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REVIEW

Impact of arsenic on male and female reproductive function: a review of the pathophysiology and potential therapeutic strategies

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Abstract

Arsenic is a ubiquitous metalloid and heavy metal that contributes to the global decline in human fertility. Humans are constantly exposed to arsenic through biotic and abiotic sources, especially ingestion of arsenic-contaminated food and water. Its exposure is associated with several adverse health challenges, including reproductive toxicity. In spite of its reported adverse effects, arsenic exposure remains a global challenge. Hence, this study provides a comprehensive review of the literature on the impact and mechanism of arsenic on male and female reproductive function. Additionally, a review of the potential therapeutic strategies is presented. Evidence from the literature reveals that arsenic upregulates reactive oxygen species (ROS) generation which mediates arsenic-induced suppression of the hypothalamic-pituitary–gonadal axis and inactivation of 3β-HSD and 17β-HSD activities, leading to reduced gonadal steroidogenesis. Through several oxidative stress-dependent signaling, arsenic induces the apoptosis of the germ cells, thus contributing to the development of infertility. At the moment, there is no specific treatment for arsenic-induced reproductive toxicity. However, increasing data form the scientific literature reveals the benefits of antioxidants in ameliorating arsenic-induced reproductive toxicity. These molecules suppress ROS generation and maintain optimal activities of the hypothalamic-pituitary–gonadal axis, leading to optimal steroidogenesis and gametogenesis as well as improved germ cells. Overall, this study revealed the impact and associated mechanism of arsenic-induced reproductive toxicity. It also provides evidence from the literature demonstrating potential therapeutic measures in managing arsenic-induced reproductive toxicity.

Keywords Arsenic · Apoptosis · Heavy metals · Infertility · Metalloid · Oxidative stress

Introduction

Humans are constantly exposed to metalloids and heavy metals such as mercury, chromium, cadmium, lead, and arsenic, which are major contaminants of air, water, food, and soil, thus posing a risk to the ecosystem (Balali-Mood et al. 2021; Besong et al. 2023a, b). Out of these heavy metals, arsenic remains the most potent environmental toxicant, exerting its toxicity to animals and plants (Rahman and Singh 2019). It is a natural earth crust element that is ubiquitously distributed in the environment due to natural sources and human activities (Yin et al. 2022). It exists in numerous organic and inorganic states with different toxicity profiles. Commonly, it exists in three valence states: As(0) (metalloid arsenic, 0 oxidation state), As(III) (trivalent state, such as arsenites), and As(V) (pentavalent state, such as arsenates) (ATSDR 2007).

Recent evidence suggests that arsenic exposure causes potent toxicity to the reproductive system (Wirth and Mijal 2010; De Palma et al. 2022). Studies have also affirmed that the male reproductive system is more susceptible to arsenic toxicity because of the direct binding to sulfhydryl groups of proteins such as sperm chromatin and flagellum (De Palma et al., 2022). Conversely, in the female reproductive system, arsenic exposure alters reproductive hormones and biogenic amines that regulate spermatogenesis and oogenesis

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(Jana et al., 2006). It has been thought that arsenic produces ROS by the oxidation of arsenite to arsenate through arsenic methylation leading to oxidative stress (OS) which can cause damage to physiological functions of the cell leading to various diseases such as cancers, diabetes, atherosclerosis, cardiovascular disease, and infertility which can be concluded that arsenic triggers potential mechanisms to induce OS. Arsenic exposure reduces the number of sperm due to reduced GSH and increased malondialdehyde (MDA) as well as increasing inflammatory factors such as tumor necrosis factor-alpha (TNF-α), cyclo-oxygenase (COX), nuclear factor-kappa B (NF-kB), and caspase 3 (Shao et al. 2018; Im Chang et al. 2007). Moreover, arsenic has been documented to also increase urinary concentration of total arsenic and lowers semen volume, sperm concentration and motility, and serum testosterone levels (Akhigbe et al. 2024).

It also increases ROS levels in the testes and alters hormonal secretion and spermatogenesis via the inhibition of androgen receptor activity (Jana et al. 2006; Rosenblatt and Burnstein 2009; Saberi Sis and Zargari 2017). Arsenic also inhibits the activities of DNA-binding domain (DBD) of steroid receptors and causes alterations in enzymes such as lactate dehydrogenase (LDH), acid phosphatase (ACP), γ-glutamyl transpeptidase (GGT) (Renu et al. 2018; Minatel et al. 2018; Wai et al. 2019; Palma-Lara et al. 2020). It is also noteworthy to know that arsenic also affects the female reproductive system through the alteration of some regulator enzymes in steroidogenesis such as 3β-hydroxysteroid dehydrogenase (3-βHSD) and 17β-hydroxysteroid dehydrogenase (17βHSD) due to low levels of gonadotropin (Ilieva et al. 2021; Shao et al. 2018), alteration in the levels of some neurotransmitters (reduction LH, FSH and estradiol), and reduction in gonadotropin secretion (Ilieva et al. 2021; Bhardwaj et al 2021).

