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An Overview of the Impact of Heavy Metal Toxicity on Reproductive Health

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Abstract

Heavy metals have immense industrial significance owing to their multiple applications in domestic, medical, and agricultural sector. However, the reports of their adverse health effects have raised concerns about environmental safety leading to restrictions on their use. Lead, arsenic, chromium, and mercury are among the most toxic heavy metals having serious implications for health. Heavy metals in general are endocrine disruptors which interfere with processes mediated by endogenous hormones of the organism, negatively affecting their endocrine functions. Since reproduction is critically regulated by hormones, there are obvious connections between reproductive health and heavy metal toxicity. Some studies have correlated heavy metal exposure with male infertility. Up-to-date literature links environmental contaminants and human reproductive health worries. Male reproductive function is vulnerable to different environmental and occupational factors, of which only a few have been well identified. These studies have generally confirmed that even moderate- to low-level exposure to lead affects certain reproductive parameters, and that exposure to cadmium affects the prostate function and serum testosterone levels. The masculine reproductive function is vulnerable to several environmental and occupational hazards. Only a few studies have investigated reproductive effects of concomitant exposure to several metals and controlled for potential confounders. Future studies should consider the contribution of combined exposure to various metals and/or other factors that may influence individual susceptibility to reproductive health impairment.

Keywords: Endocrine Disrupting Compounds, Heavy Metal, Reproductive Health, male fertility, Health Effect

Introduction:

Metals have prominently been in use by human beings since very ancient times. So much so that the various phases of human civilizations (e.g., iron age, bronze age etc) have been defined

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in terms of the predominance of metals and the development of technology required for their extraction and refinement. Heavy metals are of special significance because of some recent revelations regarding their pros and cons which have necessitated a revision and rethink on their traditional status. Certain heavy metals such as lead (Pb) and mercury (Hg) have been extensively used in various applications and were considered safe. For instance, lead (Pb) has been the most favoured metal for making pipes in plumbing. Similarly, mercury (Hg) was profusely used in dental fillings, barometric measurements and batteries. One adverse outcome of the industrialization age has been the proliferation of heavy metal pollution in air, water and land. Rising pollution levels, changing life style, and disturbed circadian cycles have jointly led to an alarming increase in health-related disorders (Agarwal et al, 2015). There are phenotypic and genotypic factors which affect the health of an individual. Environment which appears to have a direct bearing on the phenotype has also been shown to alter genotypes through some well established mechanisms in which DNA is altered by some environmental ingredient.

On the basis of their relative toxicity, heavy metals have been graded into nontoxic, low toxic, moderately toxic and highly toxic categories. Such a classification of heavy metals based on their toxicity according to the US geological survey 1133 (1995) is given in table 1. Interestingly, the same heavy metals which are essential as trace elements for normal metabolism, become toxic at higher concentrations. One of the major concerns regarding the toxicity of heavy metals is their non biodegradability which leads to their accumulation. After consumption, heavy metals persist for indefinite time and cannot be biodegraded. Gradual accumulation of these metals over time leads to the formation of their complexes and at higher concentration these complexes may form within the cells and tissues thereby disrupting their

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function. A large number of diseases are attributed to heavy metals exposure which is often occupational.

Table 1: Classification of heavy metals based on toxicity

S. No.	Nontoxic	Low toxic	Moderately toxic	Highly toxic
1.	Aluminum	Tin	Antimony	Uranium
2.	Bismuth	Scandium	Beryllium	Vanadium
3.	Calcium	Barium	Boron	Zinc
4.	Iron	Germanium	Actinium	Zirconium
5.	Magnesium	Gold	Cadmium	Tungsten
6.	Manganese	Erbium	Chromium	Radium
7.	Lithium	Gallium	Hafnium	Ruthenium
8.	Sodium	Holmium	Copper	Thorium
9.	Rubidium	Neodymium	Indium	Thallium
10.	Strontium	Terbium	Lead	Titanium
11.	Potassium	Thulium	Mercury	Silver
12.	Molybdenum	Tin	Nickel	Polonium
13.		Ytterbium	Platinum	
		samarium	Palladium	

Infertility is a rising health hazard among men and women across the globe. The modern definition of infertility was framed by the American Society for Reproductive Medicine according to which it is defined as the failure to get pregnant even after one year or more of regular unprotected (without the use of contraceptives) sexual intercourse. It can be due to an impairment of the capacity of reproduction, individually or with the partner. Globally, 15% of worldwide couples suffer from infertility, which is equivalent to 48.5 million couples. Specifically, male partners are responsible for 20–30% of the overall infertility cases. Further,

