontaneous abortions, congenital malformations, infertility and inhibition of ovulation (from animal studies), menstrual cycle abnormalities including changes in bleeding patterns and cycle length.	74,75

Exposure to EDs which need not have to work on dose dependent manner arise several complications to female reproductive physiological system like menstrual irregularities, polycystic ovarian syndrome, endometriosis and sterility [52]. Several chemicals, synthetic compounds, metals, and other environmental toxicants have been associated with adverse reproductive effects to female reproductive health at high concentrations but yet we do not know with certainty if there is a safe threshold.

Greater risk of developmental defects in offsprings is result by endosulfan if female expose throughout developmental period [53]. India is one of the largest manufacturer and consumer of pesticides in south Asia and about 81,000 metric tonnes of endosulfan was manufactured in India during 1999-2000 [54]. The results of some recent studies have revealed that contact of pregnant mice to endosulfan at 1 mg/kg/day from day 12 during parturition interfere spermatogenesis in progeny. Exposure to endosulfan during fetal gonadal differentiation altered the process of spermatogenesis in rat by affecting testicular lactate dehydrogenase and sorbitol dehydrogenase [55]. Oral administration of the pesticides endosulfan, methyl parathion and mancozeb inhibits compensatory ovarian hypertrophy, decreases the number of healthy follicles, increases the number of atretic follicles, and affects the oestrous cycle in rats. Whether endosulfan directly affect the ovary or made an indirect approach to induce toxic effect on ovary through hypothalamus or pituitary, or to a desensitization of the ovary to gonadotropins are yet to be ascertained [56]. However, endosulfan mediated developmental/ reproductive toxicity or endocrine disruption is doses dependent.

It is reported that the persistent organic pollutants (POPs) such as insecticide DDT and its metabolites, by-product of dioxins and the industrial compounds PCBs, alkylphenols act as antagonist to androgen receptor (AR) and progesterone receptors (PR). There are also several agrochemicals, pesticides and biocides e.g. (chlorinated insecticides, organotins, imidazoles and triazoles) and other industrial compounds (several phenol compounds such as bisphenol A) act as agonists of estrogen receptors (ER). Both DDT and its

major subtle metabolite DDE alter ovarian function and reduce female fertility. DDT and DDE act via different steroidgenic pathways. The endocrine and reproductive effects of these chemicals are may be due to their ability to: (1) mimic the effect of endogenous hormones like 17β-estradiol, (2) antagonize the effect of endogenous hormones, (3) disrupt the synthesis and metabolism of endogenous hormones like androgen and estrogen and (4) disrupt the synthesis and metabolism of hormone receptors. Excess accumulation of DDT and its isomers in body may disrupt the reproductive physiology of human and other animals. Lindenau *et al* [57] reported that DDT affects progesterone secretion, thereby reduce ovulation rate. The inhibition of progesterone synthesis or action could be the reason of abortion or pre-term birth [58].

Benzene hexa chloride (BHC) is most potent pesticides used throughout world for controlling pests in agricultural products and also for house hold purposes [59]. A study conducted in rat by Foster *et al* [60] showed that BHC has no direct effect on steriodgenesis whereas TCDD inhibit ovulation by rupturing follicular structure. The studies conducted in Sprague-Dawley female rat by administration of TCDD and related compounds exhibit a broad spectrum of antioestrogenic responses. The toxicokinetic study also reveals TCDD affects pregnancy and parturition and it distribute and/or redistribute itself to fetuses and neonates by placental and lactational transfer [61]. TCDD alters reproductive function in the immature female rat model via effects on the hypothalamic-pituitary axis as well as by direct effects on the ovary by decreasing EGF receptor binding in the female rat thus inhibit the 17 beta-oestradiol function, increase peroxidase activity, oestrogen and progesterone receptor levels, EGF receptor and c-fos protooncogene mRNA levels. The aryl hydrocarbon (Ah) receptor was identified in the rat uterus. The Ah receptor (AhR) is a ligand-dependent transcription factor that mediates a wide range of biological and toxicological effects result from exposure to a structurally diverse variety of synthetic and naturally occurring chemicals [62]. TCDD and related compounds act in dose-dependent manner. A study conducted in porcine by Gregoraszczuk [63] has further visualize this statement. 6-Methyl-1, 3, 8-trichlorodibenzofuran (MCDF) is relatively non-toxic compared to TCDD. TCDD and its related compounds show anti-oestrogenic properties by bind to the aryl hydrocarbon receptor (AhR), resulting in the activation of a battery of genes, including the cytochrome P450s (CYP1A1, CYP1A2). This inhibitory effect of TCDD on growth, differentiation and apoptosis exclusively used to treat ovarian cancer [64].

