Chapter

Reproductive Toxicology: An Update

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Abstract

Human reproduction and development is a succession of symbiotic events. Nearly, at every point of this phenomenon found to be the principle target of one or more reproductive toxicants. Chemical agents, physical factors, as well as biological intruders can pose antagonistic effects on reproductive potential of an organism. The pathways are different *viz.*, either damaging embryo and sometimes fetus or inducing mutation in a parent's germ cell. The outcomes are declined fertility to impulsive abortion, functional discrepancies, developmental retardation, structural anomalies, etc. It is a now essential to establishing proper databases for reproductive and developmental toxicity chemicals, physical and biological factors including appropriate awareness among the society. Although many *in vitro* and *in vivo* toxicology studies are in pipeline which are independent studies but combination with other hazardous studies could give us an accurate numbers.

Keywords: reproduction, toxicity, fertility, infertility, mutagens

1. Introduction

Reproduction (procreation; conception) is one of the most essential requirements of all organisms where producing a transcript, helps in the survival and perpetuation of the species [1]. Parenthood is one of the most comprehensively preferred priorities of mankind and which happens at ease, when couples are vigorous and normal. According to earlier archaic studies of anthropologists and evolutionary biologists, *Homo sapiens* displayed a better cognitive development about 2,00,000 years ago and hence, had a "reproductive consciousness" [2]. Ancient mythologies and civilizations respected and worshipped fertility Gods and Goddesses like, Egyptian goddess *Maat* [3], Mesopotamian's *Erua* [4], Babylonian's *Ishtar*, Persian's *Anaitis*, Greek's *Actemia* [2], and also they had a deep desire for conception, and a strong perception of fertility, which can be correlated with human sustainability and existence.

The reproductive cycle of a mammalian individual involves of a sequence of several phases and unified events. According to ICH guideline [5]:

A. Pre-mating to birth (mature male and female conceptive ability, growth and maturation of gametes, reproductive nature, and conception).

B. Conception to implantation (mature female conceptive ability, pre-implantation development, cleavage, morula, blastula, and implantation).

C. Implantation and organogenesis (mature female conceptive ability, development of embryo, and foremost organ development).

D. Fetal development (until the end of gestation, mature female conceptive ability, fetal development and growth, and growth and development of organs).

E. Birth and pre-weaning development (mature female conceptive ability, parturition, lactation, neonate adaptation to extrauterine life, pre-weaning development, and growth).

F. Post-weaning development up to sexual maturity (growth, adulthood, adaptation to independent life, and achievement to full sexual function).

According to World Health Organization (WHO) info, at present globally 50–80 million people are facing infertility [6]. Significant studies have reported that female infertility occurs 50%, infertility because of male factors is 20–30%, and rest is shared by both genders [7]. These findings are considerably broader than previously reported.

2. Reproductive toxicity

Since a decade, human reproductive disruption by various factors including xenobiotics such as drugs, occupational, and environmental exposures leading to reproductive toxicity which is has become a growing concern. Reproductive toxicity defined as: "the antagonistic effects of a substance on any characteristics of the male or female sexual reproductive cycle, together with an impairment of reproductive function, and the induction of adverse effects in the embryo, such as growth retardation, malformations, and death which would interfere with the production and development of normal offspring that could be reared to sexual maturity, capable in turn of reproducing the species" [8].

The first essential introduction in reproductive toxicology was given by Wilson and Warkany in 1965 [9]. The first test guideline was published by the Food and Drug Administration (FDA) in 1966 [10], followed by the Committee on Safety of Medicines [11], Ministry of Health and Welfare (MHW) of Japan [12], and rest of the other nations. It was provisionally terminated by International Federation of Teratology Societies (IFTS), pharmaceutical industry and the health authorities of EEC, Japan, and USA with the aid of ICH Harmonized Tripartite Guideline "Detection of Toxicity to Reproduction for Medicinal Products" in June 1993 [13, 14].

Reproductive toxicity is categorized as follows:

2.1 Reproductive toxicity

Reproductive toxicity has been defined as "any effect of chemicals that would interfere with reproductive ability or potential," with consequent effects on lactation and the development of the progenies [15]. It includes, variations in the reproductive system of men and women, adverse impacts on the beginning of adolescence, normal reproductive cycle, production and transport of healthy gametes, sexual activities, fertility, parturition, early conceptive senescence, and alterations in any other activities which are reliant on the integrity of the reproductive systems [16]. Reproductive toxicity effects could be via lactation too but such classes are treated separately [17]. This is because it is desirable to be able to classify chemicals

specifically for adverse effect on lactation so that a specific hazard warning about this effect can be provided for lactating mothers.

Classes of reproductive toxicity include:

- Male fertility
- Female fertility
- Parturition
- Lactation.