Moreover, mounting evidences have revealed potential therapeutic strategies in the management of arsenic-induced reproductive toxicity with a swift approach of a chelation therapy such as dimercaprol (BAL), meso-2,3-dimercaptosuccinic acid (DMSA), and 2,3-dimercapto-1-propanesulfonic acid (DMPS) to bind and remove arsenic from the body (Kalia & Flora 2005); antioxidant supplementation to combat arsenic-induced reproductive toxicity (Flora et al. 2007); Phytochemicals for arsenic removal and detoxification (Sinha et al. 2007); and gene therapy approaches to enhance arsenic metabolism and excretion (Drobná et al. 2010).

Human anthropogenic and agricultural activities such as mining, smelting metal, burning fossil fuels, and using pesticides for home and agricultural usage can contaminate the environment with arsenic (Chung et al., 2014). Environmental, medicinal, and occupational sources are the main sources of human exposure to arsenic (Wang et al. 2012). However, ingestion of arsenic-contaminated food and water remains the main source of exposure (Chung et al., 2014). In high-endemic areas of arsenic, the exposure level can range from tens to hundreds, and occasionally even thousands, of micrograms per liter (μg/L), which is much higher than the WHO limit of ≤ 10 μg/L (WHO 2018; Shaji et al. 2021). According to estimates, approximately 500 million people worldwide could be exposed to unacceptably high doses of arsenic (Shaji et al. 2021).

Arsenic exposure is associated with deleterious adverse effects such as neurological manifestations, gastroenteritis, metabolic disease, vascular changes, and cancers like lung, bladder, kidney, prostate, and hepatocellular carcinoma (Abernathy et al. 2003; Adegunlola et al. 2012; Bibha et al. 2023). Human and experimental studies have also revealed that arsenic induces reproductive toxicity via its endocrine-disrupting activity (Wang et al. 2016; Gunduzoz et al. 2019; Besong et al. 2023b). Evidences on epidemiological studies show the deleterious impact of arsenic exposure on reproductive functions. In Bangladesh, it was documented that men with high arsenic exposure showed significantly lower sperm count, motility, and morphology compared to men with lower arsenic exposure (Hossain et al. 2021). Several of the highly exposed men were diagnosed with azoospermia (complete absence of sperm in semen). However, the study highlighted the detrimental effects of chronic arsenic toxicity on male fertility in this region (Hossain et al. 2021). More so, some data document the link between arsenic and spontaneous abortion and stillbirths in pregnant women with relative risks ranging from 1.8 to 3.1 cases and a significant correlation between higher arsenic levels in drinking water and an increased incidence of spontaneous abortion (Huynh et al. 2020; Biswas et al. 2021). Sharma et al. (2022) demonstrated that arsenic contamination correlates positively with preterm birth (3.1, 95% CI: 1.8–5.3), low birth weight (2.9, 95% CI: 1.6–4.9), and gestational diabetes (2.4, 95% CI: 1.3–4.2). Recently, Nguyen et al. (2023) reported the negative impact of arsenic exposure on reproductive health.

Despite its reported deleterious effects, arsenic exposure remains a global challenge. The understanding of arsenic exposure, the mechanisms of its reproductive toxicities, and the potential benefits of drug candidates from experimental studies will open novel therapeutic windows in the management of arsenic-induced reproductive toxicity. Therefore, the present study provides a comprehensive review of the literature on the impact and mechanism of arsenic on male and female reproductive function. Additionally, a review of the potential therapeutic strategies is presented.

Methods

This study was based on the data from the scientific literature that were retrieved from a search conducted using these databases: PubMed, EMBASE, Scopus, and Google Scholar. The following keywords were used alone and in combination: "arsenic," "reproductive function," "male reproduction," "female reproduction," "sperm," "sperm cells," "testis," "germ cell," "ovary," "ova," and "ovum." Searches were performed without restrictions to the year of publication and country of origin.

Arsenic exposure, metabolism, and mechanism

Sources of arsenic exposure are basically classified as abiotic and biotic (Bibha et al. 2023). Abiotic sources comprise geological elements like minerals, underground water, and geothermal processes, as well as manmade elements like farming, manufacturing, and mining operations. Arsenic used industrially, like in antifungal wood preservatives, has the potential to contaminate soil (Yanitch et al. 2020). Arsenic is also used in pharmaceuticals, optical, and glass industries, in the manufacture of sheep dips, alloy, antifouling paints, arsenic-containing pigments, microelectronics, pesticides, and insecticides (Yang et al. 2018). Through leaching, arsenic-contaminated soil contaminates surface and ground water (Bibha et al. 2023). Erosion and leaching from geological formations or anthropogenic sources, the use of pesticides and fertilizers, and metal processing, industrial, and mining activities contribute to soil contamination (Yang et al. 2018). Cigarette smoking contributes significantly to arsenic bioavailability by inhibiting arsenic methylation (Yang et al. 2018). Inhalation of arsenite and arsenate and the use of arsenic-containing cosmetics also add up to human exposure (Yang et al. 2018).

