Chapter

Impact of Arsenic on Reproductive Health

Sweety Nath Barbhuiya, Dharmeswar Barhoi and Sarbani Giri

Abstract

Arsenic is ubiquitously present in the earth's crust. Population across the world gets exposed to arsenic mainly through drinking water, responsible for causing diseases like hypertension, skin pigmentation, skin lesion, cardiovascular diseases, and even cancer. However, arsenic also disturbs the male and female hormone balance in the body, thus, interfering with the process of spermatogenesis and oogenesis. This eventually leads to infertility in the reproductive system irrespective of gender. Cohort studies have revealed that when pregnant women get exposed to arsenic-contaminated water; it leads to abortion, preterm birth, and stillbirth. Thus, arsenic contamination from any source has a devastating effect on the life of organisms and also on the environment.

Keywords: arsenic, stillbirth, groundwater, testosterone, estrogen, endocrine disruptor

1. Introduction

Arsenic is one of the major environmental toxicant that is ubiquitously present all around the earth's crust. Arsenic holds the highest ranking concerning toxicity, frequency, and potential for human exposure since 1997 on the US Agency for Toxic Substances and Disease Registry (ATSDR) substance priority list [1]. Many countries are known to be highly contaminated with arsenic like Hungary, Argentina, Chile, Mexico, the United States of America, and also Asian countries *viz.* Bangladesh, China, Inner Mongolia, and Taiwan, including India [2]. According to World Health Organization (WHO) report, 140 million people from around 50 countries are exposed to arsenic through drinking arsenic-contaminated groundwater [3] at a concentration of 10 μg/L. Arsenic contamination in the groundwater occurs from natural geological sources and also anthropogenic activities [4]. Anthropogenic activities include combustion of fossil fuel, mining, utilization of arsenical pesticides, herbicides, and agricultural additives for livestock are responsible for enhancing arsenic in groundwater and soil [5]. There are two forms of inorganic arsenic: AsIII and AsV, and it is reported that AsIII is the most toxic species [6]. Intake of inorganic arsenic induces cancer of the skin, bladder, and lung [7]. Chronic arsenic exposure is reported to cause cardiovascular, respiratory, hepatic, hematological, neurological, diabetes, and reproductive effects in humans. Studies have reported that arsenic exposure for a longer period in animal models induces reproductive toxicity in both males and females; characterized by impaired ovarian and testicular steroidogenesis, alteration of tissue architecture, and cessation of spermatogenesis and folliculogenesis [8].

2. Chemistry of arsenic

In the natural environment, arsenic shows diverse chemical behavior. Arsenic has the potential to readily change oxidation state and bonding configuration, producing inorganic and organic forms [9]. In the periodic table, arsenic is in the 33rd position of the periodic table, secures a position in Group 15, being a member of the nitrogen family. The atomic number of arsenic is 33 and its atomic weight is 74.921, thus it is heavier than iron, nickel, and manganese but lighter than silver, lead or gold. The electronic configuration of the stable form of arsenic, As (0) is: $1s^2\ 2s^2\ 2p^6\ 3s^2\ 3p^6\ 3d^{10}\ 4s^2\ 4p^3$. There exist four oxidation states of arsenic *viz.* arsines and methyl arsines, elemental arsenic, arsenite, and arsenate, the inorganic form of arsenic is highly lethal and mobile in the atmosphere compared to the organic form. Arsenite is found to be 10 times more poisonous than arsenate [10].

3. Global scenario of arsenic contamination

Arsenic is a matter of global concern because of its adverse health effects. Arsenic is widespread at a high concentration in the groundwater throughout the world: Asia (Bangladesh, China, India, Inner Mongolia, and Taiwan), Europe (Hungary), and the Americas *viz.* Argentina, Chile, Mexico, and the northeast and western United States of America [2]. It was reported that about 150 million people across the world were affected by arsenic and the number is increasing as newly affected areas are discovered continuously [11]. In 2019, the number of affected people has increased to 500 million around the globe [12].

4. Sources of contamination

The establishment of a stable society largely depends upon the availability of safe and reliable water bodies. In the recent world, due to numerous anthropogenic actions, water bodies are contaminated with heavy metals like arsenic [13]. Millions of people across the globe are under the threat of arsenic-related diseases. There are various routes of arsenic exposure but the major one is through the drinking water available from the groundwater [14]. The main reason behind arsenic contamination in the groundwater may be attributed to both natural and anthropogenic activities, producing hazardous effects on health and the environment [11]. In developing countries, owing to a huge number of industries, unfortunately, pollute the air due to the generation of various chemicals, of which arsenic is one of the most toxic chemicals. The occurrence of arsenic in the air as particulate matter is considered to be associated with various diseases [14]. According to the World Health Organization guidelines, the recommended level of arsenic in the aquatic ecosystem, including drinking water is <10 μg/L and this threshold was chosen based on the limits of diagnostic and treatment techniques [15].

