Chapter

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

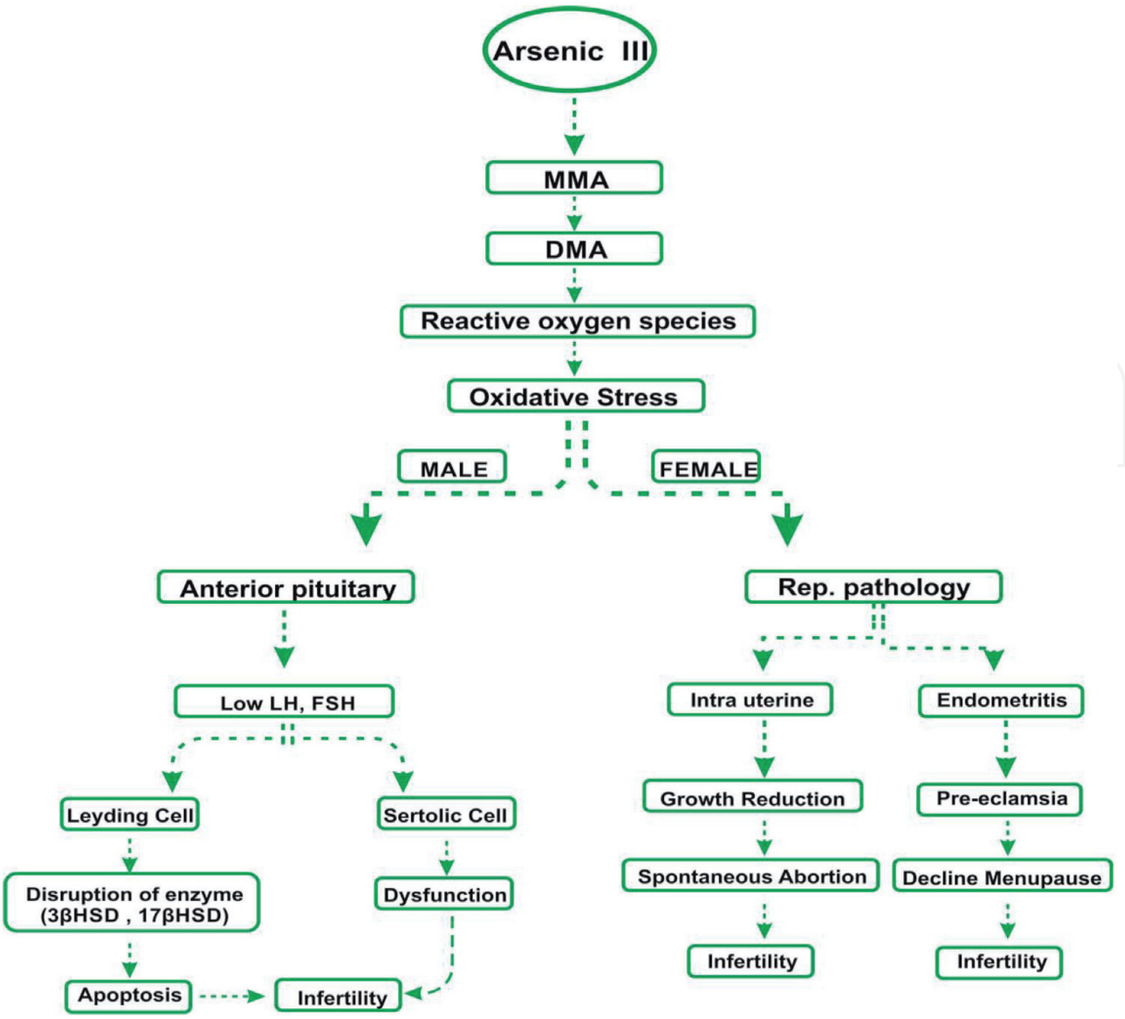

Figure 1.
Reproductive toxicity of arsenic.

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 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 antioxidant 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].

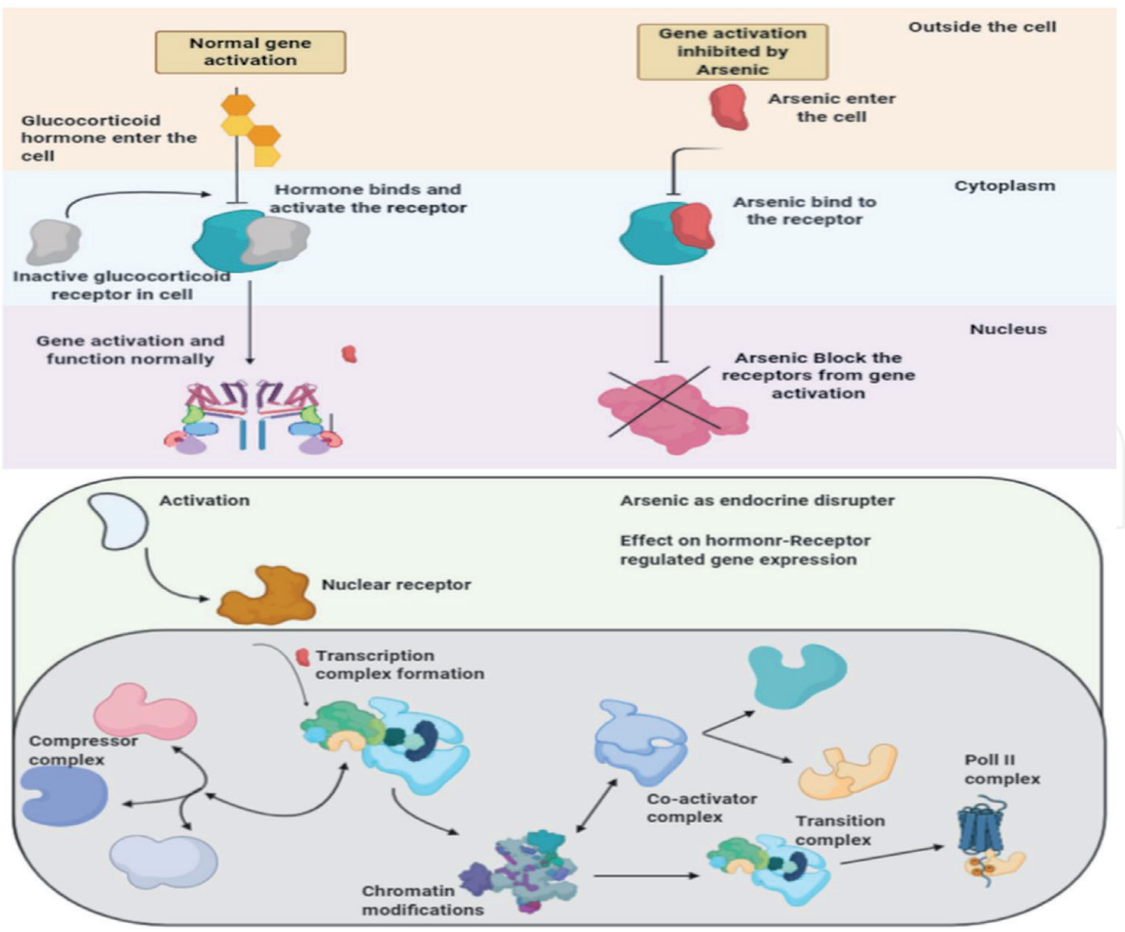

Figure 2.
Genotoxicity of arsenic adapted from [35].

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 and 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.

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