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Review Article

ADVERSE EFFECT OF REPROTOXIC SUBSTANCES ON HUMAN HEALTH

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ABSTRACT

The arenas of reproductive and developmental toxicology are multifaceted areas of significant importance and intense study, for the human population, as well as for animal species. Due to impact from various toxicants, from pharmaceuticals to environmental contaminants increases risks of adverse effects to Reproductive systems and developing embryos and foetuses. There is lots of information found in relation with environmental toxicants and their effects on reproductive system of male and female as well as on foetus. There is need of scientific Research about effects of toxicants on the process of reproduction and on developing foetus through molecular, physiological and anatomical studies including reversibility of their impacts. Also, studying fewer common exposures like new types of chemicals, occupational factors and exposure by inhalation. People may encounter substances that have harmful impact on reproductive health as well as developing embryo and foetus through water, air, soil, dust, food, or consumer products. The ultimate aim of all scientific toxicological research is to utilize unfailing and predictive toxicity testing to prevent exposure to potentially harmful toxicants on reproducing animals, humans as well as developing individuals. Also, study of role of the placenta in developmental toxicity of chemicals is essential.

INTRODUCTION

Entire aspects of reproduction are inside the scope of Reproductive Toxicology, which includes the development and maturation of adult i.e., male and female gametes, sexual function, the measures adjacent to the fusion of gametes and the development and maturation of the fertilized ovum, nourishment and transportation of the conceptus within the genital tract, implantation, embryogenesis, intrauterine growth, placentation and placental function, parturition, lactation and neonatal survival. Adverse reproductive impacts on both the males and females will be considered significant.

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To make available all scientific information related to this topic, there is a need of equal emphasis to the clinical, animal as well as in vitro research. Typical endpoints that will be studied by contributors include infertility, sexual dysfunction, spontaneous abortion, malformations, abnormal histogenesis, stillbirth, intrauterine growth retardation, prematurity, behavioural abnormalities, and perinatal mortality [1].

The last few decades show that due to chemical exposures, there is the impact on course of pregnancy, foetal development, alters the functioning of the offspring's organ systems the developmental trajectories of the foetus, so health issues later in life. Here the recognition of the potential for epigenetic moderation by chemicals opens up for a deeper understanding of the developmental origin of health and disease [2]. In today's era, primary infertility is major problem and the environment may play important role in this case too [3,4]. Nowadays, the reproductive systems of male and female have more occupational and environmental exposures, but we are

unaware about its consequences on fertility and foetal development.

Chemicals are universal substances having both positive as well as negative effects found across worldwide workplaces. If combined with other agents like radiation and bacteria, these chemicals may adversely effects on the reproductive systems of males and female. Numerous environmental toxicants are supposed to be responsible for adverse health effects on the reproductive system in various organisms. Contact to these toxicants before and after the conception period can affect parents, foetuses as well as their offspring. There are mainly three most common occupational factors in pregnant women tend to be concerned are tobacco smoke, video-display terminals and the quality of indoor air. Additionally, biological stressors like shift work may also harmfully impact on workers reproductive systems. In spite of the controversies and uncertainties about reprotoxic substances and the lack of data concerning about other possible occupational health hazards, the significances of toxic exposure are essential issues that have to be deftly raised by occupational health and safety counsellors in their discussions with pregnant working women [5].

The number of existing toxicants is huge. Establishment of toxicological database for each chemical's hazard and risk assessment poses one of the greatest challenges to this field. So, there is need to establish methods which enable hazard forecast based on deficient or even no testing in biological systems. To endure the development of the field of reproductive and developmental toxicology, this research section inspires interdisciplinary research between disciplines, ranging from material and chemical science, exposure assessment, epidemiology, in vitro and experimental animal science, basic and molecular biology, in silico modelling, and risk assessment.

