Heavy Metals and their Effect on Mammalian Fertility

Jahanvi D.

School of Science, Navrachana University, Vasna Bhayli Road, Vadodara – 391410, Gujarat, India

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Corresponding Author: jahanvidesai23@gmail.com

Abstract

Heavy metals such as Lead, Mercury, Nickel, Chromium, Copper etc. are naturally occurring metals found in Earth's crust with high densities and are one of major pollutants. These metals are essential for all living organism in lesser quantities, exceeding its level may lead to toxicity. Some of the heavy metals are. These metals are released into environment either by industrial waste, agriculture runoff or fossil fuels combustion. These metals affect all the major organs in body causing toxicity. The range of toxicity depends upon factors such as dose, chemical species and route of exposure. These metals also lead to chronic reproductive toxicity causing impairments in gametogenesis by lowering the number of sperms or hampering the maturation of oocyte or egg, steroidogenesis by altering the levels of testosterone and estrogen and altering the reproductive tract functions by accumulating in the tissues and destroying the structure of tract. Prolonged exposure of these metals leads to infertility or subfertility. This paper summarizes the effect of heavy metals - (Nickel, Cadmium, Lead and Mercury) on the reproductive organs studied on mammalian model organisms.

Keywords

Heavy metals, Reproductive toxicity, infertility, subfertility.

Introduction

Environmental contaminants are chemicals, biological or radioactive waste which are released into environment and causes pollution. These contaminants are toxic to any living organism including humans. The most common sources of these contaminants are

combustion of fossil fuels, mining and mineral processing industries, households, forestry and agriculture and industrial production which lead to the release of heavy metals, volatile organic compounds, greenhouse gases, organochlorides etc[1].

Heavy metals are naturally occurring metals having high densities and are one of the major causes of environmental contaminant. The use of heavy metals has been increased with time and they are commonly used in industries, mining, smelting and thermal power plants. The most frequently found heavy metals at national and international levels are arsenic, cadmium, chromium, copper, lead, nickel and zinc[2]. These metals have a crucial role in biological functions of body as they play an important role in oxidation – reduction reaction and also are an important constituent for various enzymes[3]. The exposure of these metals can be either by inhalation, food chain or skin contact. The exposure of these metals affects the cellular organelles and its components such as mitochondria, cell membrane, nuclei, lyzosomes and endoplasmic reticulum. These metals also affect the enzymes which are involved in normal metabolism, damage repair and detoxification[4]. The metal ions interact with DNA and nuclear protein initiating DNA damage and conformational changes in the proteins which lead to cell cycle modulation, carcinogenesis or apoptosis. The basic mechanism involved in causing toxicity is the production of Reactive Oxygen Species (ROS). When the heavy metals attack the cells, there is an increase in ROS and the antioxidant enzymes. This increase results in oxidative stress which eventually leads to apoptosis. The heavy metals act on the nervous system causing inhibition of neurotransmitter and neuronal damage and thereby leading to neurotoxicity. Neurotoxicity is when the damage is done to the nervous system which alters the normal activity of system[3.] These metals also inactivate the regulatory molecules such as p53 and other transcription factors leading to carcinogenesis. Carcinogenesis is also caused when these heavy metals directly act on DNA repair mechanism by altering the enzymes structure and damaging the DNA due to generation of free radicals. When the free radicals generated due to these metals acts on the lipid membrane of cell, it leads to cell membrane damage which ultimately damages the cell. The action of free radicals on protein causes either inactivation of enzymes or protein misfolding, aggregation and conformational change in the end leading to loss of cellular function[3].

Reproduction is one of the important fundamental traits of all the living organisms. When any organism is subjected to the heavy metals exposure if often leads to reproductive toxicity. These metals hinder the basic functioning of the system by mimicking the ion, disrupting cell signaling pathways, oxidative stress, altering gene expression, apoptosis, disrupting testis – blood barrier, inflammation and endocrine disruption[5]. The toxicity also leads to infertility and subfertility. The couple is considered infertile when they cannot conceive naturally while subfertility is when there is a delay in conceiving. Infertility has become one of the prime problems in current scenario with an increase in number of population becoming infertile owing to environmental contaminants and current lifestyle[1]. According to World Health Organization (WHO), 1 in every 4 couple is infertile[6]. According to WHO, the common causes of infertility in male are semen ejaculatory problems, abnormal sperm morphology, count and motility while in female, the causes can be due to a range of abnormalities in ovaries, uterus, oviduct and hormone secretion[6].

This paper reviews the toxic effects of Nickel, Mercury, Cadmium and Lead on the mammalian fertility. These metals are the most commonly found heavy metals in the environment causing toxicity.