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the incidence of male infertility also depends on the geographical region. The increased prevalence of infertility could be due to social factors, changes in seminal quality due to lifestyle habits (alcohol and tobacco consumption) and changes in sexual behavior. The decline of male fertility shows a global trend and is a matter of concern. It is well documented since available studies suggest a lower semen quality over the years. The quality of semen is judged on the basis of sperm count, motility and proportion of abnormal forms (Guzick et al, 2001). Compromised fertility of males involves low sperm count (oligozoospermia), immotile sperms (asthenozoospermia), and the presence of abnormal forms (teratozoospermia). Worldwide data revealed a gradual-P decrease in sperm concentration (−0.64 million/mL per year) from 1973 to 2011. Retrospective evidence and some recently conducted basic studies have shown the dependence of low sperm count and overall sperm quality on poor diet, increased obesity rates and exposure to environmental toxins (Mann et al, 2020; Lindgren, 2018).

Up-to-date literature links environmental contaminants and human reproductive health worries. Male reproductive function is vulnerable to different environmental and occupational factors, of which only a few have been well identified (Kenkel et al, 2001). Different compounds are considered to be the main culprits for male fertility reduction, such as pesticides, dioxins, solvents and heavy metals. At this point, it is important to emphasize that environmental quality has recently decreased mainly due to anthropic activities that increase the level of environmental pollutants (Zareba et al, 2013). Some of these pollutants can act as certain endogenous hormones and are therefore a cause for concern. They are the so-called endocrine disrupting compounds (EDCs) and are considered exogenous substances that are involved in the processes regulated by endogenous hormones of the organism, thus disrupting endocrine functions. This group includes different substances, such as dioxins, bisphenol A and heavy

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metals. Although there is no authoritative definition for the term heavy metals, this group of elements has been considered as "naturally occurring metals having atomic number (Z) greater than 20 and an elemental density greater than 5 g/cm−3". Therefore, a total of 51 different elements can be included in the category of "heavy metals". In most cases, contaminated food is the main source of exposure to these species.

Since the human body has no biochemical pathways to detoxify them, prolonged exposure to heavy metals leads to their accumulation in the body (Sheweita et al, 2005). For this reason, the risks to health and development derived from the exposure to heavy metals have generated a lot of interest among researchers. In particular, the suspected role of heavy metal toxicants on various parameters of male reproductive physiology has been rigorously investigated leading to unravelling of possible mechanisms of heavy metal-induced induced toxicity (Brugo-Olmedo et al, 2003). For example, copper (Cu) and chromium (Cr) were found in the semen samples of a father and his son from the 'Land of Fires' in Italy. This region is known to have high levels of environmental pollution and is exposed to diverse chemicals including heavy metals. In addition to changes in semen quality the results obtained from this research showed alterations in the content of sperm nuclear basic proteins (SNBP) and a low DNA binding affinity (Ramos-Treviño et al, 2018). Besides, the son's proteins showed unstable DNA binding thereby making the DNA susceptible to damage. Such evidence highlights the transgenerational inherited consequences of environmental-pollution exposure on molecular alterations in the sperm cell. Furthermore, men from highly contaminated regions showed higher levels of zinc (Zn), chromium (Cr) and copper (Cu) along with lower iron (Fe) concentrations in semen, lower sperm motility and higher DNA damage than those that had not been exposed to environmental pollutants.

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Methodology

First, generic searches were performed using the "Google scholar" portal. This allowed us to identify important concepts relating human male fertility with heavy metal exposure, but also helped to select the final keywords to use them in a more comprehensive search through some specific scientific databases. The identified keywords which was used for the search were being the keywords "Male Fertility" and "Heavy Metals", "Human Sperm" and "Human Spermatogenesis".

A full search was performed on online databases related to the issue under study to achieve an accurate bibliometric and bibliographic analysis and to be aware of the bibliographic load indexed in each one of the online databases. The selected databases were PubMed and Web of Science (WOS).

