We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Reproductive Toxicity of Arsenic: What We Know and What We Need to Know?

*Hafiz Ishfaq Ahmad, Muhammad Bilal Bin Majeed,
Abdul Jabbar, Ruqia Arif and Gulnaz Afzal*

Abstract

In the most recent the environmental provident and threatening conduct of arsenic has increased the consideration of the world due to its pollution and hazardous effects throughout the world. Arsenic contamination is serious issue throughout the world and is substantial risk factor in most of countries including China, U.S.A, India, Bangladesh, Mexico and Argentina. Several experimental models have been established to understand the diseases caused by arsenic exposure. However reproductive and developmental toxicity have been poorly understood. The objectives of this study are to discuss current landscapes and future horizons of arsenic toxicity in human and animals in relation to various toxicity routes including oral route involving food and water or through inhalation of agricultural pesticides. Addition of current evidence on the development of destiny and actions of arsenic toxicity in human and animal population and other species will lessen the uncertainties in the hazard assessment for arsenic. This effort would help to protect the public health against the toxic and carcinogenic effects associated with arsenic exposure.

Keywords: arsenic, reproduction, toxicity, endocrine, spermatogenesis

1. Introduction

In the most recent the environmental provident and threatening conduct of arsenic has increased the consideration of the world due to its pollution and hazardous effects throughout the world [1, 2]. Arsenic contamination is serious issue throughout the world and is substantial risk factor in most of countries including China, U.S.A, India, Pakistan, Bangladesh, Mexico and Argentina. Human revelation to arsenic is through oral route involving food and water or through inhalation of agricultural pesticides [3–5]. According to World Health Organization fact sheet, arsenic contamination is major public issue requires emergency amendments [6]. As the arsenic contamination of ground water is most serious issue for human health in China, India, Pakistan, inner-Mongolia and Bangladesh [7]. Arsenic is present round the earth in environment and is extremely toxic for life. It is metalloid occurring 20th in earth crust, 14th in sea water and 12th in human body [8]. Toxic effects of arsenic on health is wide spread in both humans and animals [9], as epidemiological substantiation proved that chronic arsenic exposure is associated with increased risk of liver, bladder and skin cancer, cardiovascular diseases, diabetes mellitus

neuropathies, and ocular diseases [10–12]. Arsenic ingestion leads to accumulation in liver, kidney and lungs and small amount in gastrointestinal tract, muscle nervous system and spleen because these organs are rich in oxidative enzymes [13]. The toxic effects of arsenic mostly occur from chronic exposure to humans and animals. Epidemiological studies have revealed that chronic arsenic exposure is associated with elevated risk of liver, lung, kidney, and skin cancer in addition to other ailments such as vascular, diabetic, reproductive and neurologic [14, 15]. On the contrary arsenic has been considered as an effective chemotherapeutic agent in the treatment of human cancer [16]. Various experimental models have been developed to understand the diseases caused by arsenic exposure. However reproductive and developmental toxicity have been poorly understood. Numerous studies documented elevated spontaneous abortion and stillbirth and decreased birth weight by utero arsenic exposure [17]. Arsenic as a risk factor for developing fetus has primarily been studied through murine studies, signifying the reproductive toxicity of arsenic. In animal's studies on arsenic toxicities revealed that arsenic is associated with spermatotoxicity [18] inhibition of testicular steroidogenesis and reduction of weight of testes and accessory organs [19]. In the current review, we try to summarize the existing information on arsenic toxicity from the available literature. We initiate by describing how and when the arsenic contamination took place by considering the course through current literature lens. We present an overview of how human and animals have been affected in the light of colors of various exposure sources by considering the relationship between arsenic toxicity and environment influenced by human activities. Furthermore, we conclude with a preview of future directions and challenges for this field.

Endocrine Disruption.

The gene regulation of mineralocorticoid, glucocorticoids, and androgen and progesterone receptors is disrupted by arsenic [20]. The mechanistic effect of arsenic on these four steroid hormones is studies on glucocorticoids receptors. Arsenic altered receptor of transcription regulation of DNA dependent glucocorticoids, signifying that transcriptional machinery is required for glucocorticoids regulation [21]. Comprehensive mutational investigation of glucocorticoids revealed that only receptor is not the causal target for arsenic effect, as studies that entire C-terminal and N-terminal domains can be removed from glucocorticoids receptors without altered arsenic effects, which indicate the primary mediator of the response of central DNA binding domain. However mutation of almost all the predicted sites of DNA binding domains did not eliminate function and also did not ablate the arsenic effects [21] Abnormalities of male reproductive system such as hypospadias, prostate, testicular cancer and cryptorchidism, may instigate through endocrine disruption [19].