Another main source of arsenic exposure is arsenic contamination of water bodies through improper disposal of untreated sewage and the use of arsenic-based agrochemicals, thus leading to increased arsenic consumption by aquatic animals (Kumari et al. 2017; Liu et al. 2019), as well as contamination of crops through irrigation (Kaur et al. 2017). Consumption of these arsenic-contaminated aquatic animals and plants contributes to human exposure (Bibha et al. 2023). Following exposure to inorganic arsenic, there is a reduction of As V to As III, which in turn undergoes oxidative biomethylation under the action of methyltransferase to generate monomethylarsonic acid, pentavalent organic arsenicals, and dimethylarsinic acid that are in turn voided through the urine (Afolabi et al. 2016). Photooxidation may also be important in the metabolism of arsenic (Amyot et al. 2021). Arsenic is rapidly distributed to body tissues and accumulates over time. Accumulation of arsenic and its metabolites distorts numerous physiological processes, including reproductive functions. Arsenic crosses the blood-gonadal barrier and accumulates in the testis and ovarian where it alters testicular and ovarian structure and functions (Huang et al. 2016; Akhigbe et al. 2024).

Arsenic-induced reproductive toxicity is mediated by the induction of OS which causes loss of mitochondrial organization, leading to an alteration in the mitochondrial integrity and membrane potential. Moreover, the release of apoptotic proteins (cyt-c and activation of Bax) and decreased expression of Bcl-2 promotes apoptosis. Mitochondria produce ROS through complex I and III (Muller et al. 2004; Mishra et al. 2008). The methylation of arsenic is a detoxification of arsenic that is associated with its methylation in the liver by As3MT, and the production of its methylated metabolites includes MMA^{V}, MMA^{III}, DMA^{V}, and DMA^{III}. In this pathway, arsenic needs glutathione (GSH) and other thiols. Depleting GSH and other thiols alters the redox status, producing arsenic methylated metabolites which in turn increase oxidative stress (Thomas et al. 2007; Dopp et al. 2010).

Additionally, changes in certain signaling pathways, including the tyrosine phosphorylation and mitogen-activated protein kinase (MAPK) pathways as well as transcription factors, including NF-kB, AP-1, apoptosis, p53 activation, and Bax expression, all contribute to the production of ROS, which raises OS (Nagesh et al. 2019). Arsenic causes damage to proteins, carbohydrates, lipids, and DNA by producing OH or O2 radicals that leads to the production of carbonyl, aldehydes, and keto compounds. This metalloid also damages some amino acid residues such as cysteine and methionine, which can in turn lead to protein structure alteration, degradation, unfolding, and fragmentation and the inactivation of enzymes (such as antioxidant enzymes, pyruvate dehydrogenase) and also the production of advanced glycation end products (AGEs) (Zargari 2021). Arsenic causes damage to carbohydrates and lipids leading to the production of ketoamines, ketoaldehydes, and fatty acid radicals (ROO) as well as changes in the carbohydrate metabolism (i.e., the inhibition of pyruvate dehydrogenase complex, hyperglycemia, and glucose intolerance) and MDA, HNE, the oxidation of cellular membranes, and the inactivation of membrane-bound receptors (Wirtitsch et al. 2009; Sabir et al. 2019). Arsenic also damages DNA leading to alterations in DNA bases (such as the production of 8-OHdG, in turn, the altered bases can modify the site of binding of transcription factors and change the expression

of related genes), alterations in DNA repair enzymes, DNA strand break, and the cross-linkage of DNA–protein (De Vizcaya-Ruiz et al. 2009).

Arsenic and male reproductive function

According to Chakraborti et al. (2002), exposure to arsenic can have both acute and long-term harmful effects, putting people at risk for serious health issues like skin cancer, diabetes, liver, kidney, and CNS illnesses. Also, arsenic exposure results in reproductive toxicity, including testicular damage (Sarkar et al. 2008). Moreover, studies suggest that arsenic exposure causes testicular toxicity by directly affecting the hypothalamic-pituitary–testicular axis by affecting the secretion and function of gonadotropins, primarily gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) (Besong et al. 2023b). Research suggests that arsenic exposure can reduce the sensitivity of gonadotroph cells to GnRH, leading to decreased secretion of LH and FSH (Jana et al. 2006). This reduction in gonadotropins impairs the stimulation of Leydig cells which are responsible for testosterone production, thus lowering testosterone levels via both direct inhibition of steroidogenesis in Leydig cells and reduced sensitivity of these cells to LH (Jana et al. 2006).

It has also been revealed that a high arsenic level may suppress the sensitivity of gonadotroph cells to GnRH as well as gonadotropin secretion by elevating plasma levels of glucocorticoids. This has led ultimately to the development of gonadal toxicity (Sarkar et al. 2008; Pant et al., 2004). Nevertheless, exposure to arsenic poisoning has led to the inhibition of testicular androgenesis and reduction of the testicular weight and accessory sex organs (Sarkar et al., 2003; Pant et al., 2004). Moreover, following exposure to arsenic exhibited severe cellular damage in spermatogenic cells indicating a cellular degeneration in the eosinophilic multinucleated giant cell of the seminiferous tubule (Omura et al. 2000). These results demonstrate that after arsenic exposure, spermatogonia's meiotic maturation has been significantly disturbed (Omura et al. 2000). The testis of arsenic-exposed rats showed a degeneration of interstitial Leydig cells, which could put a chemical strain on cellular function (Omura et al. 2000). Leydig cell atrophy may develop from cellular exhaustion owing to a persistent stress effect while the initial increase in cell width may be a better indicator to adapt the metal-produced stress (Omura et al. 2000). Sarkar et al. (2008) found that testicular shrinkage and a gradual, dose-dependent decrease in the number of Leydig cells in the interstitium were the outcomes of exposure to sodium meta arsenite (30 or 40 mg L1 for 30, 45, or 60 days).