In spite of very few information regarding possible reproductive health effects, various potentially toxicants are still used in a many of workplaces, and various workers are exposed to such risks every day at work places. Certain toxic substance-workplace circumstances, some workers may develop sexual or reproductive complications later in life. However, there is need for regulations regarding protective equipment's for workers which are handling these toxic chemicals. Therefore, collecting more information regarding the reprotoxic impacts of chemicals in human health and safety endures to be a prosperous area of research. So, this review article summarizes significant current and pending developments in the field of every possible reprotoxic chemicals used in day-today as well as workplaces and reports some of the significant health implications regarding reproductive system.

AIM: To study the various toxicants and their impact on reproductive system.

OBJECTIVES

1. To study the concept of reproductive toxicity.
2. To study commonly found reprotoxic substances.
3. To study effect of reprotoxic substances.
4. To study preventive measures.

METHODOLOGY

Reproductive Toxicity

Reproductive toxicology is a hazard accompanying with some chemical or environmental toxicants that they will affect in some way with normal reproduction. Such toxicants are called as reprotoxic. It includes impacts on sexual function and fertility in adults as well as developmental toxicity in the offspring. It also defined as adverse effect of hazardous substances on sexual function, fertility in adults as well as developmental toxicity in the offspring[6]. Developmental toxicity means adverse effects on the developing embryo or foetus. It developed by chemicals by two ways i.e., one can act directly on cells of the foetus leads to cell death or damage leading to abnormal development of organs and another way is chemical may induce mutation in a parent's germ cells and transmitted to the fertilized ovum. Furthermore, complication is mutated fertilized ova may develop into abnormal embryos. There are three types of developmental toxicity are as follows [7]:

Table 1: Types of developmental toxicity

S.N.	Types	Effects
1.	Embryo lethality	Failure to conceive, spontaneous abortion, stillbirth
2.	Embryotoxicity	Growth retardation or delayed growth of specific organ system
3.	Teratogenicity	Irreversible conditions that leave permanent birth defects in live off spring

Many chemical substances can impact on the human reproductive system. Their adverse effect can be hormonal contraception, minor unwanted side effect like antidepressants and major public health problem. Although, most of the studies of reprotoxic substances focused on occupational and environmental chemical hazards.

Occupational disorders due to toxicants affect all system organs which includes pulmonary disorders, musculoskeletal injuries, malignancy, traumatic injuries, occupationally induced cardiovascular disease, reproductive illnesses, neurotoxic disorders, noise-induced hearing loss, dermatological manifestations, and psychological illness. Most of these

disorders are clinically indistinguishable from non-occupational diseases in terms of etio-pathogenesis. In these cases, diagnosis is very difficult due to long latency period between occupational exposure to a toxicant and the onset of disease. A proper history taking of occupational exposure to a toxicant is the main tool for a diagnosis of work-related disease. There is need of proper and accurate diagnosis of disease for proper management of affected patient which provides a basis for recognition of similarly exposed workers who may at risk of toxic exposure [8].

Female Reproductive Toxicants

Industrial chemical Exposures can affect the reproductive functions in women as well as male adult. Toxicants that target the ovary lead to significant effect on fertility, menstrual cycle, timing of puberty and menopause. The effect of occupational and environmental exposure on the female reproductive system is less known than that for the male reproductive system, due to germ-cell production in a female is difficult to monitor and amenorrhea or irregular menstruation frequently occur enough. Also, it is quite difficult to determine whether the cause is due to maternal embryonic deficiencies or abnormalities, or to an external chemical exposure in the environment [9]. The pregnant woman may transfer these toxicants, together with active metabolites to the foetus by various mechanisms which impact the development of foetus. Reproductive toxicants may also disrupt not only the transport of male and female germ cells to the site of fertilization in the fallopian tube, but also the conveyance of the zygote to the implantation position and growth in the uterus. Hormonal balance during the time of pregnancy may hamper due to these toxicants leads to adverse effects on the foetus. So, lots of targets exist for industrial toxic substance to disrupt female reproduction and development of the foetus suggesting the need for additional scientific research to help moderate risks to working women. Developing children may be exposed directly to industrial or environmental chemicals through the contamination of air, water, foodstuffs, soil, contaminated clothing etc. Impact on foetus development may also induced due to inheritance of genetic damage of the germ cells of one or both parents. The developmental toxicity may lead to embryo/foetal death, birth defects or congenital anomalies, growth retardation along with developmental delay. It also includes preterm delivery, altered sex ratio, and cancer in early childhood [10]. The induction of adverse structural changes during development is called as teratology and substance that induce such adverse effects are known as teratogens. Exposure to reprotoxic or teratogenic substances during period of conception to delivery and breastfeeding is uncertain and it is the greater threat to healthy human reproduction [11,12].