According to a recent study by Bundschuh et al. [16] in Latin America, seven possible sources of arsenic are being determined and they are as follows:

i. Volcanism and geothermalism

ii. Mining and related activities leads to deposition of natural lixiviation and accelerated mobilization from (mostly sulfidic) metal ore

iii. Deposition of coal and their exploitation

iv. Hydrocarbon reservoirs and water produced during exploitation

v. Transportation of solute and sediment via rivers to the sea

vi. Atmospheric Arsenic through dust and aerosol

vii. Exposure of arsenic through involuntary ingestion and geophagy.

Thus, there are several pathways through which people get exposed to arsenic in different regions but the outcome of the exposure is dangerous to both living organisms and the environment.

5. Reproductive health

5.1 Arsenic induced reproductive toxicity in human

A study was carried out among the population of Dhaka, Bangladesh; consisting of a total number of 192 participants (married women of reproductive age 15–49 years). From the study, it was observed that the women exposed

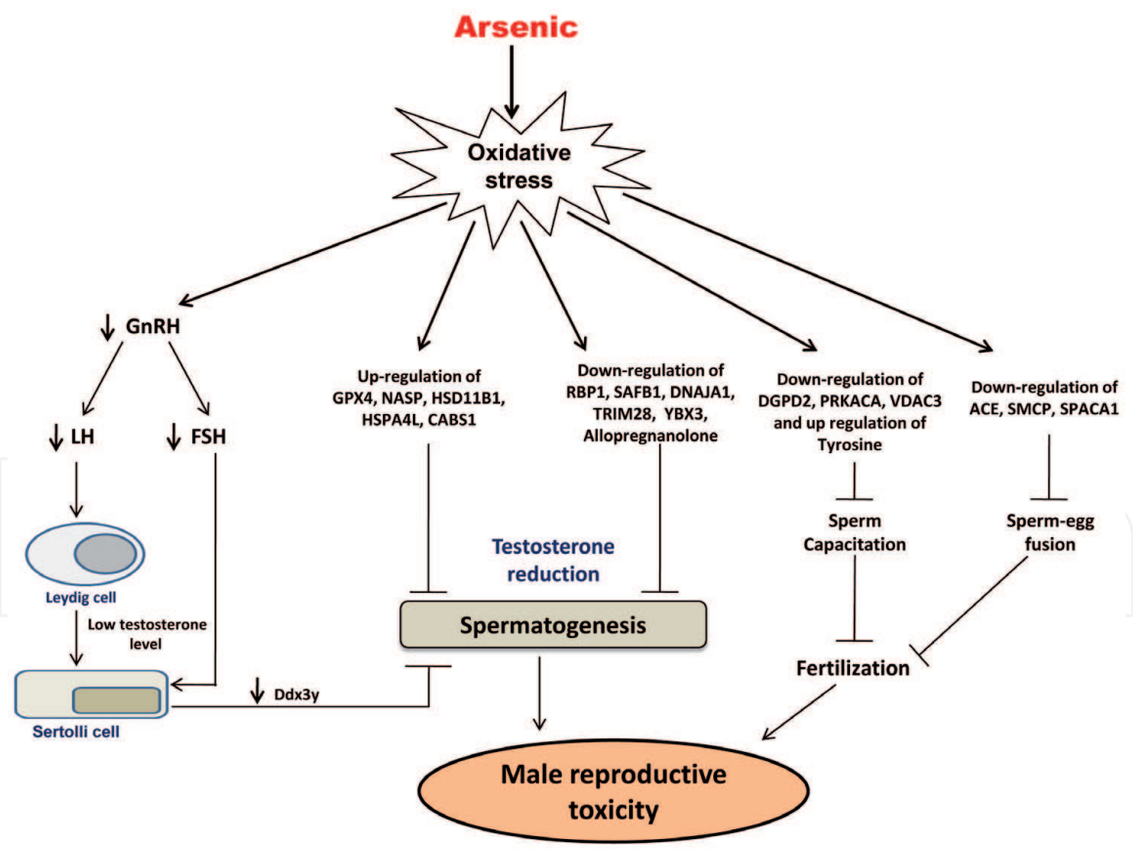

Figure 1.
Schematic representation of the pathways through which arsenic induces male reproductive toxicity. GPx4: glutathione peroxidase, NASP: nuclear autoantigenic sperm protein, HSD11B1: 11β-hydroxysteroid dehydrogenase, HSP4AL: heat shock 70 kDa protein 4-like, CABS1: calcium-binding and spermatid-specific protein 1, RBP1: retinol-binding protein 1, SAFB1: scaffold attachment factor B1, DNAJA1: DNAJ homolog subfamily a member 1, TRIM 28: transcription intermediary factor 1-beta, YBX3: Y-box binding protein 3, GPD2: glycerol-3-phosphate dehydrogenase, mitochondrial, PRKACA: cAMP-dependent protein kinase catalytic subunit alpha, VDAC3: voltage-dependent anion-selective channel protein 3, ACE: angiotensin-converting enzyme, SMCP: sperm mitochondrial-associated cysteine-rich protein and SPACA1: sperm acrosome membrane-associated protein 1.

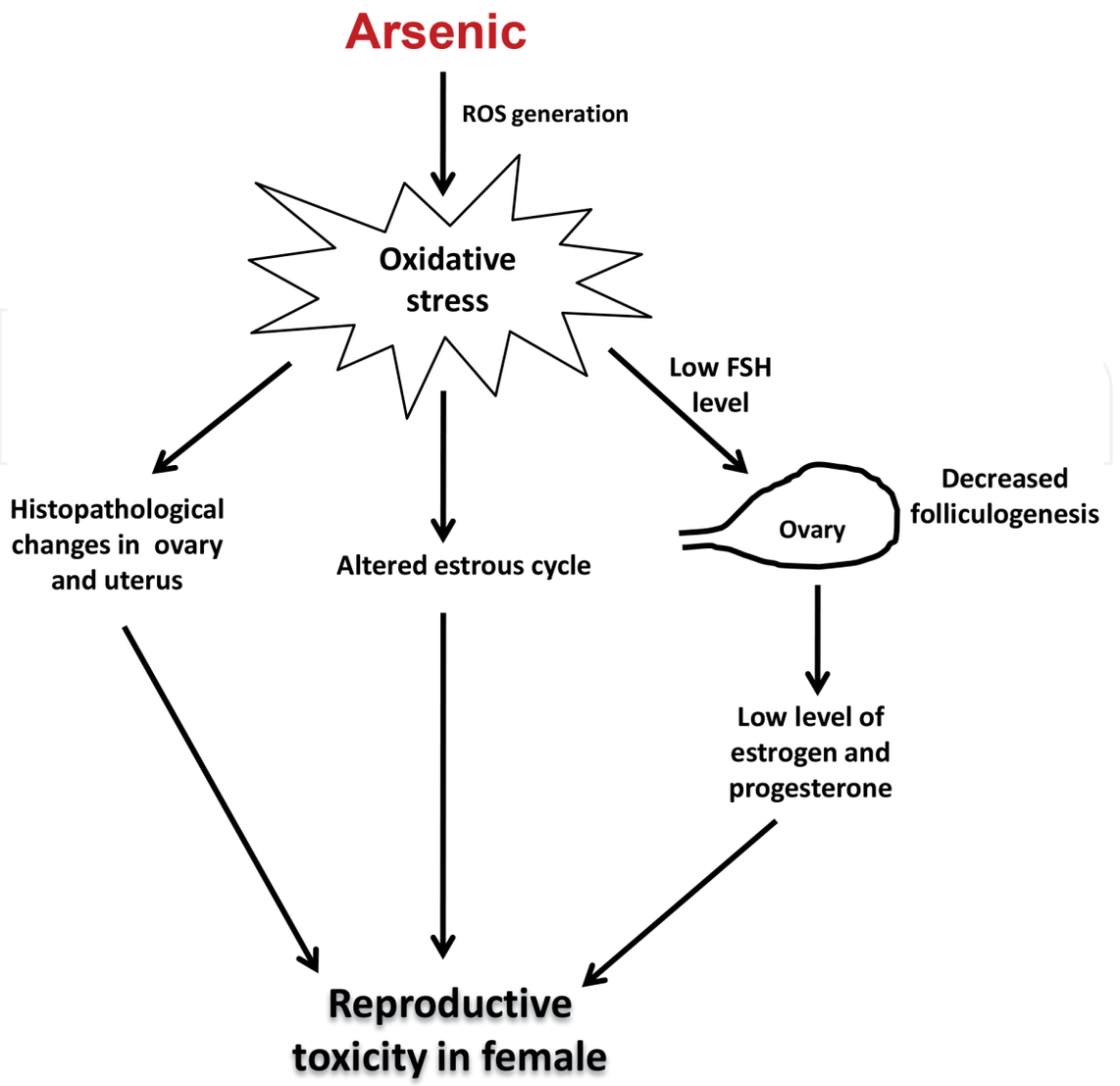

Figure 2.
Schematic overview of arsenic induced reproductive toxicity in female.