In healthy women chemicals like PCBs delayed ovarian cycle and ovulation by affecting synthesis of gonadal steroids [65]. Reprotoxic effects that have been associated with pesticide exposure in women are decreased fertility, spontaneous abortions, stillbirth, premature birth, low birth weight, developmental abnormalities, ovarian disorders and disruption of the hormonal function. Further, to infer that concurrent exposure and. over accumulation of EDs result female reproductive disorders like ovarian dysgenesis syndrome at later stage of female life and in middle age women leads to sub-fertility and infertility. A recent study has shown that when TCDD, PCBs and phthalates are present significantly at higher concentrations in peritoneal fluid of women leads to endometriosis result chronic inflammation, stimulation of endometrial cells derived from retrograde menstruation. PCBs and DDT congeners may cause a small, increased risk for endometrial cancer. Developmental toxicants like plastics adversely affect the developing embryo or fetus. Some mothers may be exposed to these in the occupational setting. These reprotoxicants are directly affect reproductive health throughout the life course, including the period before conception, at conception, fertility, pregnancy, child and adolescent development, adult health and even transferred the physiological defects to next generation. The administration of vinclozolin to gestating rats and mice are known to promote epigenetic transgenerational inheritance of adult onset disease in subsequent generations (F1–F4) following ancestral exposure during fetal gonadal sex determination [66]. The study done by Manikkam *et al.*,[67] to determine whether mixture of plastic derived endocrine disruptor compounds bisphenol-

A (BPA), bis(2-ethylhexyl) phthalate (DEHP) and dibutyl phthalate (DBP) show the same effect as vinclozolin? When gestating F0 generation females were exposed to either the "plastics" or "lower dose plastics" mixture during embryonic days 8 to 14 of gonadal sex determination and the incidence of adult onset disease was evaluated in F1 and F3 generation rats. There were significant increases in the incidence of total disease/abnormalities in F1 and F3 generation male and female animals from plastics lineages. Pubertal abnormalities, testis disease, obesity, and ovarian disease (primary ovarian insufficiency and polycystic ovaries) were intensified in the F3 generation animals. The ability of an environmental factor (*i.e.* endocrine disruptor) to promote an epigenetic transgenerational phenotype impacts the potential hazards of environmental toxins, mechanisms of disease etiology and evolutionary biology and epigenesis.

Neonates on exposure to an epoxide methoxychloro (MXC) show reduce ovulatory rates and ovarian functions at adult stage. Accumulation of such organic chemicals those impair ovulating capacity of adult ovary after ovarian stimulation. They work in time- and dose dependent manner [68]. The effects of lindane and pentachloro benzene, DDT, group of PCBs and other organochlorine chemicals after biomagnifications when enter into mature female that adversely affect pregnancy rate. This result spontaneous abortion and congenital disorder in neonates. However, there are two contradictory reports available from the cohort study done in 2 different population resided in 2 different geographical location i.e. one is in mid east of Turkey (Asia) by Jarrel *et al* [68] [which state that there is strong correlation between presence of concentration of hexachlorobenzene in serum and miscarriage of women] which was contradictory to other publish report by Leoni *et al* [69] done in Italy (western Europe) [which state that there is no correlation between presence of concentration of hexachlorobenzene and miscarriage of women]. Geographical allocation and spatial distribution may combat adverse effect of EDs?

Effect of radiation on female reproductive system

In the female, the response of the ovary to the irradiation varies with age as well as dose. However, the effect of radiation on ovarian function, associate hormone of HPG axis and fertility is not clear-cut. An ovarian dose of 4 Gy may cause a 30 % incidence of sterility in young women, but 100 % sterility in women over 40 years of age. Pelvic irradiation may also have a profound effect on the uterus, with arrested growth in the prepubertal girl, and failure of uterine expansion during pregnancy with subsequent miscarriages and premature labor [70]. The main adverse effects of radiation exposure to reproductive organs are hereditary disorders and congenital defects or birth defects.

Heavy metals

Increasing urbanization and industrialization can lead to the elevated risk of human exposure to heavy metals, and consequently give rise to reproductive problems. Heavy metal-induced fertility impairment from genetic, epigenetic and biochemical level [71]. Exposure to heavy metals like Cd, Hg, Pb etc. generated from different sources adversely affect female reproductive health (Table 4).

Biological agents

The role of OS in female reproduction cannot be underestimated. There is evidence that OS plays a role in conditions such as abortions, pre-eclampsia, hydatidiform mole, fetal embryopathies, preterm labor and pre-eclampsia and gestational diabetes which are associated to a number of reproductive diseases such as endometriosis, polycystic ovary syndrome (PCOS), and unexplained infertility. Pregnancy complications such as spontaneous abortion, recurrent pregnancy loss can also develop in response to OS. Readers are suggested to refer excellent review by Agrawal *et al* [76] for oxidative stress related complications on reproductive functions of females.