2. Male reproductive effects

Male reproductive system is directly affected by arsenic exposure, as it targets particular reproductive organs and neuroendocrine system and it also disrupt sertoli cells during fetal development. Sertoli cells propagate during prepubertal, fetal, neonatal period and these stages are chiefly susceptible to adverse effects of arsenic (**Figure 1**) [22]. The interruption of spermatogenesis at cell differentiation stage can decline the overall sperm count, and cause sperm DNA damage [23]. Arsenic accumulation in seminal vesicles, prostate and epididymis reduces the progressive sperm motility [24]. Beyond this arsenic also cause hormonal disturbance through affecting endocrine system, disturbing the secretion of androgen from leyding cells, it has significant association between arsenic exposure and

Figure 1.
Reproductive toxicity of arsenic.

sperm motility in arsenic exposed patients [24]. Environmental epidemiological evidences show that in general environmental conditions there is association between arsenic exposure and sperm quality in male [25]. The total arsenic concentration and sperm concentration are strongly correlated in the seminal plasma of heavily exposed human population [26]. The quality of semen of arsenic exposed population is decreased and there was a strong association between sperm percentage of the group exposed by arsenic, as the sperm concentration was lower in arsenic exposed group than non-exposed group [27].

3. Effects on spermatogenesis

The interference in spermatogenesis at cell differentiation stage can reduce the overall sperm count, increased anomalous sperms, and impaired constancy of sperm [28]. As accumulation of arsenic in seminal vesicles, seminal fluid, prostate, and epididymis may impair the sperm progressive motility [29]. In addition arsenic causes hormonal disproportion affecting neuroendocrine system and androgens, as there is strong evidence that oxidative stress vulnerably affect the spermatozoa due to extreme production of reactive oxygen species resulting in the peroxidation of poly unsaturated fatty acids in the plasma membrane [30]. Arsenic increase the reactive oxygen species production and decrease the glutathione, and other anti-oxidant level which lead to lipid per oxidation of cell membrane causing apoptosis

leads to oxidative DNA damage [31, 32]. Damage of sperm membrane reduces sperm motility and ability to fuse with oocyte, whereas the sperm DNA damage compromise parental genomic involvement to the embryo [33] and increase the risk of infertility, and serious disease in offspring [34].

4. Effects on male fertility

In addition to affecting sperm quality, some epidemiological studies documented that arsenic exposure in the environment is increasing the sterility risks in populations which result in decrease androgen hormones level in body, sexual dysfunction and chromosomal aberration (Figure 2) [36]. As level of hormones and arsenic concentration is measured in the blood of infertile males which indicated that the concentration of arsenic and blood luteinizing hormones are strongly negatively correlated. LH can stimulate testosterone production in interstitial cell, the dysfunction or absence of testosterone lead to male infertility [37]. Epidemiological studies revealed that in Taiwan due to drinking of arsenic contaminated water the risk of prostate cancer is 6 times more than other population [38]. In many studies it is documented that risk of arsenic exposure affect genetic integrity in chromosome repeat region and it has certain effect on Y chromosome [38]. A group reported that arsenic exposure may increase erectile dysfunction; the experimental showed that the risk of erectile dysfunction was 3.4 fold higher in arsenic exposed population [39].

Figure 2. Genotoxicity of arsenic adapted from [35].

5. Female reproductive toxicity

Recent data has summarized toxicological effects on female reproductive system in humans and animals implicating impaired fertility effects [40]. Infertility has been predicted as substantial public health hazard and becoming medical challenge round the globe [41], as it ahead of any uncertainty that lifestyle and quality of ambient environment can play fundamental role in reproductive success in both human and animal population [42]. It is demonstrated that exposure to toxic metals such as arsenic, lead and cadmium may be extremely involved in impaired fertility [43]. Arsenic is highly toxic and hazardous for pregnant humans and animals because it can disrupt the neuroendocrine system as it may inhibit estrogen binding receptors and un-regulate the progesterone receptors and it is potential source of estrogen dependent diseases such as breast cancer, endometritis and spontaneous abortions in human population [44]. Elevated endometrial cancer risk is associated with intake of arsenic [45]. Arsenic exposure may also affect angiogenesis in endometrium during pregnancy which is the most important for embryogenesis. These ailments lead to endometrial dysfunction, premature birth, subfertility, sterility and spontaneous abortions [17].