Heavy Metals and their association with Reproductive Toxicity

1. Nickel - Nickel is one of the essential metals for human body but when its concentration increases it becomes toxic to body. Nickel toxicity is a common in nickel ore smelting workers. It directly binds to DNA causing DNA damage and stimulating reactive oxygen species[7].

Impact on Rats

Nickel increases the level of circulating prolactin when a dose of 10 and 20mg/Kg $NiCl_2$ was given to male rats. Prolactin increases the luteinizing hormone receptors in leydig cells, to secrete testosterone which is vital for spermatogenesis[8]. Adedara et al., reported a decrease in level of FSH and LH in pituitary in adult male wistar rats[9]. Pandey et al. reported a dose dependent decrease in the body to organ weight ratios of testes, seminal vesicles, prostate gland and seminal vesicles[11]. The histology of testes, seminal vesicles and epididymis also changes. The sperm count and motility also decrease. The seminiferous tubules shrink and the number of basal spermatogonia decreases[12]. Pandey and Srivastava observed an increase in sperm abnormalities at higher doses[13].

In female rats, it was observed that with a dose dependent increase; the ovulation was inhibited[10]. During pregnancy, there was a reduction in the number of pups and number of implantation frequency. The fetus if born is either abnormal or still born[7].

Impact on Humans

Nickel accumulates inside the cell resulting in an increase in oxidative stress. This increase in oxidative stress increased the level of lipid peroxidation in both ovaries and testes, damaging the lipid bilayer membrane and other lipid containing molecules[7]. However, in ovaries there is a decrease in level of total ascorbic acid, protein, glutathione and that of superoxide dismutase and catalase. Whereas, in testes, the concentration of protein and lactate dehydrogenase decreases and the level of testicular glycogen and cholesterol increases. Nickel also alters the enzyme activity be decreasing its activity. There is a decrease in the activity of two enzymes involved in steroidogenesis which are 3 β hydroxysteroid dehydrogenase which is involved in conversion of Pregnenolone to Progesterone, Dehydroepiandrosterone to Androstenedione and Androstenediol into Testosterone and 17 β hydroxysteriod dehydrogenase which is involved in conversion of Dehydroepiandrosterone into Androstenediol, Androstenedione into Testosterone and Estrone into Estradiol[14, 15].

2. Mercury – It occurs in elemental, organic and inorganic form. The exposure of human usually takes place either via food chain or through button cells, cosmetic creams, broken thermometers, fluorescent light bulb or dental amalgams[5].

Impact on Rats and other animals

Merlo et al observed that when female wistar rats were treated with $MgCl_2$ there was an irregularity in estrouse cycle and the time period of each phase of cycle was abnormal. There was a reduction in number of ovarian antral follicles and an increase in the lipid deposition and atretic ovarian follicle number[5]. The histopathology of ovaries alters when exposed to mercury vapor. It was observed that there was reduction of the total number of primordial germ cell, primary germ cell and graafian follicles. The mean volume of corpus luteum, graafian follicles and ovaries was found to be reducing. The fetal losses during pre-implantation and early post implantation period were found to be increased in female mice when treated with 7.5 mg methyl mercury chloride[19].

A study done on male hamsters, guinea pigs and mice showed that mercury causes impairment of spermatogenesis, decreases the motility of spermatozoa. Also, degeneration of spermatogenic cells and testicular degeneration along with cellular damage of leydig cells and seminiferous tubules was observed[20, 21].

Impact on Humans

When mercury enters the body, it starts disrupting the protein structure especially tertiary and quaternary by binding to free functional groups present in proteins, catalyzing the amino acid side chain or by displacing the essential metal ions in metalloproteins thereby impairing the cell structure. It accumulates in the ovaries and causes change in the reproductive behavior, leads to ovarian failure and infertility. A review on the effect of mercury on humans reported that high level of mercury can be associated to fertility and subfertility. High levels of mercury were found in hair, blood and urine samples among infertile subjects who had idiopathic infertility. It also increases the incidence of menstrual and hormonal disorders along with adverse reproductive consequences[16, 17].

It is shown to have an inhibitory effect on the release of follicle stimulating hormone and luteinizing hormone from anterior pituitary which can alter the levels of estrogen and progesterone leading to irregular or painful menstruation, premature menopause and ovarian dysfunction[18].

3. Cadmium – Its major use is in nickel – cadmium batteries, alloy bearing, electroplating and is also found ores[5].

Impact on Mice

In female mice, it accumulates in the ovaries and decreases the relative volume of growing follicles along with distorted Graafian follicle and increases the atretic follicle and stroma. In the oviduct, cadmium changes the structure and function by disintegrating capillary wall and inflammation of tissue[23, 24, 25].