2.2 Developmental toxicity

According to Globally Harmonized System the developmental toxicity is defined as, "adverse effects induced during pregnancy, or as a result of parental exposure," which "can be manifested at any point in the life span of the organism" [15]. The exposure to specific exogenous substances prior to conception in either of the parent, exposure during gestation, or exposure during prenatal or postnatal development from birth to sexual maturation may result in developmental toxicity. Developmental toxicity has varied end points such as impulsive abortions, still-births, deformities, and early postnatal mortality, reduced birth weight leading to structural anomaly, altered growth, functionally deficit, and death of the developing organism [18].

Classes of developmental toxicity include:

- Mortality
- Dysmorphogenesis (structural abnormalities)
- Alterations to growth
- Functional impairment.

Due to the fact that, male and female reproductive anatomy and biologic mechanisms are differing, they have a speckled result for reproductive toxicants. It is therefore essential to recognize reproductive toxins and their mechanisms and sites of action and to learn about species (especially human) vulnerability to them. Reproductive toxicants or reprotoxicant are chemical, biohazardous (e.g., viruses), or physical (e.g., radiation), agents that can impair the reproductive capabilities in men and/or women. Developmental toxicants interfere with proper growth or health of the child acting at any point from conception to puberty. The chemical agents which elevate the occurrence mutations above natural level by damaging the genetic material of an individual are known as mutagens. Incidences of defective cells or cancerous cells found when these mutations are inherited. As the name suggests, embryotoxins are lethal to embryos, where they may exterminate, distort, impede the growth and development of embryo, and may cause postnatal problems. The compounds like, mercury, lead, other heavy metals, and organic compounds *viz.*, formamide are some of the well-known examples of embryotoxins. Additionally, agents which can interrupt or leads to deformity in the development of an embryo or fetus are called as teratogens, which have the potential to miscarriage or cause children with birth defects.

The fundamental biological mechanisms of reproductive toxicity are multifaceted and involve absorption, distribution, metabolism (toxification, and/or detoxification), excretion, and repair [19]. The mechanism of reproductive toxicants disturbs the flow of matter, energy, or information that are necessary for normal functioning of cells, organs, or organisms. Later, toxicant will distribute to the target organ (gonad, hypothalamus, pituitary, uterus, epididymis, liver, etc.) where it employs its antagonistic effect before it is metabolized. The action of reproductive toxicant is either direct by the virtue of structural similarity to an endogenous compound (*viz.*, hormone, vitamin, or nutrient) or because of chemical reactivity (i.e., alkylating agent, denaturant, and chelator) or indirect (requiring metabolism before exerting a toxic effect) on reproductive system [19].

Formerly debated male fertility decline is no longer controversial. Several substantiating reports have confirmed a fall in sperm counts and semen quality in men over the last several decades globally [20]. The causative factors are not only obesity, illicit substance use, smoking rates, and alcohol abuse, but also due to chronic reproductive toxin exposures of the modern age. The spermatozoa with abnormal genetic material, which supports irregular spermatogenesis, abortions, progenies with genetic defect and diseases, etc., are some of the adverse effect of causative factors on male fertility. The investigation of male reproductive function begins with measurement of testis size, semen analysis, accessory gland functionality, reproductive hormone estimation, impotence or reduced libido, and fertility [21].

Many studies have been reporting weakening of female reproductive capacity over the past half century, which could be because of cultural change (e.g., delayed childbearing and increased contraception in women), but environmental exposures to the fetus, mother, or father may also contribute [22]. The women's health practitioners, obstetricians, and gynecologists have been advised to increase communication with their patients about the potentially detrimental effects of reproductive toxicants on reproductive health [23]. Among women of US and Danish the conception rate have declined to 44% since 1960 [24] and hormone-related diseases such as disorders of pubertal development, polycystic ovary syndrome (PCOS), endometriosis, and uterine fibroids have become common.

Reproductive difficulties and developmental abnormalities constitute a significant medical problem and greatly contribute to human suffering. The following provides a summary of the Globally Harmonized System (GHS) system as it relates to classification of health hazards [15]. The GHS system defines developmental toxicity with reproductive toxicity, but later classifies them separately. While classification, the GHS system define reproductive toxicity as, antagonistic effects on sexual activity and fertility amongst adult men and women comprising its adverse effect on sexual deeds, parturition, pregnancy outcomes [15].

These are the following categories of reproductive and developmental toxicants:

2.2.1 Category I: satisfactory reports with human evidence

The toxicants which are found to be human reproductive and/or developmental hazards are considered as category-I agents. The research reports which assist the above hypothesis with satisfactory epidemiologic confirmations or studies involving humans along with solid subsidiary animal study for at least one adverse reproductive effect. Though, the research data with human study is limited to support this classification, at present there are agents which fall under this category. The list includes biological, physical along with chemical hazards which pose potential reproductive effects, are the resultant of studies included humans and animals (**Table 1**).