6. Female endocrine disruption

Arsenic is well recognized for its reproductive toxicity, as in case of male reproductive system it is accounted that to hinder activities of spermatogenetic enzymes and impede spermatogenesis [28]. Arsenic may act on brain or pituitary or on germ line cells and affect the female reproductive system such as it reduce ovarian steroidogenesis, prolong diestrus, degenerate ovarian follicles and decrease the plasma level of estradiol and progesterone [46]. Furthermore reduced plasma gonadotrophin level may decline activities of ovarian 3β -HSD (Hydroxysteroid dehydrogenase) and 17β -HSD (Hydroxysteroid dehydrogenase), which are essential regulatory enzymes for steroidogenesis [47]. As it is observed that low plasma level of estradiol may be the cause of diestrus. Furthermore, arsenic exposure in human causes reproductive toxicity, including elevated incidence of miscarriages, still birth and low birth weight in offspring [17]. Similarly, it also effect on viability in the conceptus, dam mortality and weight gain of fetus [48]. Arsenic plays a potential role in disruption of female hormonal function, such as interfering hormone synthesis and hormone normal function. All hormones are differing in their structure and function and have various routes of synthesis with numerous steps. Arsenic exposure through pesticides and other products may disrupt the chain of hormone synthesis such as inhibition of estrogen biosynthesis [49], by preventing the conversion of androgen into estrogen [50]. Methylated arsenic may interfere in dopamine beta hydroxylase activity resulting in reduced conversion of dopamine into nor-epinephrine [19] which may lead to hindrance of hypothalamic catecholamine activity involved in generation of pro-estrus surge in LH, which stimulates ovulation [51]. It also inhibits various other enzymes which are involved in progesterone synthesis [52]. Disruption in LH timing surge could alter the viability and quality of oocytes [51] and inhibition of progesterone secretion may lead to poor conception (**Figure 1**) [48]. The distorted estrogen signaling may cause over expression of estrogen receptors through promoter region hypo-methylation and cause epigenetic change to produce estrogen like effect by direct or indirect stimulation of estrogen receptors.

7. Developmental toxicity

Inorganic arsenic affect the nervous system causing behavioral changes and peripheral neuropathies [53], as chronic exposure of arsenic during pregnancy may affect fetal brain development as a result mutilation of behavioral skills, including cognitive abilities and social competency. It is further conformed that exposure of chronic arsenic increase the risk of spontaneous abortions and stillbirths [54]. Significant association of arsenic exposure was found during pregnancy causing spontaneous abortions and stillbirth [3, 55]. It was reported that the elevated the risk of still birth and neonatal mortality amongst 200 married women in Bengal [55, 56]. All pregnant women were provided proper care in arsenic exposed area, showed significant association between arsenic concentration and birth defects. In the recent study spontaneous abortions and still births were observed between exposed and unexposed women, which included 240, women living in arsenic exposed area in West Bengal of India with high concentrated arsenic drinking water [55, 57] as well as [58] documented the most common arsenic exposed regions in West Bengal, and miscarriage was observed due to arsenic contaminated water. However spontaneous abortions and still births were observed in almost all the arsenic exposed areas throughout the world [55]. Furthermore, a hospital based study was conducted in Texas community with low level of arsenic exposure through inhalation primarily arsenic based agricultural products reported spontaneous abortions and stillbirths [59].

8. Effect on female fertility

According to WHO documentation more than 10% of women are at the risk of infertility through the exposure of heavy metals such as arsenic which are the major environmental contaminant which may cause reproductive disorders [60]. WHO surveyed that the problem of infertility was pre dominantly greater in female than in males. Ovulation disturbances account for common cause of sub fertility in women [61, 62], as ovulation disturbances are present in uneven or lacking menstrual periods and can overcome through reproductive hormones. The risk of infertility increased in women due to hormonal disturbance, delay ovulation, chromosomal aberration in oocytes by higher exposure level of toxicity. Hormonal imbalance is an important cause of infertility in females due to endocrine disruption by arsenic toxicity which is the major cause of infertility in females (**Figure 2**) [40]. It may also cause cycle abnormality, such as decline in estrus cycle number and elevated duration of diestrus [63]. Ovulation issues, endocrine interference with estrogenic properties may inhibit ovulation and the mid cycle LH surge from pituitary gland in females which may lead to female fertility problems [40, 64]. However, most studies revealed that the arsenic exposure through pesticides and insecticides is the major cause of infertility in females, as these decrease the number of mature follicles and elevate the number of atretic follicles and this indicates potential reduction in fertility [65]. Increased exposure to methylated arsenic may lead to decrease in uterus weight which may affect implantation and increase pre-implantation embryonic loss which leads to infertility in females [66]. A recent study revealed that the women exposed to pesticides have longer menstrual cycle and increased probability of missed periods, as studied in USA; infertile women were observed have three times more exposure to pesticides, in which whole chain of gametogenesis is affected [67].

9. Genotoxicity of arsenic

Several studies have documented the elevated inter individual variability in receptiveness of arsenic toxicity underlying genetic factor as a cause of variability. The genotoxicity of arsenic cause deoxyribonucleic acid modification such as chromosomal aberrations, mutation, micronuclei formation, deletion, sister chromatid exchange [68]. Numerous studies have been done to explain the genotoxic effect of arsenic, over and above stimulation of oxidative stress and distorted DNA repair [69]. For the purpose of understanding several studies confirmed the manipulation of genetic polymorphism in gene coding enzymes involved in mechanism of arsenic metabolism and detoxification [70]. It has been demonstrated that arsenic does not affect DNA directly and is considered a poor mutagen, as regardless of its low mutagenicity it affects the mutagenicity of other carcinogens. For illustration, an elevated increase in mutagenicity of arsenic with ultraviolet light has been observed in mammalian cells [71]. Progression of experimentation proposed that arsenic genotoxicity is associated with the generation of reactive oxygen species during its biotransformation [68]. The generation of reactive oxygen species is able to break DNA strands, cross links and chromosomal aberration [72]. One of the mechanisms of arsenic destroys to DNA is base adjustment in particular 8-oxoguanine is one of the most frequently formed DNA nuclease modifications which are a mutagenic miscoding lesion that lead to G: C to T: A transverse [73].