to arsenic-contaminated drinking water (>0.05 mg/L) had adverse pregnancy outcomes *viz.* abortion, stillbirth, and preterm birth at a much higher rate than the non-exposed (<0.02 mg/L) groups [17]. Another study conducted on 202 married women in West Bengal, India showed that pregnant women exposed to arsenic-contaminated drinking water had a six times higher rate of stillbirth than compared to non-exposed pregnant women [18]. According to a cohort study done in Bangladesh, comprising of 1458 women, it was observed that arsenic exposure is directly proportional to the adverse reproductive and maternal health of the exposed women [19]. In the year 2008, a group of researchers reported that drinking arsenic-contaminated water by the woman was associated with a higher risk of stillbirth. In this study, the total number of cases studied was n = 30,984 and it was conducted in the rural area of Bangladesh [20]. According to a report, there is an increase in the rate of arsenic methylation effectiveness and total arsenic content of urine in pregnant women (n = 1613) of Bangladesh. The samples (urine) were collected at two prenatal time periods: first at 4–16 weeks and the second at 21–37 weeks of pregnancy [21]. Arsenic is a well-known toxicant and a prospective study was taken up from two studies conducted in Matlab, Bangladesh. This study included 809 girls who participated at the age of their menarche and had a previous report of prenatal exposure to arsenic via the tube well water that was used by

their mother during pregnancy. The outcome of the study is that girls prenatally exposed to arsenic have delayed menarche, indicating endocrine disruption that eventually may impair the total reproductive system [22]. Arsenic exerts its toxicity by following different pathways as detailed in **Figures 1** and **2**.

5.2 Arsenic mediated toxicity in animal models

5.2.1 Toxicological implications in the male reproductive system

Chemical	Animal model	Treatment	Observation	Reference
Arsenic	Swiss albino mice	Arsenic was administered at a concentration of 30 and 40 mg/L for a period of 30, 45, and 60 days via drinking water.	The results showed a relative decline in the testicular weight in experimental animals, with dose-dependent gradual diminution in seminiferous tubule diameter and gametogenic cell population. Leydig cell atrophy increased in the arsenic exposed groups, indicating the ill effects of arsenic on spermatogenesis.	[23]
Arsenic	Swiss albino mice	The experimental animals were exposed to arsenic at a level of 53.39, 133.47, 266.95, and 533.90 μmol/L for 35 days through drinking water.	The results revealed that at the lower doses (53.39, 133.47, and 266.95) μmol/L, the sperm count, motility, and morphological abnormalities are similar to the control group. However, at the highest dose, i.e., 533.90 μmol/L, a sharp decline in sperm count and motility, along with abnormal sperm cells was evident.	[24]
Arsenic	Swiss albino mice	Mice were treated with 53.39 μmol/L sodium arsenite (4 ppm As) via drinking water for 365 days.	A marked decrease in the absolute and relative testicular weight was observed. The sperm count, motility was decreased upon arsenic exposure while there is an increment in abnormal sperm. The long-term arsenic exposure decreased the activities of marker testicular enzymes such as sorbitol dehydrogenase, acid phosphatase, and 17β-hydroxysteroid dehydrogenase (17β-HSD), but those of lactate dehydrogenase and, y-glutamyl transpeptidase (y-GT) were significantly increased.	[25]
Arsenic	Rat	Arsenic (sodium arsenite) treatment of 5 mg/L through drinking water was given for 4 weeks	The results indicated decreased testicular weights, accessory sex organ weight, and low sperm count, as well as degeneration of a wide variety of germ cells at the 7th stage of the spermatogenic cycle.	[26]
Arsenic	Mice	Mice received arsenic (arsenic trioxide) through oral gavage daily at a level of 3 and 4 mg/kg BW for 56 days.	The study reveals that arsenic treatment causes damage to the spermatogonia and the testosterone level decreases with an increase in the extent of arsenic exposure.	[27]
Arsenic	Swiss albino mice	Mice were treated with arsenic at a level of 10, 25, 50, 100, and 200 ppm for 40 days.	Mice treated with arsenic showed a dose-dependent decline in testosterone level.	[28]