Male Reproductive Toxicants

Exposure from industrial chemicals targets the human testis resulting toxicant-induced testicular injury. It is due to the high rates of proliferation, differentiation and metabolic activity along with the production of large quantities of mature sperm. There are three main target cells in the testis such as the Leydig, Sertoli, and germ cells for toxic chemicals to disrupt spermatogenesis. Many of them target various cell types, leading germ-cell apoptosis and spermatogenic failure [13].

The common reproductive toxicants and their impact on reproductive system are as follows [14,15,16]:

Schedule 1: Sufficient human evidence

S.N.	Chemicals	Effects on reproductive system
1.	Aniline	Female infertility, spontaneous abortion, growth retardation, developmental disorders
2.	Bulsulfan	Male and female infertility, spontaneous abortion, birth defects, and growth retardation
3.	chemotherapeutic drugs (e.g., methotrexate, cyclophosphamide)	Male and female infertility, spontaneous abortion, birth defects, growth retardation, some contaminate breast milk
4.	Carbon disulphide	Reduced male sex drive, male and female infertility, spontaneous abortion, growth retardation, menstrual disorders, breast milk contamination
5.	Carbon monoxide	Female infertility, spontaneous abortion, growth retardation, functional deficit
6.	Chlorambucil	Male and female infertility, birth defects, developmental disorders
7.	Dibromochloropropane (DBCP)	Male infertility, genetic defects, altered sex ratios
8.	Diethylstilbestrol (DES)	Male infertility, functional deficit, childhood cancer
9.	Dinitrotoluene (DNT)	Spontaneous abortion, male infertility, growth retardation,

		developmental disorders
10.	Ethyl alcohol	Male infertility, developmental disorders, birth defects, low birth weight or premature births
11.	Lead	Male and female infertility, spontaneous abortion, growth retardation, functional deficit, breast milk contamination
12.	Mercury (organic such as methyl mercury)	Male infertility, birth defects, growth retardation, functional deficit, breast milk contamination
13.	Methylene chloride	Low birth weight, spontaneous abortion, developmental disorders, breast milk contamination
14.	Phenol (carbolic acid)	Altered sex ratio, spontaneous abortions, impotence
15.	Polychlorinated biphenyls (PCBs)	Male and female infertility, spontaneous abortion, growth retardation, breast milk contamination
16.	Warfarin	Birth defects, developmental disorders, spontaneous abortions
17.	Toluene (methyl benzene)	Low birth weight, developmental disorders, birth defects, menstrual disorders, male and female infertility
18.	Organic solvents in general	Female: reduced fertility, menstrual disorders, foetal death, birth defects, preterm birth, neuro-behavioural effects, childhood leukaemia. Male: delayed conception, reduced semen quality, foetal death and birth defects.