Furthermore, the drop in serum testosterone may result from direct inhibition of testosterone steroidogenesis or from Leydig cells' decreased sensitivity to luteinizing hormone (Hinshelwood et al. 1994). Significantly lower levels of steroidogenic enzyme activity in the testes of experimental mice suggest a decrease in steroidogenesis, which may in turn inhibit the male mice's ability to reproduce (Sarkar et al. 2008). Since both FSH and LH are the regulators of high steroidogenic activities, variations in their levels in plasma may be the cause of this alteration in steroidogenic enzyme activity in experimental mice (Sarkar et al., 2003). Subsequent research has demonstrated that arsenic in drinking water is linked to genotoxicity and oxidative stress in mouse testicular tissue (Biswas et al. 2006; Chang et al. 2007a, b). According to Sarkar et al. (2008), these results were shown to cause steroidogenic dysfunction, which impaired spermatogenesis. Also, low gonadotropin levels in rats treated with arsenic may be the cause of the increase in the luminal parts of the seminiferous tubules linked to decreased spermatozoa mass, as these low levels also result in decreased synthesis of steroidogenic enzymes (Sarkar et al. 2008). It is known that exposure to arsenic results in a reduction in the synthesis of testicular steroidogenic enzymes (Sarkar et al. 2008).

Interestingly, the oxidative stress induced by arsenic is strongly linked with decreased sperm quality, including motility and DNA. The damage to sperm DNA and proteins compromises the integrity and functionality of sperm, reducing their ability to fertilize an egg. Moreover, the oxidative damage to mitochondrial DNA in sperm affects ATP production further impairing sperm motility. This reduction in sperm quality and motility is one of the primary factors contributing to arsenic-induced male infertility (Li et al. 2023).

Additionally, exposure to arsenic alters spermatogenesis, resulting in a decline in sperm quality, which is associated with low sperm count and motility and increases abnormal sperm, as seen in mice exposed to arsenic (Li et al. 2023). Rats exposed to arsenic also had a much increased percentage of defective sperm and dead sperm. Arsenic has a number of detrimental effects on spermatogenesis, many of which have been thoroughly investigated in experimental animals and via epidemiological studies (Renu et al. 2018). In addition to degenerating stage VII germ cells in mice and impairing spermatogenesis, exposure to arsenic also lowers testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels (Renu et al. 2018). Likewise, exposure to arsenic causes an accumulation of the metal in soft tissues, such as rodent testes and epididymis (Dua et al. 2015).

According to studies in rodents, arsenic has been shown to have deleterious effects on testicular tissue, including marked testicular spermatogenic degeneration with decreased epithelial height and tubular diameter and increased luminal diameter by the induction of oxidative stress (Jahan et al. 2015; Uygur et al. 2016). Additionally, testicular structures gradually deteriorate as a result

of arsenic exposure. Consequently, there is a gradual but noticeable decline in testosterone levels, which affects the functional characteristics of spermatozoa and suggests that arsenic affects Leydig cells, which in turn impairs spermatogenesis. Similarly, arsenic altered the histomorphometry of the testicular architecture through oxidative stress (Souza et al. 2015). Arsenic causes oxidative stress in the testes and modifies hormone levels that are crucial for spermatogenesis, like luteinizing hormone, follicle-stimulating hormone, and testosterone (Jahan et al. 2015). According to research on exposure to arsenic, sperm motility is reduced because arsenic binds to sulfhydryl or thiol groups on sperm proteins or inhibits sperm motility-related enzymes (Li et al. 2023). Additionally, a significant number of thiol-rich protamines found in sperm nuclear chromatins and flagellum make them more vulnerable to arsenic (Behairy et al. 2024). Nonetheless, it has been speculated that one of the ROS products, H2O2, may permeate the membrane and impact the sperms' essential enzymes, reducing sperm motility (Yánez-Ortiz et al. 2021).

Arsenic exposure markedly reduced the activities of GST and CAT, although SOD levels progressively increased along with a corresponding rise in lipid peroxidation in the testes, suggesting oxidative stress. Comparable outcomes were noted when exposure to arsenic caused decreased CAT activity and increased SOD activity (Kharroubi et al., 2014). Furthermore, in Swiss albino mice, exposure to arsenic also reduces GST activity (Biswas et al. 2010). It is clear that accumulated arsenic may cause testicular architecture damage. This may occur directly when arsenic crosses the blood-testis barrier and reaches germinal cells, or indirectly through interference with spermatogenesis, which results in oxidative stress in the testicular compartment and reduced male fertility.