Chemical	Reported adverse effects
Aniline	Female subfertility, natural abortion, growth impedance, and developmental disorders
Bulsulfan, methotrexate, cyclophosphamide	Male and female infertility, natural abortion, genetic defects, and growth retardation
Carbon disulfide	Lower male sex libido, infertility, abortion, abnormal growth, menstrual disorders, and breast milk contamination
Carbon monoxide	Female infertility, spontaneous abortion, growth retardation, and functional deficit
Dibromochloropropane (DBCP)	Infertility in men, genetic defects, and altered sex ratios
Dinitrotoluene (DNT)	Spontaneous abortion, male infertility, growth retardation, and developmental disorders
Ethyl alcohol	Male infertility, developmental disorders, birth defects, low birth weight, or premature births
Lead	Infertility, miscarriage, growth retardation, functional deficit, and breast milk contamination
Mercury	Male infertility, birth defects, growth retardation, and breast milk contamination
Phenol	Altered sex ratio, spontaneous abortions, and impotence
Polychlorinated biphenyls (PCBs)	Infertility, spontaneous abortion, growth retardation, and breast milk contamination.
Warfarin	Birth defects, developmental disorders, and spontaneous abortions
Toluene (methyl benzene)	Low birth weight, developmental disorders, birth defects, menstrual disorders, and male and female infertility
Bio-hazardous material	
Cytomegalovirus	Spontaneous abortion, birth defects, growth retardation, and developmental disorders
Hepatitis B virus	Growth retardation, liver disease in infected offspring, and breast milk contamination
HIV	Functional deficit and childhood cancer
Rubella virus (German measles)	Birth defects, growth retardation, and developmental disorders
Varicella-zoster virus (chicken pox and shingles)	Birth defects and growth retardation
Physical hazard	
Excessive heat	Male infertility
Heavy physical exertion	Spontaneous abortion and growth retardation
Ionizing radiation	Male and female infertility, spontaneous abortion, birth defects, growth retardation, developmental disorders, and childhood cancer

Table 1.
Category I: Satisfactory reports with human evidence [15].

2.2.2 Category II: satisfactory reports with animal evidence/limited human evidence

The toxicants which are likely found to be or possible human reproductive hazards are considered as category-II agents. In order to support this category, studies which include experimental animals and/or limited human trails can be considered.

Chemical	Reported adverse effects
Acetaldehyde	Growth retardation and developmental disorders
Acetone	Female infertility, birth defects, and menstrual disorders
Aluminum	Birth defects
Ammonia	Premature birth
Anesthetic agents	Male infertility, spontaneous abortion, birth defects, growth retardation, and breast milk contamination
Antimony	Spontaneous abortion, and breast milk contamination
Arsenic	Birth defects and spontaneous abortion
Benzene	Female infertility, spontaneous abortion, birth defects, growth retardation, and menstrual disorders
Boric acid, borates	Reduced male sex drive, male infertility, and female infertility
Bromine	Male infertility, decreased libido, impotence, and breast milk contamination
Cadmium	Infertility, birth defects, growth retardation, developmental disorders, and breast milk contamination
Carbamide (urea)	Spontaneous abortion
Carbaryl	Male and female infertility and genetic defects
Carbon tetrachloride	Male and female infertility
Chloroform	Spontaneous abortion and birth defects
Copper	Spontaneous abortion and birth defects
Dimethoate	Birth defects, spontaneous abortion, and male infertility
Dimethylformamide, N, N (DMF)	Spontaneous abortion, stillbirths, birth defects, and female infertility
Ethylene glycol monomethyl ether (EGME)	Male infertility, birth defects, and developmental disorders
Ethylene oxide	Male and female infertility, spontaneous abortion, birth defects, and growth retardation
Formaldehyde	Female infertility and spontaneous abortion
Gasoline	Female infertility, birth defects, and menstrual disorders
Lithium	Birth defects and male infertility among patients taking lithium
Manganese	Reduced male sex drive, male infertility, and breast milk contamination
Nitrous oxide	Male and female infertility, spontaneous abortion, and developmental defects
Oral contraceptives	Reduced male sex drive, female infertility, and birth defects
Paints	Spontaneous abortion and developmental disorders
Polyvinyl chloride (PVC resin)	Female infertility, spontaneous abortion, and stillbirths
Solvents	Birth defects, developmental disorders, spontaneous abortion, impotence, female infertility, menstrual disorders, and breast milk contamination
Sulfur dioxide	Spontaneous abortions, female infertility, low fetal weights, and birth defects
Styrene (vinyl benzene)	Male and female infertility, spontaneous abortion, and breast milk contamination

Chemical	Reported adverse effects
Tetrachloroethylene (perchloroethylene)	Female infertility, spontaneous abortion, developmental disorders, birth defects, menstrual disorders, and breast milk contamination
Trichloroethylene	Male and female infertility, spontaneous abortion, and birth defects
Trinitrotoluene	Male infertility
Vinyl chloride monomer	Reduced male sex drive, spontaneous abortion, birth defects, and childhood cancer
Xylene	Female infertility, birth defects, menstrual disorders, and breast milk contamination
Physical hazard	
Low atmospheric pressure (hypobaric)	Male infertility and growth retardation
High atmospheric pressure (hyperbaric)	Male infertility and birth defects

Table 2.
Category II: Satisfactory reports with animal evidence/limited human evidence [15].