S.N.	Biohazardous Material	Reported adverse effect
1.	Cytomegalovirus	Spontaneous abortion, birth defects, growth retardation, developmental disorders, breast milk contamination
2.	Hepatitis B virus	Growth retardation, liver disease in infected offspring, breast milk contamination
3.	HIV	Functional deficit, childhood cancer
4.	Parvovirus B19, Human	Adverse pregnancy outcomes
5.	Rubella virus (German measles)	Birth defects, growth retardation, developmental disorders
6.	Toxoplasmosis	Spontaneous abortion, birth defects, developmental disorders
7.	Varicella-zoster virus (chicken pox and shingles)	Birth defects, growth retardation

S.N.	Physical hazard	Reported adverse effect
1.	Excessive heat	Male infertility
2.	Heavy physical exertion (e.g., repetitive heavy lifting, stooping and/ or climbing)	Spontaneous abortion, growth retardation
3.	Ionizing radiation	Male and female infertility, spontaneous abortion, birth defects, growth retardation, developmental disorders, childhood cancer

Schedule 2: Sufficient animal evidence/ limited human evidence

S.N.	Chemicals	Adverse effect
1.	Acetaldehyde (with alcohol consumption)	Growth retardation, developmental disorders
2.	Acetone	Female infertility, birth defects, menstrual disorders
3.	Acrylonitrile	Male infertility, birth defects, reduced male sex drive
4.	Aluminium	Birth defects
5.	Ammonia	Premature birth
6.	Anaesthetic agents (e.g., nitrous oxide, halothane)	Male infertility, spontaneous abortion, birth defects, growth retardation, breast milk contamination
7.	Antimony	Spontaneous abortion, breast milk contamination
8.	Antimony potassium tartrate	Premature birth, miscarriages, female infertility

9.	Arsenic	Birth defects, spontaneous abortion
10.	Benzene	Female infertility, spontaneous abortion, birth defects, growth retardation, menstrual disorders
11.	Boric acid, borates	Reduced male sex drive, male infertility, female infertility
12.	Bromine	Male infertility, decreased libido, impotence, breast milk contamination
13.	1,3 Butadiene	Male and female infertility, birth defects, growth retardation
14.	Cadmium	Male and female infertility, birth defects, growth retardation, developmental disorders, breast milk contamination
15.	Carbamide (urea)	Spontaneous abortion
16.	Carbaryl	Male and female infertility, genetic defects
17.	Carbon tetrachloride	Male and female infertility
18.	Chemical	Reported Adverse Effects (continued)
19.	Chloroform	Spontaneous abortion, birth defects
20.	Copper	Spontaneous abortion, birth defects
21.	Dimethoate	Birth defects, spontaneous abortion, male infertility
22.	Dimethylformamide, N, N (DMF)	Spontaneous abortion, stillbirths, birth defects, female infertility
23.	Dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin)	Male and female infertility, spontaneous abortion, birth defects, breast milk contamination
24.	Epichlorohydrin	Male infertility
25.	Ethylene dibromide (EDB)	Male infertility, birth defects
26.	Ethylene glycol monoethyl ether (EGEE)	Birth defects, female and male infertility, menstrual disorders
27.	Ethylene glycol monomethyl ether (EGME)	Male infertility, birth defects, developmental disorders
28.	Ethylene oxide	Male and female infertility, spontaneous abortion, birth defects, growth retardation
29.	Ethylene thiourea	Birth defects
30.	Formaldehyde	Female infertility, spontaneous abortion
31.	Gasoline	Female infertility, birth defects, menstrual disorders
32.	Glycidyl ethers (e.g., allyl glycidyl ether, phenyl glycidyl ether)	Male infertility
33.	Lithium	Birth defects and male infertility among patients taking lithium
34.	Manganese	Reduced male sex drive, male infertility, breast milk contamination
35.	Mercury (inorganic salts and metallic Hg)	Reduced male sex drive, male and female infertility, spontaneous abortion, birth defects, growth retardation, breast milk contamination
36.	Nitrous Oxide	Male and female infertility, spontaneous abortion, developmental defects
37.	Chemical	Reported Adverse Effects (continued)
38.	Oral contraceptives	Reduced male sex drive, female infertility, birth defects
39.	Paints	Spontaneous abortion, developmental disorders
40.	Polyvinyl chloride (PVC resin)	Female infertility, spontaneous abortion, stillbirths
41.	Selenium	Spontaneous abortion, birth defects, female infertility, menstrual disorders, breast milk contamination