Results and Discussion

Diagnosis of the real cause of infertility is a great help in its prognosis. In the modern age when assisted reproductive technologies have revolutionized the management of infertility it is still preferable to prevent the occurrence of this problem which is possible only if we know the leading causes of male infertility. Localized exposure to heavy metals, e.g., due to one's occupation, or to one's lifestyle habits, is the most common type of exposure. Generally, the human population is exposed to heavy metals voluntarily. The voluntary way of exposure to these toxicants can be by oral supplementation. On the contrary, involuntary exposure can be through the intake of contaminated water or food. Nowadays, the environment is a matter of concern because heavy metals are widely distributed (Levine et al, 2017).

Although diet, which includes daily intakes of antioxidants, may be useful to improve the ROS production in semen, it is also a common way to consume heavy metals (Ko et al, 2014).

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Environmental exposure includes the exposure to environmental pollutants, including tobacco smoke. They have the potential to alter the male reproductive system, thus worsening the capacity of conceiving a healthy offspring.

Hazardous occupations in reproductive terms are evaluated based on years of service and agents of exposure. Normally, exposure data and other cause–effect parameters are insufficient to indicate which chemical factor is responsible for reproductive dysfunctions.

The World Health Organization (WHO) estimates that 60 to 80 million couples worldwide currently suffer from infertility. The prevalence varies across regions of the world and is estimated to affect 8 to 12 per cent of couples. Globally, couples usually suffer from primary infertility (inability to conceive within two years). The numerous external causes of infertility include exposure to heavy metals such as Cd, Hg, Pb, Ar, and Cr may be highly involved in impaired human fertility. Tobacco and smoking is the primary source of cadmium (Cd) and lead (Pb) intake, which are observed in serum and semen of infertile smokers (Vigeh et al, 2001). Basal cadmium excretion was significantly higher in the infertile women compared with the pregnant women. A study reported decreased sperm density, low number of sperms per ejaculate, decreased semen volume, and presence of abnormal forms in the presence of high Cd levels. Exposure to cadmium, lead and inorganic arsenic may also contribute to prostate cancer development. Heavy metals are found at higher concentrations in blood or urine. A number of studies reported that total mercury levels >8 μg/L in blood or >8 ng/L in seminal fluid are associated with abnormal sperm count, decreased motility and lowers the semen quality.

Heavy metal exposure has been identified as an influential factor on male sperm production and fertility. However, the mechanisms that alter the reproductive processes are complex. The

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toxicant effects can be directly produced by the action on the reproductive organs, or, indirectly, by impairing the hormonal regulation. Moreover, different biological matrices are used to evaluate male reproductive risks. The biological matrices usually analyzed are blood, serum, semen, seminal plasma, urine, or hair.

Almost all the masculine reproductive tract units are targets of EDCs. Testes are the direct target of a lot of toxicants, such as Cd. Elements such as Cd, mercury (Hg) and Pb produce a dysfunction in Sertoli cells (SCs). Toxicants affecting Leydig cells can cause anomalies in the testosterone secretion, which results in an impaired SCs function and in a defective spermatogenesis.

There is evidence that certain toxicants interact with the secretion of hypothalamic releasing factors, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), all of which play a major role in maintaining sperm quality (Plunk et al, 2020).

Conclusion

These studies have generally confirmed that even moderate- to low-level exposure to lead affects certain reproductive parameters, and that exposure to cadmium affects the prostate function and serum testosterone levels. Adverse effects of mercury, manganese, chromium and arsenic on semen quality and altered serum hormone are less well documented. There is no clear evidence that boron exposure may impair reproductive health in men. Only a few studies have investigated reproductive effects of concomitant exposure to several metals and controlled for potential confounders.

The masculine reproductive function is vulnerable to several environmental and occupational hazards. Those compounds have not been totally identified, but substances such as dioxins, polychlorinated biphenyls, phthalates, polycyclic aromatic hydrocarbons, pesticides,

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alkylphenols, bisphenol A and heavy metals (Hg, Cd, Pb, As, Pb etc.) are some of them. Exposure to heavy metals, which can happen through occupational or environmental exposure is nowadays, a threat to reproductive health.

Human studies are scarce and there is a lack of homogeneity in the methodology. In addition, the nature of the biological matrix (urine, blood, blood plasma, seminal plasma, semen, etc.) shows variable results. However, it should be noticed that the sperm content could be a reliable indicator of the impact of certain toxic substances on the reproductive potential. In this backdrop there is need to undertake further studies on dissecting the precise cellular and molecular mechanisms causing male infertility because of heavy metal exposure.

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