Chemical	Reported adverse effects
Acrylamide	Male and female infertility, birth defects, and developmental disorders
Carbon dioxide	Birth defects and male infertility
Carbon tetrachloride	Male and female infertility, developmental disorders, and birth defects
Chromium	Birth defects and infertility
Dimethyl phthalate	Birth defects and developmental disorders
Dimethyl sulfoxide (DMSO)	Developmental disorders
Epichlorohydrin	Male infertility
Ethylene thiourea	Birth defects
Halothane	Developmental disorders and birth defects
Methyl alcohol	Developmental disorders
Methyl ethyl ketone (MEK)	Developmental disorders
Methylformamide, N	Birth defects
Methylpyrrolidone	Birth defects
Nickel	Birth defects
Polybrominated biphenyls (PBBs)	Birth defects and developmental disorders
Ribavirin (virazole)	Birth defects and spontaneous abortion
Toxaphene (camphechlor)	Developmental disorders, infertility, and breast milk contamination
1,1,1-Trichloroethane	Low fetal weight, birth defects, and developmental disorders

Table 3.
Category III: Suspect/insufficient reports with animal evidence but not humans [15].

To support this class, minimum criteria is a single, systematic experiment on one animal species for one adverse reproductive effect. Below **Table 2**, enlisted the toxic effects of potential reproductive toxicants based on the observation of studies comprised animals and humans.

2.2.3 Category III: suspect/insufficient reports with animal evidence but not humans

This category consists of agents with probable or indeterminate reproductive hazards. Though they possess adverse effect on reproductive health but data are inadequate. Present details in **Table 3**, is only of studies with animal experiments with no human trials.

3. Chemical factors

Chemicals are omnipresent elements with both positive and negative effects found in workplaces across the globe. Several environmental chemicals together with other agents (e.g., radiation and bacteria), chemicals may also destructively affect the reproductive systems of male and female workers (**Table 4**). Exposure to toxicants before and after conception can affect parents, fetuses, and newborns. In most of the working environments, huge numbers of workers are exposed to the substances which are potentially toxic to reproductive health even after knowing. Exposure to industrial chemicals can alter reproductive functions in females. The ovary of a female is vulnerable in most of the cases therefore, have a significant effect on fertility, menstrual (estrous) cyclicity, and the timing of puberty and menopause [26]. Many toxic chemical agents, active metabolites from mother may reach the womb by different routes of mechanisms causing unfavorable environment to its development. This toxicity could reach to the deepest point, where it may not only obstructs the transport of male and female gametes to the site of fertilization but also stops fertilized egg moving to the site of implantation and development in the uterus. It is also found that, abnormal hormonal control during pregnancy is influenced by toxicants resulting in potential adverse effects on the fetus. The primary manifestations of developmental toxicity are embryo/fetal death, malformations (birth defects), growth retardation, and developmental delay. Adverse fetal outcomes may also include preterm delivery, altered sex ratio, and childhood cancer. The human tests is the house of high rates of proliferation, differentiation, as well as a metabolic activity associated with the production of large quantities of mature sperm which makes it more vulnerable to chemicals. The toxicants will target the Leydig cells (LC), sertoli, and germ cells of a testis which are the site of spermatogenesis, leading to germ-cell apoptosis and spermatogenic failure. Examples of chemicals toxic to the male reproductive system are presented in **Table 5**.

3.1 Heavy metals

Metals exert an extensive diversity of hazardous effects on reproduction and development including influence on fertility, intrauterine growth retardation, abortions, malformations, birth defects, and developmental effects, mainly those on the nervous system [21]. More recent, important mechanisms of action are those related to endocrine disruption and oxidative stress. Endocrine disruptors (EDs) have been defined as "exogenous chemical substances or mixtures able to alter the structure or function of the endocrine system and to cause adverse effects on organisms or their progeny" [28].