When male mice were exposed to cadmium, it induced alteration in sertoli cells, seminiferous tubules; blood test is barrier and spermatozoa loss. This was observed in humans as well. In leydig cells, the development and function is altered along with induction of tumors. The blood test is barrier is damaged due to disruption in vascular system. The epithelium of seminiferous tubules starts degenerating and germ cells mortality takes place when mice are exposed to cadmium orally[26]. The study which focused on the mechanism of cadmium

induced toxicity in male micerevealed dose dependent severity of testes injury. At low doses, the thickness of seminiferous tubule walls decreased, while a medium dose caused the thinning of germinal epithelium, decreased spermatogenesis and bleeding in testicular stroma and a high dose, caused excessive thinning of germinal epithelium, testicular stroma abnormalities and low level of spermatogenesis in seminiferous tubules[26].

An increase in malondialdehyde while a decrease in superoxide dismutase, catalase, glutathione, lactate dehydrogenase and alkaline phosphatase is observed when rats received subcutaneous dose of 3 mg/kg body weight once a week for four weeks[22].

Impact on Humans

A study on women who were occupationally exposed to cadmium showed that the follicle stimulating hormone and luteinizing hormone decreases and an increase in level of malondialdehyde and hydrogen peroxide is observed with decrease in catalase, superoxide dismutase and glutathione peroxidase[27].

4. **Lead –** It is used in paints, lead acid batteries, smelters, printing presses, and coloring agents and in the form of alloy as shielding material[5].

Impact on Mice

When mice were exposed to lead, the accumulation was found in ovaries with dysfunction folliculogenesis, where primordial follicles were decreased but atretic antral follicle was increased[29].

Histomorphology of ovaries was found to be altered. Atresia in all levels of folliculogenesis, edema and necrosis in ovarian follicles. In uterus, inflammatory alteration characterized by narrow uterine lumen, endometrium atrophy, and vacuolar degeneration in endometrial epithelium and damaged and decreased number of endometrial gland[32, 33, 34].

In males, lead reduces decreases the spermatozoa quality by impairing spermatogenesis by affecting the hypothalamic – pituitary – testicular axis thereby suppressing testosterone production. The exposure affects the spermatozoa viability, motility, chemotaxis of sperm – oocyte fusion and DNA fragmentation by increasing the generation of reactive oxygen species[35].

Histomorphology of testes in mice reported disorganization of seminiferous tubules, shrunken and distorted tubules with complete absenteeism of spermatogenesis process, edema, inflamed tunica albuginea and hydrocele[36].

In a dose dependent study on male rats, it was observed that the blood capillaries in the interstitium were dilated, the basal membrane was undulated and the seminiferous tubules had empty spaces and the apoptosis of spermatogenetic cells was increased[37].

A study in male rats found that there was an increase of ROS levels, lysosomal enzyme activity and Malondialdhyde levels (MDA) whereas a decrease in serum LH and testosterone level, testicular 17 β hydroxysteriod dehydrogenase activity, androgen receptor expression, spermatozoa count, viability and motility and catalase and SOD levels[38,39].

Impact on Humans

A study showed that lead exposure leads to hormonal imbalance thereby causing reproductive impairment and accumulation in endocrine gland. The hypothalamic pituitary axis was affected which caused blunt response of thyroid stimulating hormone, growth hormone and luteinizing hormone and follicle stimulating hormone to thyrotropin releasing hormone, growth hormone releasing hormone and gonadotropin releasing hormone[28]. A study on female workers working in lead storage batteries found increase incidence of polymenorrhea, hypermenorrhea, prolonged and abnormal menstruation and spontaneous abortion[13]. With increase in blood lead levels, an increase in serum FSH level was observed in postmenopausal women, premenopausal women and in those where ovaries were removed, suggesting that lead exposure affects ovarian FSH and LH concentration[30, 31].

Current Research Gaps

There are a number of studies which show the effect of metal toxicity on reproductive organs but in all of these studies the major target organs are ovaries and testes, there are very few studies done in order to see the effect of toxicity on accessory organs. The accumulation of these metals in human is through bioaccumulation, so the dose at which these metals would start getting toxic would vary in humans as compared to the one shown in model organism. The dose for human is still unknown yet.

Future perspectives

The studies done this far is majorly on the effect of toxicity on the reproductive outcomes. With increase in use of nanoparticle technology, the toxicity is also increasing and there are limited studies which shows protective role of some vitamins or constituents against the toxicity[40]. Research can be done on drug discovery with natural constituents which can be used against these toxicities to lessen its severity. Studies can also be conducted to assess the genotoxic effect of heavy metals in mammals. Moreover, strategies for the prevention of toxicity should be investigated such as giving protective gears to those who are occupationally exposed to these metals, industrial water should not be discarded into the water bodies in order to avoid accumulation into aquatic organisms and use of such metal salts in agriculture should be avoided.

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