Arsenic and female reproductive function

Arsenic as a toxic drug can adversely affect female reproductive capacity via the induction of oxidative stress (Barsøe et al. 2021). Ovarian functions can be affected by increased production and interaction of free radicals since cyclic metabolic events take place in the ovary during the reproductive period of mammals (Erkan et al. 2021). Experimentally, the ovary of a mouse model has been previously reported to show oxidative damage following arsenic exposure (Wang et al. 2012). In that study, arsenic triggered follicular-mitochondrial dysfunction via the stimulation of p66Shc which catalyzes the formation of free radicals from mitochondrial proteins (cytochrome C) (Ommati et al. 2020a, b). Mitochondrial function is very crucial in the development and maturation of follicles, fertilization, and succeeding embryo growth, being the site for energy production (Santulli et al. 2015). An increased level of free radicals forced open transition pores on the follicular-mitochondrial membrane, breaking into the follicle cytosol to induce follicular oxidative damage (Betts et al. 2014). Arsenic caused apoptosis of oocytes via ROS-antioxidant imbalance (Agarwal et al. 2012). During oocyte maturation, surrounding granulosa cells nurse the developing oocyte via the supply of antioxidants to create ROS-antioxidant balance, and secretion of hyaluronic acid needed for fertilization (Huang and Wells 2010). Many studies on animal models and humans have reported anovulation, which weakened the body's enzymatic antioxidant defense (Budhwar et al. 2017). Arsenic downregulates ovarian glutathione levels to induce oxidative damage on the pre-antral follicle via the increased ROS interaction (Niringiyumukiza et al. 2019). Arsenic has been reported to inhibit the surrounding granulosa cell growth via the alteration of granulosa cell-related genes (*PTGS*, *TNFAIP6*, and *HAS2*). Hyaluronic Acid deficiency and meiosis abruption decrease the chances of fertilization and embryonic growth in natural conception and IVF. The inflow of generated free radicals into the oocyte's nucleus and interaction with DNA can result in the breakage of the paired strand of DNA, resulting in ovarian toxicity and consequent infertility (Kitchin 2001; Akram et al. 2018).

Arsenic has been reported to abrupt ovarian steroidogenesis via the interruption of the hypothalamo-pituitary-ovarian axis (Chen et al. 2022a, b). Arsenic increases serotonergic neurotransmission in the pre-optic area of the hypothalamus (POA). However, serotonin elevation inhibits the proliferation of GnRH neurons in the hypothalamus causing a negative feedback on the release of gonadotropins (follicle-stimulating hormone and luteinizing hormone). FSH and LH suppressions in turn inhibit ovarian steroidogenic enzymes, 3β-HSD and 17β-HSD (Rosenfield et al. 2021). In addition, arsenic-induced gonadotropin suppression may also be due to excessive secretion of glucocorticoids and catecholamines from the adrenal cortex having established their effects in gonadotropic cell resistance to GnRH (Ghosh et al. 2013). Arsenic has been reported to interrupt the estrogenic signaling pathway via alteration of estrogen-related gene expression resulting in infertility since the expression of estrogen-regulated genes in an ovary/uterus depends on the sensitivity of estrogen receptors to estrogen (Amir et al. 2021). Estrogen receptor resistance in the uterus interrupts the estrogen signaling pathway via inactivation of cell growth proteins responsible for endometrial cell proliferation (Amir et al. 2021). The expression of estradiol-regulated vascular endothelial growth factor (VEGF) genes which initiate cyclical angiogenesis in the uterus can also be downregulated by arsenic, which may be a cause for unconstrained miscarriages (Dickson and Stancel, 2000). Additionally, expression of steroidogenic factor-1 (SF-1) needed for ovarian steroid hormone synthesis could be altered by arsenic methylation

instead of DNA, affecting ovarian steroidogenesis and follicular development (Huang et al. 2020; Chen et al. 2022a, 2022b). Furthermore, arsenic exposure has been reported to induce estrogen-dependent diseases like breast and uterine cancer, and spontaneous miscarriages in humans (Amir et al. 2021). Although mechanisms of arsenic-induced hypothalamo-pituitary-ovarian axis interruption remain unclear, it was presumed to exert an opposing action on the ovary which may alter LH and FSH levels and resulting oocyte impairment (Mukherjee and Gopalakrishnan 2023). Female infertility could result from hypothalamo-pituitary-ovarian axis interruption and consequent hormonal imbalance which can be created by arsenic toxicity (Rattan et al. 2017).