It is believed that, partial exposure to certain chemicals will decreases the puberty, causes abnormal semen quality and quantity, impairment of sex ratio, occurrence of hypospadias, testicular cancer, infertility, miscarriages, and genetic defects. In an *in vitro* study, concentration over 1 mmol of copper significantly

Agent	Industry or occupational group	Reported effects of female exposure	Reported effects of male exposure
Organic solvents in general	Painting, degreasing, shoemaking, printing, dry cleaning, metal industry, and several other fields of industry	Reduced fertility, menstrual disorders, fetal loss, birth defects, preterm birth, neurobehavioral effects, and childhood leukemia	Delayed conception, reduced semen quality, fetal loss, and birth defects
Benzene	Petrochemical industry and laboratory personnel	Fetal loss, reduced fertility, and low birth weight	
Carbon disulfide	Viscose rayon industry	Menstrual disorders	Decreased libido and potency
Some ethylene glycol ethers and their acetates	Electronics industry, silk screen printing, photography and dyeing, shipyard painting, metal casting, chemical industry, and other industries	Reduced fertility, fetal loss, birth defects, and menstrual disorders	Reduced semen quality
Tetrachloroethylene	Dry cleaning and degreasing	Reduced fertility and fetal loss	
Toluene	Shoe industry, painting, and laboratory work	Reduced fertility and fetal loss	
Metals			
Lead	Battery industry, lead smelting, foundries, pottery industry, ammunition industry, and some other metal industries	Reduced fertility, fetal loss, preterm birth, low birth weight, birth defects, and impaired cognitive development	Reduced semen quality, reduced fertility, fetal loss, and birth defects
Inorganic mercury	Lamp industry, chloralkali industry, and dental personnel	Reduced fertility, menstrual disorders, and fetal loss	Fetal loss
Pesticides[a]	Agriculture, gardening, and greenhouse work	Reduced fertility, fetal loss, birth defects, preterm birth, reduced fetal growth, neurodevelopmental effects, and childhood leukemia	Reduced sperm quality, reduced fertility, fetal loss, birth defects, and childhood cancer
Pharmaceuticals			
Anesthetic gases	Operating rooms, delivery wards, and dental offices	Fetal loss, reduced birth weight, preterm birth, birth defects, and reduced fertility	
Nitrous oxide	Operating rooms, delivery wards, and dental offices	Fetal loss, reduced birth weight, and reduced fertility	

Agent	Industry or occupational group	Reported effects of female exposure	Reported effects of male exposure
Antineoplastic agents	Hospital workers, pharmaceutical industry	Menstrual dysfunction, reduced fertility, fetal loss, premature birth, low birth weight, and birth defects	
Carbon monoxide	Iron and steel foundries, welding, food industry, car repair, and service stations	Preterm birth and intrauterine death	

[a]*Examples of pesticides with adverse effects in men include dibromochloropropane (DBCP), 2,4-dichlorophenoxyacetic acid (2,4-D), ethylene dibromide, chlordecone, carbaryl, alachlor, atrazine, and diazinon.*

Table 4.
Adverse reproductive effects of some chemical agents that have been reported in human studies (Source: [25]).

reduced the human sperm motility, where sperm motility is considered as one of the prime attribute of a male gamete to reach oocyte [29]. Cadmium, for example, may affect steroidogenesis by mimicking or inhibiting the actions of endogenous estrogens [30]. Several metals such as, iron, copper, cobalt, and lead will lead to oxidative stress by increasing the production of reactive oxygen species, decrease the levels of glutathione and other antioxidants. Lead interrupts the hypothalamic-pituitary axis and has been reported to alter hormone levels [31, 32], alter the onset of puberty, and decrease overall fertility [31]. The industrial discharges and emissions, batteries and most of the thermometers are the primary sources of mercury. Currently, mercury concentrations can be found in food chain especially in tainted seafood, leading to bioaccumulation amongst humans who are consumers of such foods which leads to reproductive toxicity [31] by disrupting normal spermatogenesis and fetal development [32]. Amongst heavy metals, boron is widely employed in the production of soap and cement including in leather industries, which is found to disrupt the HPG axis like lead [32]. Cadmium is another metal which is reported to cause testicular necrosis in mice and notable libido activity and infertility (**Table 5**) [33].

3.2 Insecticides

Insecticides are described as "chemicals used to control insects by killing them or preventing them from engaging in undesirable or destructive behaviors" by United States Environmental Protection Agency [34]. Considering the chemical structure, insecticides could be divided into five groups: (i) organochlorines, (ii) organophosphates, (iii) carbamates, (iv) pyrethrins/pyrethroids, and (v) nicotine/neonicotinoids. Insecticides could be characterized as "endocrine disrupters" due to their adverse effects on reproductive hormone pathway [35]. Exposure to permethrin, fenvalerate, and cypermethrin showed drastic drop in serum testosterone levels and elevated follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels. It is understandable that, decrease in testosterone levels provides a negative feedback to HPG axis, helping FS and LH to rise. Impairment of spermatogenesis, anti-androgenic effects, and alterations in reproductive enzyme pathways, decreased sperm quality and motility are key elements in insecticide-induced male infertility [36]. Organophosphates could alter the spermatozoon chromatin structure, DNA, acrosome, motility and, have toxic effects on HPG axis