Chemical	Animal model	Treatment	Observation	Reference
Arsenic	Swiss albino mice	Arsenic trioxide at a dose of 3 and 4 mg/kg BW were administered orally to mice for 8 weeks.	Arsenic treatment causes decreased testosterone level and elevated luteinizing hormone. This indicated impairment of Leydig cells, leading to poor sperm production and eventually led to infertility in experimental animals.	[29]
Arsenic	Sprague-Dawley rat	Treatment of arsenic was given to rats (male) at a dose of 1, 5, and 25 mg/L for 6 months.	Arsenic concentration in serum was found to range from 0.18–0.67 μg/ml, while in testis it was recorded as 0.35–1.74 μg/ml. This suggests that arsenic can pass through the blood-testis barrier and accumulate in rat testis, causing adverse effects in the male reproductive system. In the present study, five proteins (GPX4, HSD11B1, NASP, HSP4AL and CABS1) were found to be upregulated while five other proteins (SAFB1, TRIM28, RBP1, DNAJA1, YBX3) were downregulated including one metabolite (Allopregnanolone) in response to arsenic exposure during spermatogenesis, causing impaired spermatogenesis and formation of low-quality sperm. Arsenic treatment represses three proteins (VDAC3, PRKACA and GPD2) as well as increases the L-tyrosine level, causing disruption of protein tyrosine phosphorylation, necessary for sperm capacitation, leading to inhibition of fertilization and male infertility. Arsenic exposure also affects fertilization by decreasing the expression levels of SPACA1, ACE and SMCP in rat testis, inhibiting the binding and fusion of sperm to egg. It was observed that the differential proteins and metabolites associated with male reproduction, was also found to be involved in ERK/AKT/NF-κ B pathway. The up-regulation of ERK1/2, PI3K, AKT, IKKγ and NFKB gene expression, alongwith enhanced phosphorylated ERK/AKT level in rat testis, it was reported that arsenic may induce male reproductive toxicity through activated ERK/AKT/NF-κ B pathway.	[30]
Arsenic	Wistar rats	Rats were treated with 0.1 and 10 mg/L of sodium arsenite and sodium arsenate daily for 56 days via drinking water.	Arsenic treatment showed a dose-dependent decrease in the sperm-count parameters and epididymal morphometry. This indicates arsenic exposure causes adverse effects to male reproductive functions in adult Wistar rats.	[31]
Arsenic	Mice	The experimental animals were treated with arsenic trioxide at a dosage of 1, 2 and 4 mg/L via drinking water for 60 days.	It was observed that subchronic arsenic exposure induces downregulation of Ddx3y expressions in the testis and epididymis, which may adversely affect spermatogenesis, leading to male reproductive toxicity.	[32]

5.2.2 Arsenic mediated toxicity in the female reproductive system

Chemical	Animal model	Treatment	Observation	Reference
Arsenic	Sprague-Dawley rats	50, 100, and 200 ppm of arsenic was administered to the animals through drinking water for 28 days.	Treatment of arsenic to immature rats showed decreased uterine diameter and epithelium height. The thickness of the endometrium and myometrium also got reduced.	[32]
Arsenic	Albino Wistar strain rats	10 mg/kg bodyweight of arsenic was administered orally to the experimental animals for 8 days.	The study showed reduced glutathione peroxidase, superoxide dismutase, and catalase activities. Treatment of arsenic also induced DNA break and necrosis in the uterine tissues. Arsenic exposure even leads to disruption in the steroidogenesis process.	[33]
Arsenic	Albino Wistar strain rats	The experimental animals were treated with an aqueous solution of arsenic trioxide at a dose level of 3 ppm/rat/day orally.	Serum estradiol level decreased due to arsenic exposure. Degeneration of Ovarian DNA was prominent in the treated groups.	[34]
Arsenic	Kunming mice	Arsenic is injected with distilled water as vehicle control to the experimental animals at a concentration of 8 mg/kg per day bodyweight on every alternate day for 16 days.	Treatment of arsenic increased reactive oxygen species (ROS) generation in the ovary of treated mice.	[35]
Arsenic	Wistar albino rats	Three doses 10, 30, and 50 μg/L of arsenic were administered to the mice via drinking water for 60 days.	Arsenic exposure disrupted the estrous cycle with a prolonged diestrous and metestrus phase. An increase in many follicular atresia was evident from the study.	[36]
Arsenic	Sprague-Dawley rats	The experimental animals were treated with a dose of 4 μg/ml per day for 28 days.	The results indicated that arsenic exposure disturbed the gonadotropins and estradiol levels, causing disintegration of the luminal epithelial, myometrial and stromal cells of the uterus. The study also showed that arsenic exposure leads to downregulation of the downstream components of the estrogen signaling pathway.	[37]
Arsenic	Albino rats	Albino rats were treated with arsenic (sodium arsenite) at a dose of 0.4 ppm for 28 days.	The arsenic-treated rats showed a prolonged diestrous phase. Treatment with arsenic also led to a significant diminution of the entire uterine diameter. It was also evident from the study that the endometrium is not well-defined and the lumen became narrow and unfolded, indicating damage in the reproductive system of the female upon exposure to arsenic.	[38]