Moreover arsenic can induce DNA strand breaks even at low concentration [70], as single strand breaks are caused by reactive oxygen species on DNA base directly or indirectly during base excision repair mechanism [74]. As it was observed that human fibroblast cells demonstrate single strand break and chromatid substitute interfering with polyadenosinediphosphate ribose polymerase activity which is a protein important for single strand DNA break and double strand DNA break repair process (**Figure 2**) [75]. Recent studies revealed that chronic arsenic exposure induces oxidative DNA damage, reduced thymic functions and subsequent immunosuppression in childhood [76]. Arsenic is well known inducer of chromosomal aberration which involves both clastogenic and a euploidogenic [77]. Recent studies documented cytogenetic monitoring by using chromosomal aberration and micronuclei assay in order to observe genotoxic effects of arsenic in human and animal population [78]. Inhibition of DNA repair is considered one of the most important effects of genotoxicity of arsenic. Nucleotide excision repair and base excision repair are the two process of DNA repair which are inhibited by reactive oxygen species of arsenic [79]. Earlier studies revealed that arsenic exposure may hinder the nucleotide excision repair mechanism of DNA repair but in recent studies it is observed that it also inhibit the base excision repair mechanism (**Figure 2**) [80]. Changes in DNA repair mechanisms have been confirmed in human exposed population, as arsenic exposure was linked with reduced expression of excision repair to at low dose. They have found that arsenic metabolites can affect several processes in the cell [81–83]. Particularly cellular activity of human 8-oxoguanine DNA glycosylase was the most sensitively affected by dimethylmonoarsenic acid [80]. Recently, epidemiological studies revealed that arsenic may affect single nucleotide polymorphism in genes of DNA repair pathways [84]. Arsenic causes DNA damage and changes cellular capacity for DNA repair. Consequently alterations in DNA repair capacity is associated to the presence of polymorphisms in DNA repair genes which are related to risk of developing disturbance induced by arsenic [85].

10. Conclusions

One of the most important revelations is the effect of toxic metals on reproductive system in mammals. In the preceding section we attempted to provide a recent and clear glimpse in all aspects regarding arsenic toxicity on reproduction in mammals. It is the most important concern that should be explored for better understanding and seeking preventive measures to get rid of this striking issue. Arsenic is an important environmental toxicant that affects the reproductive system of mammals. These toxic effects are influenced by variant sources and routes as well as doses and periods of exposure. Integration of novel information on the formation of fate and actions of arsenic toxicity in human and animal population and other species will reduce the uncertainties in the risk assessment for arsenic. This effort would help to protect the public health against the toxic and carcinogenic effects associated with arsenic exposure.

Acknowledgements

Authors are thankful to anonymous reviewers for their valuable comments in critical review of the manuscript.

Author details

Hafiz Ishfaq Ahmad^{1*}, Muhammad Bilal Bin Majeed¹, Abdul Jabbar², Ruqia Arif³ and Gulnaz Afzal⁴

¹ Department of Animal Breeding and Genetics, University of Veterinary and Animal Sciences, Lahore, Punjab, Pakistan

² Department of Clinical Medicine, University of Veterinary and Animal Sciences, Lahore, Punjab, Pakistan

³ Institute of Biochemistry and Biotechnology, University of Veterinary and Animal Sciences Lahore, Punjab, Pakistan