Chemical hazards	Species effect observed (h = humans, a = animals)	Examples of occupations where hazards may occur
Alcohol	h	Social threat
Alkylating agents	h, a	Chemical and drug industrial
Anesthetic gases nitrous oxide	a, h	Medical, dental, and veterinary employees
Cadmium	h, a	Storage batteries and smelter workers
Carbon disulfide	h, a	Viscose rayon manufacture and soil treaters
Carbon tetrachloride	a	Chemical laboratories and dry cleaners
Diethylstilbestrol (DES)	a, h	DES producers
Chloroprene	h, a	Rubber labors
Ethylene oxide	a, h	Health-care workers (disinfectants) and users of epoxy resins
Hair dyes	a	Cosmetic manufacturers, hairdressers, and barbers
Lead	h, a	Storage batteries, policeman, and smelter workers
Manganese	h	Welders, ore smelters, and roasters
Nickel	a	Smelters and welders
Organic mercury compounds	a	Pesticide workers
Tris (flame retardants)	a, h	Clothing and textile work
Pesticides	a, h	Farmworkers and pesticide manufacturers
Dibromochloropropane	—	Exterminators
Vinyl chloride	h	Polyvinylchloride manufacture and processing
Elevated carbon dioxide	a	Brewery workers and chemical manufacture
Elevated temperature	h, a	Bakers, glassblowers, foundry, and oven workers
Microwaves	h, a	Radar operators, flight crew or pilots, and transmitter operators
X-irradiation	h, a	Health workers and radiation workers

Table 5.
Examples of agents toxic to the male reproductive system [27].

including reduced levels of testosterone [37]. Organochlorines such as dichlorodiphenyltrichloroethane (DDT), methoxychlor, chlordane, heptachlor, aldrin, endrin, and lindane are reported to cause oxidative stress within epididymis by decreasing antioxidant defense [38]. Endosulfan was found to cause irregular sperm maturation amongst farmers who employed this chemical into their fields. These insecticides not only hazard to male but also to female reproductive system (**Table 6**). They disrupt endocrine system and ovarian physiology in females via HPG axis leading to follicular maturation anomaly, disordered ovarian cycle, prolonged pregnancy, stillbirth, and subfertility also DNA damage and apoptosis amongst cells [39]. Endosulfan, an organochlorine, triggered apoptosis via

Hazard	Outcome
Anesthetic gases	Miscarriage and neonatal deaths
Hepatitis B	Newborn hepatitis and liver cancer
Organic mercury	Cerebral palsy and brain malformation
Lead	Abortions and premature birth (polychlorinated biphenyls)
Radiation	Miscarriage, brain defects, and skeletal defects [suspected reproductive hazards (based on human studies)]
Carbon monoxide	Slowed growth
Cytotoxic drugs	Abortions
Ethylene oxide	Abortions
Hexachlorophene	Birth defects
Organic solvents	Cleft palate, miscarriage, newborn infection, childhood cancer, physical stress (including heat), and prematurity
Vinyl chloride	Brain defects

Table 6.
Examples of reproductive hazards to humans.

oxidative stress induction in the follicle cells. Moreover, it induced the expressions of steroidogenic acute regulatory protein (StAR), CYP19A1a and aromatase, causing improper ovarian maturation organochlorines (**Table 7**) [38].

3.3 Genital tract infection

The male accessory gland infection and genital tract infections, by numerous bacteria, viruses, and fungi have an adverse effect on male fertility aptitude by infecting semen, inducing oxidative stress, which damages testicles, colonizing genital tract leading to obstruction, and directly disturbing sperm function, morphology [40]. The sexually transmitted pathogens and uro-pathogens such as, *Chlamydia trachomatis*, *Escherichia coli*, *Staphylococcus epidermidis*, *Klebsiella*

Insecticides	Effects on endocrine system
Aldicarb	17 beta-estradiol and progesterone inhibition
Aldrin	Androgen receptor binding
Carbofuran	Estradiol and progesterone increase; testosterone decrease (chlordane)
Deltamethrin	Estrogenic activity
Dieldrin	Androgen receptor binding, inducing estrogen receptor production in the cell (endosulfan)
Lindane	Luteal progesterone decrease, androgen, estrogen, and progesterone receptor binding
Methoxychlor	Estrogenic effect, pregnane X cellular receptor binding (parathion)
Parathion	Gonadotrophic hormone synthesis inhibition
Fenoxycarb	Testosterone metabolism disruption
Endosulfan	Androgen receptor binding, inducing estrogen receptor production in the cell
Chlordane	Androgen receptor binding, estrogenic pathway inhibition

Table 7.
Selected insecticides and their effects on endocrine system.