Chemical	Animal model	Treatment	Observation	Reference
Arsenic	Wistar rats	Sodium arsenite was administered at a dose of 3 ppm during the pre-natal and post-natal development.	Arsenic exposure resulted in decreased folliculogenesis, the morphological characteristic of the ovaries were disturbed, and modified the adrenocortical cell number, causing the delayed onset of puberty.	[39]
Arsenic	Wistar rats	Rats were orally administered with sodium arsenite (0.4 ppm) for two time periods—16 and 28 days.	Arsenic treatment reduced ovarian steroidogenic dehydrogenase activity. The study also showed diminished levels of luteinizing hormone, follicle-stimulating hormone, and estrogen upon exposure to arsenic.	[40, 41]
Arsenic	Mice	Arsenic (arsenic trioxide) was administered at a dose of 0, 0.2, 2 and 20 ppm to the parents from 35 days before breeding and is continued until weaning. The female offspring received the same treatment until maturity.	Arsenic trioxide (As_2O_3) exposure at a higher dose in the prenatal or parental stage via drinking water induces autophagy in the ovaries of mature F1-female mice via activation of autophagic genes (PDK1, TSC2, P13K, P62, ATG13, AMPK, ULK1, ATG12, ATG5, LC3, Beclin1, ATG3, ATG7 and p62) and proteins (Beclin1, LC3-I, II and mTOR), resulting in decreased female gametes number as compared to the control.	[42]

6. Epigenetic effect of arsenic on reproductive system

Epigenetics is the study of how cells control gene activity without altering the DNA sequence. It was reported that arsenic causes hypermethylation of the of the p53 gene and thus, gained the attention of the researchers regarding the epigenetic effects of arsenic [43]. Exposure to inorganic arsenic is found to be associated with epigenetic modifications like gene specific DNA methylation, histone acetylation, phosphorylation, methylation and altered expression of miRNAs, which may induce carcinogenesis or other diseases [44]. According to a report, arsenic exposure during gestation increases the hypomethylation of active Long Interspersed Nuclear Element (LINE) and Long Terminal Repeat (LTR) subfamilies of the offspring sperm, causing transgenerational effects. The study indicates that retrotransposon methylomes in the sperm is one of the main targets of arsenic when exposed during gestation period [45]. Another study showed that arsenic (As_2O_3) exposure to parents at a dose of 1 mg/L has adverse transgenerational effects on the reproductive phenotype in both male and female offspring after attaining maturity, which may be due to an altered global DNA methylation pattern in gonadal tissue [46]. Thus the studies indicate that arsenic exposure at the gestation period is enough to induce toxicity in the reproductive system of the future generations.

7. Conclusion

Arsenic is a well-documented toxicant available all around the earth's crust. Arsenic has the potential to cause various diseases *viz.* cardiovascular diseases,

hypertension, diabetes, skin lesion, and also cancer. So, its presence in the environment both in the groundwater or air is very harmful to the livelihood of organisms as well as for the atmosphere. Arsenic has the potential to decrease the male reproductive hormones like testosterone and may inhibit spermatogenesis. It can also adversely affect the folliculogenesis of females by disturbing the female monthly cycle. This is brought about by arsenic due to its massive capacity to reduce hormone synthesis (follicle stimulating hormone and estrogen). The exposure to arsenic in the case of a pregnant woman leads to severe implications like stillbirth, preterm birth, and abortion. Thus, sources of arsenic exposure may vary from region to region but the ill effects of it are very much prominent and thus, suitable techniques and methodologies are to be adopted to reduce the burden of diseases associated with arsenic exposure.

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