⁴ Department of Zoology, The Islamia University, Bahawalpur, Pakistan

*Address all correspondence to: ishfaq.ahmad@uvas.edu.pk

IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] Rahman M, Sohel N, Yunus FM, Alam N, Nahar Q, Streatfield PK, et al. Arsenic exposure and young adult's mortality risk: A 13-year follow-up study in Matlab, Bangladesh. *Environment international*. 2019;123:358-67.
- [2] Liao N, Seto E, Eskenazi B, Wang M, Li Y, Hua J. A comprehensive review of arsenic exposure and risk from rice and a risk assessment among a cohort of adolescents in Kunming, China. *International journal of environmental research and public health*. 2018;15(10):2191.
- [3] Rahman MM, Bodrud-Doza M, Muhib MI, Hossain KFB, Hossain MS, Akter S, et al. Human Health Risk Assessment of Nitrate and Trace Metals Via Groundwater in Central Bangladesh. 2019.
- [4] Landrigan PJ, Fuller R, Acosta NJ, Adeyi O, Arnold R, Baldé AB, et al. The Lancet Commission on pollution and health. *The Lancet*. 2018;391(10119):462-512.
- [5] Shahid M, Niazi NK, Dumat C, Naidu R, Khalid S, Rahman MM, et al. A meta-analysis of the distribution, sources and health risks of arsenic-contaminated groundwater in Pakistan. *Environmental pollution*. 2018;242:307-19.
- [6] Ahmad SA, Khan MH, Haque M. Arsenic contamination in groundwater in Bangladesh: implications and challenges for healthcare policy. *Risk Management and Healthcare Policy*. 2018;11:251.
- [7] Bhowmick S, Pramanik S, Singh P, Mondal P, Chatterjee D, Nriagu J. Arsenic in groundwater of West Bengal, India: A review of human health risks and assessment of possible intervention options. *Science of the Total Environment*. 2018;612:148-69.
- [8] Khalid S, Shahid M, Bibi I, Sarwar T, Shah A, Niazi N. A review of environmental contamination and health risk assessment of wastewater use for crop irrigation with a focus on low and high-income countries. *International journal of environmental research and public health*. 2018;15(5):895.
- [9] Zubair M, Martyniuk CJ. A review on hemato-biochemical, accumulation and patho-morphological responses of arsenic toxicity in ruminants. *Toxin Reviews*. 2018:1-11.
- [10] Keshavarzi B, Seradj A, Akbari Z, Moore F, Shahraki AR, Pourjafar M. Chronic arsenic toxicity in sheep of Kurdistan province, Western Iran. *Archives of environmental contamination and toxicology*. 2015;69(1):44-53.
- [11] Rana T, Bera AK, Bhattacharya D, Das S, Pan D, Das SK. Chronic arsenicosis in goats with special reference to its exposure, excretion and deposition in an arsenic contaminated zone. *Environmental toxicology and pharmacology*. 2012;33(2):372-6.
- [12] Thakur BK, Gupta V. Arsenic-Contaminated Drinking Water and the Associated Health Effects in the Shahpur Block of Bihar: A Case Study From Five Villages. *Arsenic Water Resources Contamination: Springer*; 2020. p. 257-71.
- [13] Sarma SD, Hussain A, Sarma JD. Advances made in understanding the effects of arsenic exposure on humans. *Current science*. 2017;112(10):2008.
- [14] Sinha D, Prasad P. Health effects inflicted by chronic low-level arsenic contamination in groundwater: A global

- public health challenge. *Journal of Applied Toxicology*. 2020;40(1):87-131.
- [15] Chen C-J. Health hazards and mitigation of chronic poisoning from arsenic in drinking water: Taiwan experiences. *Reviews on environmental health*. 2014;29(1-2):13-9.
- [16] Khairul I, Wang QQ, Jiang YH, Wang C, Naranmandura H. Metabolism, toxicity and anticancer activities of arsenic compounds. *Oncotarget*. 2017;8(14):23905.
- [17] Milton AH, Hussain S, Akter S, Rahman M, Mouly TA, Mitchell K. A review of the effects of chronic arsenic exposure on adverse pregnancy outcomes. *International journal of environmental research and public health*. 2017;14(6):556.
- [18] Waalkes MP, Ward JM, Liu J, DiwanBA. Transplacental carcinogenicity of inorganic arsenic in the drinking water: induction of hepatic, ovarian, pulmonary, and adrenal tumors in mice. *Toxicol Appl Pharmacol*. 2003;186(1):7-17.
- [19] Kim M, Seo S, Sung K, Kim K. Arsenic exposure in drinking water alters the dopamine system in the brains of C57BL/6 mice. *Biological trace element research*. 2014;162(1-3):175-80.
- [20] Davey JC, Nomikos AP, WungjiranirunM, ShermanJR, IngramL, Batki C, et al. Arsenic as an endocrine disruptor: arsenic disrupts retinoic acid receptor–and thyroid hormone receptor–mediated gene regulation and thyroid hormone–mediated amphibian tail metamorphosis. *Environmental health perspectives*. 2008;116(2):165-72.
- [21] Meakin CJ, Szilagyi JT, Avula V, Fry RC. Inorganic arsenic and its methylated metabolites as endocrine disruptors in the placenta: Mechanisms underpinning glucocorticoid receptor (GR) pathway perturbations. *Toxicology and Applied Pharmacology*. 2020;115305.
- [22] Amann RP. The cycle of the seminiferous epithelium in humans: a need to revisit? *J Androl*. 2008;29(5):469-87.
- [23] Hess RA. Effects of environmental toxicants on the efferent ducts, epididymis and fertility. *JOURNAL OF REPRODUCTION AND FERTILITY-SUPPLEMENT-*. 1998:247-59.
- [24] Renu K, Madhyastha H, MadhyasthaR, MaruyamaM, VinayagamS, Gopalakrishnan AV. Review on molecular and biochemical insights of arsenic-mediated male reproductive toxicity. *Life sciences*. 2018;212:37-58.
- [25] Li P, Zhong Y, Jiang X, Wang C, Zuo Z, Sha A. Seminal plasma metals concentration with respect to semen quality. *Biol Trace Elem Res*. 2012;148(1):1-6.
- [26] Xu W, Bao H, Liu F, Liu L, Zhu Y-G, She J, et al. Environmental exposure to arsenic may reduce human semen quality: associations derived from a Chinese cross-sectional study. *Environmental Health*. 2012;11(1):46.
- [27] Sanocka D, Miesel R, Jedrzejczak P, Kurpisz MK. Oxidative stress and male infertility. *J Androl*. 1996;17(4):449-54.
- [28] Zeng Q, Yi H, Huang L, An Q, Wang H. Reduced testosterone and Ddx3y expression caused by long-term exposure to arsenic and its effect on spermatogenesis in mice. *Environmental toxicology and pharmacology*. 2018;63:84-91.
- [29] Bashandy SA, El Awdan SA, Ebaid H, Alhazza IM. Antioxidant potential of *Spirulina platensis* mitigates oxidative stress and reprotoxicity induced by sodium arsenite in male rats. *Oxidative medicine and cellular longevity*. 2016;2016.