In addition, arsenic exposure can significantly disrupt the hypothalamo-pituitary-ovarian (HPO) axis by interfering with the controls and release of gonadotropins (FSH and LH), which are essential for ovarian follicular development, ovulation, and the production of sex hormones like estrogen and progesterone. Arsenic also impacts estrogen signaling by altering the expression of genes involved in this pathway such as the estrogen signaling that is important for various reproductive processes (Mukherjee and Gopalakrishnan 2023). Arsenic has been shown to cause estrogen receptor (ER) resistance, particularly in the uterus by modifying the expression of estrogen-regulated genes. This resistance disrupts the normal estrogen signaling pathway leading to the inactivation of cell growth proteins essential for endometrial cell proliferation and vascularization. Specific genes affected by arsenic include the vascular endothelial growth factor (VEGF) genes which are critical for angiogenesis during the menstrual cycle and pregnancy (Mukherjee and Gopalakrishnan 2023). Additionally, arsenic alters the expression of other estrogen-related genes, such as PTGS2, TNFAIP6, and HAS2, which are involved in granulosa cell function, cumulus expansion, and hyaluronic acid production. These alterations may impair follicular development, ovulation embryo implantation, suppression of gonadotropins and ovarian steroidogenesis, and poor endometrial receptivity further contributing to infertility (Amir et al. 2021). Overall, the impact of arsenic on the HPO axis and estrogen signaling pathways underscores the importance of addressing environmental exposures in reproductive health to improve fertility outcomes and reduce the risk of reproductive disorders.

The hypothalamus is the master controller of gonadal steroid synthesis, which rhythmically releases gonadotropin-releasing hormone (GnRH) into circulation. Arsernic-induced ROS hyper-production can interrupt connections between GnRH-secreting neurons at the arcuate nucleus of the hypothalamus and gonadotropin-secreting cells inhibit pulsatile excitatory impulses for FSH and LH release (Agarwal et al. 2005). Unavailability of excitatory impulses to the gonadotropic cells of the anterior pituitary inhibits the synthesis and secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) which regulate ovarian function. Naturally, ovarian steroids (estrogen and progesterone) diminish during folliculogenesis and are constantly replenished via negative feedback on both the hypothalamus and the anterior pituitary to maintain the normal cyclical reproductive event (Spaziani et al. 2021). Also, estrogen acts as a self-stimulating steroid by exerting a positive feedback effect on granulose cells to maintain a reproductive level of estrogen. Interrupted GnRH release, diminished serum LH and FH levels, and consequential estrogen decline are accountable for arsenic-induced alterations in follicular development and maturation (Smith et al. 2003; Sarkar et al. 1991). Decreased ovarian estrogen could be attributed to arsenic-induced low LH concentrations (Kitchin 2001). Furthermore, arsenic exposure excessively triggers the pituitary-adrenocortical axis, which in turn exaggerates ACTH secretion (Liu et al. 2005). Increased level of glucocorticoids in circulation renders gonadotropic cells resistant to GnRH, and in turn, inhibits LH and FSH synthesis and release (Colognato et al. 2007). Downregulation of LH release reduces the oocytes' quantity and functions and inhibits ovulation and estrus cycle (Biswas et al. 2019). A study reported an extended menstrual cycle and infrequent menstrual flow in women following arsenic exposure (Nurminen 1995).

Oogenesis, as the process of gamete (ovum) formation in females, can be compromised during arsenic exposure. Naturally, oogonia (germ cells) undergo several changes of development before becoming mature oocytes (Gosden 2002). Oogenesis can be inhibited via the interruption of the H-P-O axis, disruption of estrogen signaling pathways by polychlorinated biphenyls, and alteration of estrogen-related genes, which have been previously reported following arsenic exposure (Rattan et al. 2017; Kang et al. 2022). Decreased primordial germ cells following arsenic exposure suggests that exposure during pregnancy can inhibit the formation of primordial germ cells from primitive steak and further interrupt their migration into the developing gonads (Legoff et al. 2019). Arsenic toxicity can impair the development, maturation, and ovulatory function of oocytes which can adversely affect female fertility (Foster and Hughes 2011). Arsenic-induced ROS influx into the follicular cytoplasm results in hypertrophy of the follicular cells and ROS interaction with the cytoplasmic components, which will in turn induce follicular oxidative damage and prevention of ovulation (Chattopadhyay et al. 2001). Arsenic toxicity also induces abnormal methylation of histone H_3 lysine 4, a marker for DNA transcription, suggesting that arsenic obstructs meiosis during oocyte maturation after puberty (Ommati et al. 2020a, b). Additionally, a study on arsenic-exposed mice reported impaired meiosis and embryo development, blastocysts'

apoptosis, and compromised blastocyst implantation which result from fertilization of arsenic-induced oxidative stressed oocytes (Navarro et al. 2004).

Potential therapies in the management of arsenic-induced reproductive toxicity

Although there is a dearth of human studies exploring possible therapeutic strategies in the management of arsenic-induced reproductive toxicity, there are compelling data from animal models (Table 1). These experimental studies provide insights into the possible mechanism of actions of various pharmacological agents and nutraceuticals in preventing and/or attenuating arsenic-induced reproductive dysfunction.