Treatment of reproductive disorders

Traditionally, both surgical and medicinal therapy has focused on alleviation of symptoms, prevention of disease progression and promotion of fertility. In spite of significant developments in medical and surgical approaches, the optimal therapy for treating infertility has yet to be established. Various allopathic, ayurvedic and

other alternatives medicines, physiotherapy with acupuncture, antioxidant therapy, ART (Assisted Reproductive Technology) such as IVF, ICSI has been carried out are been effective to enhance the pregnancy. Hormonal therapy is a logical approach of empirical drug therapy for manifesting hormonal regulation in spermatogenesis and oogenesis. However, treatment with GnRH analogues, gonadotrophins may improve pregnancy rates modestly. These adoptive technologies provide signal that may generate neuroendocrine mechanism involved in the initiation of gonadal recrudescence. However, due to high cost and associate side effects of hormonal therapy is not widely accepted by common people and ICSI/IVF always carries risks to the fetus and mothers. However, no ultimate treatment is available which can treat the dysfunction of this unique cellular portion (gonads) from somatic and germ cells level. Extensive investigations from last 2 decades to treat infertility from basal level, endorse that stem cells may have the solution. Stem cells are primal uncommitted cells present in zygote that have the ability to proliferate, perpetuate and differentiate into all the cell types required by an individual to live life. Stem cells could be stimu-lated *in vitro* to develop number of specialized cells including male and female gametes suggesting their potential use in reproductive medicine. During past few years a considerable progress in the derivation of germ cells from pluripotent stem cells like embryonic stem (ES) cells and embryonic germ cells. ES cells derived from animal models like mice provide basic mechanism to study reproduction associated complicacy. The successful derivation of gametes "oocytes" was first reported from mouse embryonic stem cells (ESCs) by Húbner *et al*., [77].

Later studies conducted on mouse ES cells demonstrated their ability to generate functional spermatozoa capable of giving rise to live offspring after use in ART intracytoplasmic injection. The basic approach to generate germ cells from ES cells is depicted in Figure 2. However, the ethical constrain surrounding use of embryonic part has restricted, ES cell research of human. The applications of reprogramming and trans-differentiation techniques to stem cells, able to generate mature and normal oocytes and spermatozoa from iPSCs (induced pluripotent stem cells) and MSCs (mesenchyma stem cells) [78]. The *in vitro* generation of male germ cells from human bone marrow stem cells was demonstrated by Nayernia *et al* [79]. Hence, stem cell-based strategies have been proposed as future clinical therapies for treating infertility and as widely translatable cellular source in reproductive medicine.

Conclusion

EDs may also explain some idiopathic infertility cases both in men and women to certain extent and may be blamed for the rising incidence of

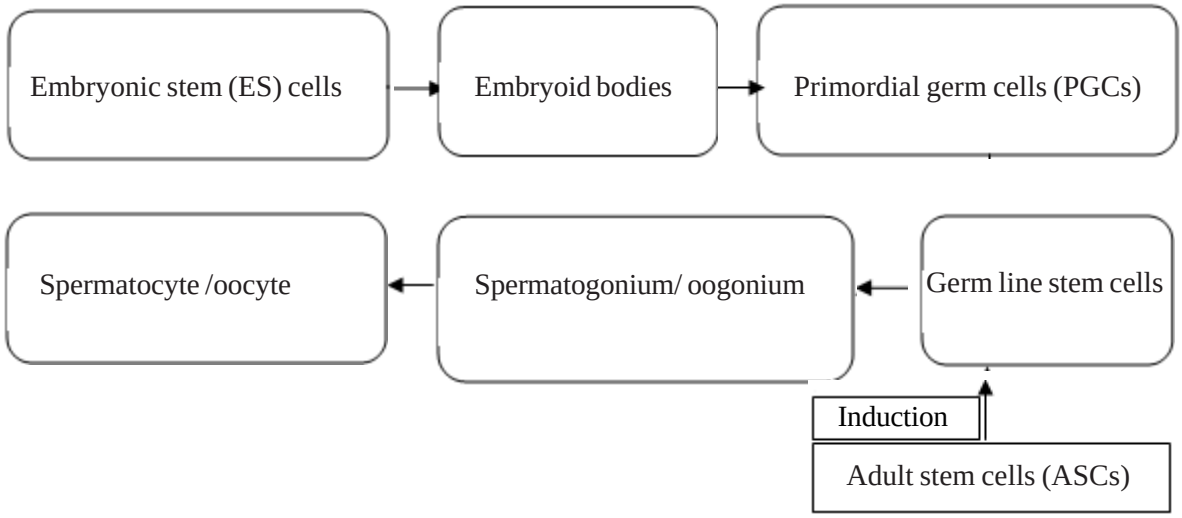

Fig. 2. *In vitro* generation of spermatocyte and oocyte from stem cells

human reproductive disorders/ diseases. Endocrine disruption is a serious public health problem that must not be ignored. The removal of these substances from the environment is neither simple nor cheap. In author's opinion this can be gained not only by implementation of law regulations and directives concerning the emission limits, but everyone must contribute to eliminate EDs from environment. So that fertility can be store without morbidity and mortality. In this context, it is a concern for all scientific communities to develop new microbial strains which could assimilate all these EDs and to develop an antidote chemicals that could able to eliminate these reprotoxic agents from environment and use of eco-friendly materials like organic manure may decrease EDs to some extent. Further research is required a detail knowledge of reproductive toxicants which is crucial for development of new therapeutic strategies to treat reproductive disorders including birth defects and able to recover from permanent effects of EDs.

Acknowledgements

Author owes thank to Ms Mahashweta Panigrahi, Ms Anulipta Satpathy and Mr Sabitra Sankalp Panigrahi for their assistance during preparation of manuscript.

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