42.	Solvents	Birth defects, developmental disorders, spontaneous abortion, impotence, female infertility, menstrual disorders, breast milk contamination
43.	Sulfur dioxide	Spontaneous abortions, female infertility, low fetal weights, birth defects
44.	Styrene (vinyl benzene)	Male and female infertility, spontaneous abortion, breast milk contamination
45.	2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)	Spontaneous abortion, birth defects, male infertility, menstrual disorders, breast milk contamination
46.	Tetrachloroethylene (perchloroethylene)	Female infertility, spontaneous abortion, developmental disorders, birth defects, menstrual disorders, breast milk contamination
47.	Trichloroethylene	Male and female infertility, spontaneous abortion, birth defects
48.	Trinitrotoluene	Male infertility
49.	Vinyl chloride monomer	Reduced male sex drive, spontaneous abortion, birth defects, childhood cancer
50.	Xylene	Female infertility, birth defects, menstrual disorders, breast milk contamination

S.N.	Physical hazard	Adverse effect
1.	Low atmospheric pressure (hypobaric)	Male infertility, growth retardation
2.	High atmospheric pressure (hyperbaric)	Male infertility, birth defects

Schedule 3: Suspect/ insufficient evidence

S.N.	Chemicals	Adverse effect
1.	Acrylamide	Male and female infertility, birth defects, developmental disorders
2.	Carbon dioxide	Birth defects, male infertility
3.	Carbon tetrachloride	Male and female infertility, developmental disorders, birth defects
4.	Chromium	Birth defects, infertility
5.	Di (2-ethylhexyl) phthalate (DEHP)	Birth defects, male infertility, developmental disorders
6.	Dimethyl phthalate	Birth defects, developmental disorders
7.	Dimethyl sulfoxide (DMSO)	Developmental disorders
8.	Epichlorohydrin	Male infertility
9.	Ethylene thiourea	Birth defects
10.	Halothane	Developmental disorders, birth defects
11.	Methyl alcohol	Developmental disorders
12.	Methyl ethyl ketone (MEK)	Developmental disorders
13.	Methyl formamide, N	Birth defects
14.	Methyl pyrrolidone	Birth defects
15.	Nickel	Birth defects
16.	Polybrominated biphenyls (PBBs)	Birth defects, developmental disorders
17.	Ribavirin (virazole)	Birth defects, spontaneous abortion
18.	Toxaphene (Camphechlor)	Developmental disorders, infertility, breast milk contamination
19.	1,1,1-Trichloroethane	Low foetal weight, birth defects, developmental disorders

S.N.	Physical hazard	Adverse effect
1.	Noise	Female infertility, spontaneous abortion, birth defects, growth retardation, developmental disorders
2.	Radiofrequency and microwave radiation (non-ionizing)	Male and female infertility, birth defects
3.	Video display terminals (VDT)	Spontaneous abortion, birth defects

Substituting workplace genotoxins with moderately benign chemicals or establishing and executing a comprehensive policy for safe handling of these chemicals denotes effective prevention measures. There are lots of methods of prevention which includes ventilation, modification in work practices, and usage of personal protective equipment.

Some of industries have supposed exclusionary policies whereby fertile women are rejected work where there are recognized or suspected reproductive health hazards. Guidelines that allow industrial workers to transfer to a different job during pregnancy or planning a child are viable alternative options. There is a need of individual responsibility of pregnant or fertile working woman that she should never join a job where she or her unborn child is likely to be exposed to occupational toxicants due to no other work is available to her [17]. The early diagnosis of occupational disease through occupational history could expose community-wide/industry-wide reproductive health diseases caused due to genotoxins and enable the introduction of appropriate preventive measures [18].