Male reproduction

Evidence of pharmacological interventions effective in arsenic-induced male reproductive dysfunction abounds in academic literature. These pharmacological interventions include phytochemicals such as *Chlorophytum borivilianum*, *Pulsatilla nigricans*, *Withania somnifera*, *Alchornea cordifolia*, and *Pistia stratiote*s and drugs like N-acetylcysteine, telmisartan, diphenyl diselenide, and melatonin. *Chlorophytum borivilianum* showed a reduction in Arsenic-induced lipid peroxidation, acid and alkaline phosphatase, and cholesterol in mouse Leydig and Sertoli cells (Sharma and Kumar 2012). It has been demonstrated that arsenic suppresses reproductive function by impairing testicular steroidogenesis and spermatogenesis via oxidative stress, lipid peroxidation, inflammation, autophagal, apoptosis, and ferroptotic mechanisms (Meng et al., 2020; Rachamalla et al., 2022). However, 30 days of co-exposure to *borivilianum* at a dose of 800 mg/kg in Swiss albino mice led to a decrease in oxidative stress evidenced by a decrease in lipid peroxidation and an increase in glutathione-mediated antioxidant defense. Co-exposure to *Chlorophytum borivilianum* improved testicular metabolic function with an associated decrease in cholesterol, alkaline phosphatase, and reproductive function with an associated increase in testosterone, sperm count, and motility (Sharma and Kumar 2012). It also hindered the degeneration of spermatogenic germ cells in the seminiferous tubules and associated cell loss (Sharma and Kumar 2012).

Oral co-exposure to extract of *Pulsatilla nigricans* for 90 days at 35 mg/kg led to an increase in levels of sorbitol dehydrogenase for sperm maturation with an associated increase in glutathione, catalase, and superoxide dismutase and a decrease in y-GT levels and lactate dehydrogenase in the testis of Charles Foster rats (Samadder et al. 2012). Similarly, *Withania somnifera* exposure at 100 mg/kg improved blood testosterone, luteinizing hormone levels, testicular histoarchitecture, spermatogenesis, sperm morphology, and libido (Kumar et al. 2015). According to Ajibade and Olayemi (2020), there was an increase in testosterone and FSH levels, sperm count, sperm motility, and the expression of anti-apoptotic B-cell-lymphoma 2 and androgen receptor binding protein following 30-day oral administration of *Alchornea cordifolia* at 100 ug/kg also known as water cabbage. *Pistia stratiotes* exerts protective effects on the testicular function of rats by restoring sperm count, semen volume, sperm viability, and motility following oral administration for 14 days at a dose of 100 mg/kg (Ola-Davies and Oloye 2019). Laboratory investigation in mice showed that N-acetylcysteine administered intraperitoneally at 75 mg/kg supports testicular function by decreasing oxidative stress and lipid peroxidation while increasing the activity of testicular enzymes 3β- and 17β-dehydrogenase and levels of testicular testosterone (Reddy and Roth 2013). The increased testosterone led to an increase in sperm quality, motility, and the weight of reproductive organs. Further, telmisartan was demonstrated to have ameliorative effects on testicular dysfunction following exposure to arsenic (Fouad et al. 2015). Administration of telmisartan markedly decreased testicular concentrations of malondialdehyde, and nitric oxide while decreasing the activity of myeloperoxidase and expression of the TNF-α, NFKB, COX-2, VEGF, and caspase 3 (Fouad et al. 2015). Therefore, telmisartan improves testicular function in arsenic-exposed rats by decreasing lipid peroxidation, inflammation, and caspase 3–dependent apoptosis.

In mice, exposure to diphenyl diselenide (DPDS) at 2.5 mg kg for 45 days improved deficits in reproductive function by abrogating testicular oxidative stress, inflammation, and caspase 3–dependent apoptosis (Adedara et al. 2019). This is evidenced by improved oxidative status and testosterone and decreased activity of myeloperoxidase, caspase 3, and levels of TnF-α, nitric oxide, and interleukin 1B levels (Adedara et al. 2019). Exposure to DPDS increased sperm parameters and ameliorated arsenic-induced histological lesions (Adedara et al. 2019). Melatonin counteracted arsenic-medicated testicular lipid peroxidation, redox imbalance, germ cell apoptosis, and histological degeneration when administered intraperitoneally and intragastrically in rats (Uygur et al. 2016). Ethanol extract of *Chromolaena odorata* at 200 mg/kg increased reproductive organ weights, endocrine properties, and sperm parameters in Wistar rats (Ola-Davies and Oloye 2019).

Ascorbic acid has been demonstrated to exert antioxidant effects ameliorating the impairment of testicular functions following arsenic exposure for 5 weeks in mice (Im chang et al. 2007). There was an increase in testicular weights on oral co-administration of ascorbic acid. It also reversed the

Table 1 Therapeutic potentials that mitigate arsenic-induced reproductive toxicity