spp., *Proteus* spp., *Ureaplasma urealyticum*, *mycoplasms*, *Trichomonas vaginalis*, *Staphylococcus saprophyticus*, *Neisseria gonorrhoeae*, and chronic viral sperm contagions *viz. human immunodeficiency virus*, *hepatitis B*, and *hepatitis C viruses* [41] are some of the prominent pathogens which infect the male accessory glands and also the genital tract leading to male infertility which is accounted for 15–20% of total infertility [42]. The testicular tenderness, urethral expulsion, epididymal inflammation, and throbbing ejaculation are some of the notable symptoms of genital infection [43]. Microbial infection triggers the immune inflammatory mechanism, by which white blood cells and pro-inflammatory cytokines such as IL-1, IL-6, IL-8, macrophages, and polymorphonuclear neutrophils will be released into the infection site, which have been found to show negative effect on sperm functionality and fertilizing ability [44]. In females, genital tract infection can lead to adverse health outcomes such as infertility, ectopic pregnancy and increased vulnerability to transmission of the human immunodeficiency virus. It is also associated with adverse pregnancy outcomes. Vaginitis and cervicitis are common lower genital tract infections usually found in females which enable uncharacteristic vaginal discharge, genital discomfort, itching, and burning sensation while urination. Generally infection occurs at soft tissue and perineal of female genital tract. The infections which are common *viz.*, bacterial vaginosis, Bartholin gland abscess, endometritis, *pyometra*, *salpingitis*, pelvic inflammatory disease, intrauterine contraceptive device-associated infection, postsurgical obstetric, and gynecologic infections.

3.4 Obesity

A medical ailment linked with excessive accumulation of white adipose tissue within the body, distressing normal health and a person with BMI 25–30 kg/m^2 can be overweight, whereas BMI ≥30 kg/m^2 is said to be obese [45]. Current evidences have shown the destructive impact of obesity on the reproductive aptitude of men by subduing spermatogenesis, causing abnormal sperm morphology, sperm DNA fragmentation, erectile dysfunction, and reduced libido [46]. Increased deposition of fat in the upper thighs, scrotum, and suprapubic area causes rise in scrotal temperature and oxidative stress, which ruins normal spermatogenesis, sperm motility, and also interferes with sperm-oocyte interaction [47]. Prevalence of menstrual dysfunction, subfertility, abortion rates, pregnancy hitches, and anovulation are commonly seen in overweighed women and they are at high risk for reproductive health. In obese women, gonadotropin secretion is affected because of the increased peripheral aromatization of androgens to estrogens. When neuro-regulation of HPG axis declines abnormal ovulatory activities can be seen [48], which is generally because of decreased sex hormone-binding globulin (SHBG), growth hormone (GH), and insulin-like growth factor binding proteins (IGFBP) leading to elevated leptin levels [49].

3.5 Tobacco consumption and smoking

Chewing tobacco and smoking are the injurious addictions [50], which contains >30 mutagenic substances, numerous toxic chemicals along with nicotine and familiar carcinogens [51], have been reported for adversely affecting semen quality and eventually male infertility [52]. The cytotoxic effect of tobacco chewing and/or smoking decreases sperm count, motility, viability and morphological mutations along with damaging testes, accessory glands/ducts leading to low semen volume, seminal leukocytes, abnormal hormonal levels, impaired spermatogenesis, sperm DNA damage, oxidative stress, cytogenetic abnormalities, spontaneous abortions, and congenital anomalies [53]. For women, smoking cigarettes can lead to reproductive

damage, reduced fertility, and difficulty conceiving. Research shows smoking may affect hormone production, making it difficult to become pregnant [54]. Several studies have indicated the adverse effects of maternal smoking during pregnancy on abnormal fetus development, newborn deaths, and problems associated with pregnancy resulting in premature conception.

3.6 Alcohol ingestion

Chronic and excessive alcohol consumption hamper the normal functioning of the HPG axis, resulting abnormal secretion of gonadotropin-releasing hormone (GnRH), FSH, LH, and testosterone that alters LCs and sertoli cell functions, and impairs spermatogenesis [55]. Furthermore, prolonged alcohol addiction causes testicular damage and shrinkage [56], abridged semen quality [57], lower semen volume [58], partial or complete spermatogenic seizure [59], and delayed seminal fluid liquefaction [60]. Eventually, decline in sex hormone levels causes loss of secondary sexual distinctiveness, Sertoli cell-only syndrome, impotence, diminished libido [61], erectile dysfunction, and ejaculation problems [62]. Heavy alcohol use may diminish ovarian reserve and fecundability in women. Detrimental effects of mild to moderate alcohol consumption may interfere with normal menstrual cycle, disturb puberty, damage reproductive capacity, and cause hormonal abnormality amongst women [63]. As alcohol easily pass through placenta, accumulates in amniotic fluid leading to decreased fetal metabolic enzyme activity [64].