- [30] Koppers AJ, De Iuliis GN, Finnie JM, McLaughlin EA, Aitken RJ. Significance of mitochondrial reactive oxygen species in the generation of oxidative stress in spermatozoa. *The Journal of Clinical Endocrinology & Metabolism*. 2008;93(8):3199-207.
- [31] Jones R, Mann T, Sherins R. Peroxidative breakdown of phospholipids in human spermatozoa, spermicidal properties of fatty acid peroxides, and protective action of seminal plasma. *Fertil Steril*. 1979;31(5):531-7.
- [32] Wellejus A, Poulsen HE, Loft S. Iron-induced oxidative DNA damage in rat sperm cells in vivo and in vitro. *Free Radical Res*. 2000;32(1):75-83.
- [33] Aitken RJ, Koppers AJ. Apoptosis and DNA damage in human spermatozoa. *Asian journal of andrology*. 2011;13(1):36.
- [34] Meeker JD, Rossano MG, Protas B, Padmanabhan V, Diamond MP, Puscheck E, et al. Environmental exposure to metals and male reproductive hormones: circulating testosterone is inversely associated with blood molybdenum. *Fertil Steril*. 2010;93(1):130-40.
- [35] Bustaffa E, Stoccoro A, Bianchi F, Migliore L. Genotoxic and epigenetic mechanisms in arsenic carcinogenicity. *Arch Toxicol*. 2014;88(5):1043-67.
- [36] Ahangarpour A, Oroojan AA, Alboghobeish S, Khorsandi L, Moradi M. Toxic Effects of Chronic Exposure to High-Fat Diet and Arsenic on the Reproductive System of the Male Mouse. *Journal of Family & Reproductive Health*. 2019;13(4):181.
- [37] Zubair M, Ahmad M, Saleemi MK, Gul ST, Ahmad M, Martyniuk CJ, et al. Sodium arsenite toxicity on hematology indices and reproductive parameters in Teddy goat bucks and their amelioration with vitamin C. *Environmental Science and Pollution Research*. 2020:1-10.
- [38] Ali S, Ali S. Genetic integrity of the human Y chromosome exposed to groundwater arsenic. *BMC medical genomics*. 2010;3(1):35.
- [39] Jang DH, Hoffman RS. Heavy metal chelation in neurotoxic exposures. *Neurol Clin*. 2011;29(3):607-22.
- [40] Rattan S, Zhou C, Chiang C, Mahalingam S, Brehm E, Flaws JA. Exposure to endocrine disruptors during adulthood: consequences for female fertility. *Journal of Endocrinology*. 2017;233(3):R109-R29.
- [41] Shahab A, Qi S, Zaheer M. Arsenic contamination, subsequent water toxicity, and associated public health risks in the lower Indus plain, Sindh province, Pakistan. *Environmental Science and Pollution Research*. 2019;26(30):30642-62.
- [42] Sharpe RM, Franks S. Environment, lifestyle and infertility--an inter-generational issue. *Nat Cell Biol*. 2002;4.
- [43] Rzymiski P, Rzymiski P, Tomczyk K, Niedzielski P, Jakubowski K, Poniedziałek B, et al. Metal status in human endometrium: relation to cigarette smoking and histological lesions. *Environ Res*. 2014;132:328-33.
- [44] Borja-Aburto VH, Hertz-Picciotto I, Lopez MR, Farias P, Rios C, Blanco J. Blood lead levels measured prospectively and risk of spontaneous abortion. *Am J Epidemiol*. 1999;150(6):590-7.
- [45] Salnikow K, Zhitkovich A. Genetic and epigenetic mechanisms in metal carcinogenesis and cocarcinogenesis: nickel, arsenic, and chromium. *Chem Res Toxicol*. 2007;21(1):28-44.
- [46] Ghersevich S, Nokelainen P, Poutanen M, Orava M, Autio-Harmainen H, Rajaniemi H, et al.