Preventing Measures

It is the duty of employer to protect the reproductive health workers from hazardous chemicals. If there is risk to pregnant women or her infant through breast feeding, employers should take the necessary actions to prevent exposure to the no risk level [19]. Similarly, in the male workers, there should be taken special attention on those chemicals which affects the male fertility. Prevention from exposure of hazardous substances of workers can be done in various ways. These are as follows:

1. Eradicating or replacing repro-toxicants for safe substitutes
2. By using simple control measures infection risk can be minimised which includes good basic hygiene, preventing incise or cut wounds by avoiding sharp cutting objects, etc.
3. Improving the workplace environment by using collective protective procedures. Like, the enclosure of the releasing process, general ventilation, local exhaust ventilation, changing work tasks and habits into safe procedures
4. Routine usage of personal protective equipment
   a. Laboratory coats: must be worn and these coats should not be used outside the workplaces. If these cloths are contaminated, removed immediately and disposed of separately.
   b. Hand-gloves: Gloves suitable for work with resistance to repro-toxins must be worn. Disposable gloves must be discarded appropriately soon after every use and non-disposable gloves must be decontaminated or washed after every single use.
   c. Suitable eyewear must be used for protection of eyes through contamination.
5. Maintenance of personal hygiene: hands should be washed with soap water followed by sanitisation after every exposure to chemicals, soon after completing any procedure at workplace and before leaving the laboratory.
6. Shifting the pregnant worker to another safer job
7. Granting maternity leave to the pregnant worker in accordance with national legislation
8. Employers must appoint a supervisor who is duty bound to inform all employees or students regarding chemicals they are working with and their hazardous effects on human reproduction.
9. Appropriate information regarding exposures, instructions for avoiding or preventing from these toxicants, training and risk management should be provided to workers.
10. Work places & laboratory containing reproductive toxins must be labelled with warning signs.
    Provide contact number and address for emergency [20-25]
11. Handling and storage procedures:
    a. Surfaces must be smooth or nonporous covered with stainless steel trays and decontaminated after every procedure.
    b. Containment equipment's are used for volatile human repro-toxins
    c. Vacuum lines are used to prevent entry of exposure in system
    d. Equipment's and contaminated material are decontaminated daily after completing the procedure. If not decontaminated, room must be labelled with DO NOT ENTER sign.
    e. Containers containing reproductive toxins must be labelled with chemical name along with warning indicating hazardous repro-toxins.

5. Maintain waste disposal with waste minimisation & when possible deactivated waste converted into non-toxic material [26,27].

DISCUSSION

Humans as well as animals are exposed to reprotoxic substances in various ways such as through broken skin, natural orifices, breathing and also from breast feeding as some toxicants are stored in fats & breast milk is rich in fat. These toxicants can impair reproductive capabilities of both male & female along with some teratogenic effects on offspring. The highest susceptibility to reprotoxic substances in women is usually during first trimester of pregnancy, as during this period, a woman may not aware about her pregnancy. The nature and sternness of these adverse effects depend on quantity, duration and route of exposure to hazardous substances. Reproductive & developmental toxicants which are fall into schedule 1 must be labelled as DANGER substances. By adapting all preventing measures and providing guidelines regarding handling and disposal of reprotoxic & developmental toxicants we can aware the workers. So, utilization of new technologies along with global regulation and guidelines for reproductive health workers can improve human health and minimises adverse effects from reproductive and developmental toxicants [28,29].

CONCLUSION

Various chemical, physical or biological components are responsible for reproductive & developmental toxicity. These chemicals act on developmental toxicity directly on embryo leading to congenital defects in offspring. Also, they induce mutation in parent's germ cells which are then transmitted to fertilized ovum. As, there are many hazardous effects on female as well as male reproductive system, there is a need of national awareness programs related different reprotoxic substances, their impact on health, preventive measures regarding handling, storage and waste management of these repro-toxicants. Also, laboratory safety programs along with personal hygiene and first aid management must be arranged by organisation.

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