3.7 Drugs

Drugs of abuse and chronic medication may have adverse effect on the fertility potential of men by disturbing HPG axis, gonadotoxic activity, or by upsetting sexual performances (ejaculation, erection, and libido) [65]. Prolonged treatment with immunosuppressive drugs (sirolimus and ciclosporine), corticosteroids, immunomodulators (mAbs and TNFα inhibitors), thyrosine kinases inhibitors, opiates (morphine and cocaine), hormonal agents (anabolic steroids and testosterone), antiandrogenic drugs (cyproterone acetate and flutamide), antibiotics (erythromycine and tetracyclines), antimicrobial drugs (metronidazole and chloroquine), antidepressant (imipramine and buspirone), antipsychotic (phenothiazines and butyrophenones), etc., will present a drastic drop in sperm count, motility and morphology [66], inhibition or low level of testosterone [67], hindering acrosomal reaction and shrinking fertility potential of spermatozoa [68], toxic effect on gonads [69], drop in testicular size, weight and volume, inhibiting dopamine synthesis [70] thereby causing erectile dysfunction [71], decreased libido [72], sedation [73] and delayed ejaculation [74], anejaculation/retrograde ejaculation [75] which will result in impotency or male infertility (**Tables 8** and **9**) [65].

3.8 Testicular hyperthermia

The normal spermatogenesis in humans and most mammals require testicular temperature 2–4°C below body temperature [77]. The rise in the scrotal temperature and its duration upsets semen quality resulting spermatogenesis seizure [78], producing more morphologically abnormal sperm, reduced sperm movement [79], destruction of mitochondria and DNA [80], declined sperm concentration [81], and death of germ cells [82], sooner or later into male infertility. The relentless exposure to several external factors such as stance/posture, outfit/clothing, lifestyle, and seasons may negotiate the ability of the scrotum to thermo-regulate leading to adverse effects on male fertility [83]. Apart from these factors, occupational exposure to

Medication	Effect on reproductive function
Anabolic steroids	Impairment of spermatogenesis (up to 1 year recovery); may cause hypogonadism through pituitary-gonadal axis
	Reversible
Antiandrogens	Impairment of spermatogenesis; erectile dysfunction
Cyproterone acetate, danazol, finasteride, ketoconazole, and spironolactone	Reversible
Antibiotics	Impairment of spermatogenesis
Ampicillin, cephalotin, cotrimoxazole, gentamycin, neomycin, nitrofurantoin, Penicillin G, and spiramycin	Reversible
Antibiotics	Impairment of sperm motility
Cotrimoxazole, dicloxacillin, erythromycin, lincomycin, neomycin, nitrofurantoin, quinolones, tetracycline, and tylosin	Reversible
Antiepiletics	Impairment of sperm motility
Phenytoin	Reversible
Antihypertensives	Fertilization failure
Antipsychotics	Impairment of spermatogenesis and sperm motility
Butyrophenones	Reversible
H2 blockers: cimetidine, ranitidine	Increase prolactin concentrations that can lead to impairment of luteal function, loss of libido, and erectile dysfunction

Table 8.
Medications and their respective effects on both male and female reproductive function [76].

Chemical	Possible reproductive effects
BPA	Inhibits binding to androgen receptor, decreased semen quality, erectile dysfunction, chromosomal abnormalities in oocyte, and recurrent miscarriage
Disinfection by-products	
Organochemicals and pesticides e.g., DDT, DDE, methoxyclor	Change in hormone levels, irregular menstruation, decreased fertility, decreased semen quality, chromosomal abnormalities in sperm, altered histology of testes, decreased libido, fetal loss, and miscarriage
Dioxins	Changes in hormone levels, altered puberty, altered start of menarche, endometriosis, decreased fertility, and fetal loss
Phthalates	Decreased semen quality, oligozoospermia, earlier menarche, altered menstrual cycle, and infertility
Solvents	Change in hormone levels, decreased semen quality, irregular menstruation, decreased fertility, miscarriage, and fetal loss

Table 9.
Chemicals and their respective effects on both male and female reproductive function [76].

extreme temperature, for example, workers at welding factories, ceramics companies, furnace workers, mechanics, and drivers are the chief victims of this risk factor facing fertility problems [47].

4. Conclusion

The male or female reproductive structure or function disturbed by any factors leading to the delivery of abnormal offspring, which has interfered with the continuation of generation is basically a reproductive or developmental toxicity. Presently, several reproductive or developmental toxicants are under routine by the people without their awareness, which obviously have negative impact on their health. In most of the working environments, due to the lack of knowledge and information many workers are occupationally exposed to such hazards and they are at the edge of reproductive toxicity. To understand the pathway of this toxicity needs a deeper research but due complexity of the mammalian reproductive cycle *in vitro* studies are quite lagging but one can slice this series of cycle and work on it independently. Currently, advancement in the field of reproductive toxicity testing has come-up with useful and promising *in vitro* models but their potential and accuracy are yet to be finalize. Though, individual tests are helping to identify certain aspects of toxicity but study can be only completed with combination of detailed toxicology reports.

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