- Rat17beta-hydroxysteroiddehydrogenase type 1: primary structure and regulation of enzyme expression in rat ovary by diethylstilbestrol and gonadotropins in vivo. *Endocrinology*. 1994;135(4):1477-87.
- [47] Schroeder HA, Mitchener M. Toxic effects of trace elements on the reproduction of mice and rats. *Archives of Environmental Health: An International Journal*. 1971;23(2):102-6.
- [48] Calderon J, Navarro M, Jimenez-Capdeville M, Santos-Diaz M, Golden A, Rodriguez-Leyva I, et al. Exposure to arsenic and lead and neuropsychological development in Mexican children. *Environ Res*. 2001;85(2):69-76.
- [49] Chatterjee A, Chatterji U. Arsenic abrogates the estrogen-signaling pathway in the rat uterus. *Reprod Biol Endocrinol*. 2010;8(1):80.
- [50] Mason JI, Carr BR, Murry BA. Imidazole antimycotics: selective inhibitors of steroid aromatization and progesterone hydroxylation. *Steroids*. 1987;50(1):179-89.
- [51] Chattopadhyay S, Ghosh D. The involvement of hypophyseal-gonadal and hypophyseal-adrenal axes in arsenic-mediated ovarian and uterine toxicity: Modulation by hCG. *Journal of Biochemical and Molecular Toxicology*. 2010;24(1):29-41.
- [52] Fugo N, Butcher RL. Overripeness and the mammalian ova: I. Overripeness and early embryonic development. *Fertil Steril*. 1966;17(6):804-14.
- [53] Sárközi K, Horváth E, Vezér T, Papp A, Paulik E. Behavioral and general effects of subacute oral arsenic exposure in rats with and without fluoride. *International journal of environmental health research*. 2015;25(4):418-31.
- [54] Rahman A, Kumarathan P, Gomes J. Infant and mother related outcomes from exposure to metals with endocrine disrupting properties during pregnancy. *Science of the Total Environment*. 2016;569:1022-31.
- [55] Von Ehrenstein O, Guha Mazumder D, Hira-Smith M, Ghosh N, Yuan Y, Windham G, et al. Pregnancy outcomes, infant mortality, and arsenic in drinking water in West Bengal, India. *American journal of epidemiology*. 2006;163(7):662-9.
- [56] Sen J, Chaudhuri A. Arsenic exposure through drinking water and its effect on pregnancy outcome in Bengali women. *Archives of Industrial Hygiene and Toxicology*. 2008;59(4):271-5.
- [57] Mukherjee SC, Rahman MM, Chowdhury UK, Sengupta MK, Lodh D, Chanda CR, et al. Neuropathy in arsenic toxicity from groundwater arsenic contamination in West Bengal, India. *Journal of Environmental Science and Health, Part A*. 2003;38(1):165-83.
- [58] Barchowsky A, Roussel RR, Klei LR, James PE, Ganju N, Smith KR, et al. Low levels of arsenic trioxide stimulate proliferative signals in primary vascular cells without activating stress effector pathways. *Toxicol Appl Pharmacol*. 1999;159(1):65-75.
- [59] Lei H-L, Wei H-J, Ho H-Y, Liao K-W, Chien L-C. Relationship between risk factors for infertility in women and lead, cadmium, and arsenic blood levels: a cross-sectional study from Taiwan. *BMC Public Health*. 2015;15(1):1220.
- [60] Apostoli P, Catalani S. Metal ions affecting reproduction and development. *Met Ions Life Sci*. 2011;8(5):263-303.
- [61] Upadhyay Y, Chhabra A, Nagar JC. A Women Infertility: An Overview. *Asian Journal of Pharmaceutical Research and Development*. 2020;8(2):99-106.

- [62] Naz B, Batool SS. Infertility related issues and challenges: perspectives of patients, spouses, and infertility experts. *Pakistan Journal of Social and Clinical Psychology*. 2017;15(2):3-11.
- [63] Biswas P, Mukhopadhyay A, Kabir SN, Mukhopadhyay PK. High-protein diet ameliorates arsenic-induced oxidative stress and antagonizes uterine apoptosis in rats. *Biological trace element research*. 2019;192(2):222-33.
- [64] Ashby J, Tinwell H, Stevens J, Pastoor T, Breckenridge C. The effects of atrazine on the sexual maturation of female rats. *Regul Toxicol Pharmacol*. 2002;35(3):468-73.
- [65] Stoker TE, Goldman JM, Cooper RL. The dithiocarbamate fungicide thiram disrupts the hormonal control of ovulation in the female rat. *Reprod Toxicol*. 1993;7(3):211-8.
- [66] Ma W-g, Song H, Das SK, Paria BC, Dey SK. Estrogen is a critical determinant that specifies the duration of the window of uterine receptivity for implantation. *Proceedings of the National Academy of Sciences*. 2003;100(5):2963-8.
- [67] Nurminen T. Maternal pesticide exposure and pregnancy outcome. *J Occup Environ Med*. 1995;37(8):935-40.
- [68] Liu S-X, Davidson MM, Tang X, Walker WF, Athar M, Ivanov V, et al. Mitochondrial damage mediates genotoxicity of arsenic in mammalian cells. *Cancer research*. 2005;65(8):3236-42.
- [69] Pierce BL, Kibriya MG, Tong L, Jasmine F, Argos M, Roy S, et al. Genome-wide association study identifies chromosome 10q24. 32 variants associated with arsenic metabolism and toxicity phenotypes in Bangladesh. *PLoS Genet*. 2012;8(2):e1002522.
- [70] Martinez VD, Vucic EA, Adonis M, Gil L, Lam WL. Arsenic biotransformation as a cancer promoting factor by inducing DNA damage and disruption of repair mechanisms. *Mol Biol Int*. 2011;2011.
- [71] Yin Y, Meng F, Sui C, Jiang Y, Zhang L. Arsenic enhances cell death and DNA damage induced by ultraviolet B exposure in mouse epidermal cells through the production of reactive oxygen species. *Clinical and experimental dermatology*. 2019;44(5):512-9.
- [72] Jomova K, Jenisova Z, Feszterova M, Baros S, Liska J, Hudecova D, et al. Arsenic: toxicity, oxidative stress and human disease. *Journal of Applied Toxicology*. 2011;31(2):95-107.
- [73] Grollman AP, Moriya M. Mutagenesis by 8-oxoguanine: an enemy within. *Trends Genet*. 1993;9(7):246-9.
- [74] Kligerman AD, Malik SI, Campbell JA. Cytogenetic insights into DNA damage and repair of lesions induced by a monomethylated trivalent arsenical. *Mutation Research/ Genetic Toxicology and Environmental Mutagenesis*. 2010;695(1):2-8.
- [75] Qin X-J, Hudson LG, Liu W, Timmins GS, Liu KJ. Low concentration of arsenite exacerbates UVR-induced DNA strand breaks by inhibiting PARP-1 activity. *Toxicol Appl Pharmacol*. 2008;232(1):41-50.
- [76] Ahmed S, Ahsan KB, Kippler M, Mily A, Wagatsuma Y, Hoque AW, et al. In utero arsenic exposure is associated with impaired thymic function in newborns possibly via oxidative stress and apoptosis. *Toxicol Sci*. 2012;129(2):305-14.
- [77] Huang H-W, Lee C-H, Yu H-S. Arsenic-Induced Carcinogenesis and Immune Dysregulation. *International journal of environmental research and public health*. 2019;16(15):2746.
- [78] Ghosh P, Basu A, Mahata J, Basu S, Sengupta M, Das JK, et al. Cytogenetic

damage and genetic variants in the individuals susceptible to arsenic-induced cancer through drinking water. *Int J Cancer*. 2006;118(10):2470-8.

[79] Lai Y, Zhao W, Chen C, Wu M, Zhang Z. Role of DNA polymerase beta in the genotoxicity of arsenic. *Environ Mol Mutag*. 2011;52(6):460-8.

[80] Ebert F, Weiss A, Bültmeyer M, Hamann I, Hartwig A, Schwerdtle T. Arsenicals affect base excision repair by several mechanisms. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*. 2011;715(1-2):32-41.

[81] Andrew AS, Karagas MR, Hamilton JW. Decreased DNA repair gene expression among individuals exposed to arsenic in United States drinking water. *Int J Cancer*. 2003;104(3):263-8.

[82] Andrew AS, Burgess JL, Meza MM, Demidenko E, Waugh MG, Hamilton JW, et al. Arsenic exposure is associated with decreased DNA repair in vitro and in individuals exposed to drinking water arsenic. *Environ Health Perspect*. 2006;114(8):1193.

[83] Mauro M, Caradonna F, Klein CB. Dysregulation of DNA methylation induced by past arsenic treatment causes persistent genomic instability in mammalian cells. *Environmental and molecular mutagenesis*. 2016;57(2):137-50.

[84] Fujihara J, Soejima M, Yasuda T, Koda Y, Kunito T, Iwata H, et al. Polymorphic trial in oxidative damage of arsenic exposed Vietnamese. *Toxicol Appl Pharmacol*. 2011;256(2):174-8.

[85] Kundu M, Ghosh P, Mitra S, Das J, Sau T, Banerjee S, et al. Precancerous and non-cancer disease endpoints of chronic arsenic exposure: the level of chromosomal damage and XRCC3 T241M polymorphism. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*. 2011;706(1):7-12.