Therapeutic method	Model	Effect	Drug duration	Health impact	Reference
DMSA (Succimer)	Human	Increased urinary arsenic excretion, improved semen parameters	4 weeks	Improved male fertility	Ahsan et al. (2006)
Diphenyl diselenide (DPDS)	Mice	Improved deficits in reproductive function by abrogating testicular oxidative stress, inflammation, and caspase 3–dependent apoptosis	45 days	Increased sperm parameters and ameliorated arsenic-induced histological lesions	Adedara et al. 2019
Antioxidant supplementation					
Chlorophytum borivilianum	Mice	Enhanced antioxidant defenses, protected against DNA damage and testicular toxicity	30 days	Prevented arsenic-induced testicular impairment	Sharma and Kumar, (2012)
Pulsatilla nigricans	Mice	Prevent cellular dysfunction in testes of male mice	90 days	Prevent arsenic-induced cellular dysfunction in the testes	Samadder et al. 2012
Withania somnifera	Rat	Enhanced antioxidant defenses, protected testicular toxicity	30 days	Foster testicular functions by improving blood testosterone, luteinizing hormone levels, testicular histoarchitecture, spermatogenesis, sperm morphology, and libido	Kumar et al. 2015
Alchornea cordifolia leaf	Rat	Increase in testosterone and FSH levels, sperm count, sperm motility	30 days	Improved male fertility	Ajibade and Olayemi (2020)
N-acetylcysteine	Mice	Supports testicular function by decreasing oxidative stress and lipid peroxidation, while increasing the activity of testicular enzymes 3β- and 17β-dehydrogenase and levels of testicular testosterone	35 days	Increase serum testosterone level, sperm quality, motility, and the weight of reproductive organs	(Reddy and Roth 2013
Telmisartan	Rat	Decreased testicular concentrations of malondialdehyde and nitric oxide while decreasing the activity of myeloperoxidase, expression of the TNF-α, NFKB, COX-2, VEGF, and caspase 3	14 days	Prevent testicular dysfunction and improve testicular functions	Fouad et al. 2015
Melatonin	Rat	Decreased testicular lipid peroxidation, redox imbalance, germ cell apoptosis, and histological degeneration	30 days	Prevent testicular dysfunction and improve testicular functions	Uygur et al. 2016
Quercetin	Rat	Increased antioxidant enzymes, improved spermatogenesis	15 days	Reversed arsenic-induced testicular damage	Baltaci et al. 2016
Chromolaena odorata	Rat	Increased reproductive organ weights, endocrine properties, and sperm parameters	12 weeks	Prevent testicular dysfunction and improve testicular functions	Ola-Davies and Oloye 2019
Ellagic and ferulic acids	Mice	Restored deficits in testosterone levels, and sperm parameters: sperm concentration, motility, structural membrane integrity, and mitochondrial membrane potential	40 days	Protected against arsenic-induced reproductive impairment	Guvvala et al. (2017)
Acetate	Rat	Prevent disrupted testicular disruption and testicular damage		Suppressing HDAC and uric acid–driven oxido-inflammatory NF*k*B/iNOS/NO response	Besong et al. 2023a, b
Ascorbic acid	Mouse	Prevent the impairment of testicular functions	5 weeks	Increase testicular weights and reversed the activities of steroidogenic enzymes 3β-HSD and 17B-HSD, epididymal sperm counts, and testicular oxidative imbalance	Im Chang et al. 2007

Table 1 (continued)

Therapeutic method	Model	Effect	Drug duration	Health impact	Reference
D-ribose-L-cysteine	Rat	Ameliorated the distortion of testicular morphology, oxidative stress, and impaired semen quality while increasing hormone concentrations	28 days	Ameliorated arsenic-induced ovarian toxicity	Ogunlade et al. 2021
Fisetin	Rat	Increased secretion of T, LH, and FSH and increase in sperm count, motility, sperm morphology	56 days	Ameliorated arsenic-induced reproductive toxicity	Ijaz et al. 2023
Ellagic and ferulic acids	Mice	Increase in sperm kinematics and increased expression of StAR, Ppargc1a, and Nfe212	40 days	Significantly reduced the accumulation of As, protein carbonylation (PC), and lipid peroxidation (LPO) in addition to altering the antioxidant enzymes (CAT and SOD) activities, reduced glutathione (GSH) and total antioxidant capacity (TAC) in the testicular tissues	Guvvala et al. 2019
Grape seed proanthocyanidin	Mice	Mitigates oxidative damage and inhibits Nrf2	5 weeks	Ameliorates reproductive toxicity	Li et al. 2015
Vitamin B	Rat	Mitigated arsenic-mediated reproductive injury by preventing abundant generation of free radicals		Mitigate arsenic-induced reproductive damage	Deb 2021
Momordica charantia		Decrease uterine oxidative stress and lipid peroxidation	8 days	Ameliorated arsenic-induced ovarian toxicity and damage	Perveen and Chattopadhyay 2024
N-acetyl cysteine	Rat	Inhibited the inflammatory condition following the inflammatory reaction to diminish the progression of ovarian-uterine apoptosis		Mitigate arsenic-induced ovarian toxicity and promote ovarian steroidogenesis and function	Dash 2021

activities of steroidogenic enzymes 3β-HSD and 17B-HSD, epididymal sperm counts, and testicular oxidative imbalance (Im chang et al. 2007).

Beyond that, this acetate has been shown to modulate metabolic processes to support reproductive function in Wistar rats (Besong et al. 2023b). Acetate inhibits histone deacetylation and oxidative and inflammatory changes to cause an increase in the activities of 3B-HSD and 17B-HSD and levels of GnRH, LH, FSH, and T. The increase in testicular steroidogenesis led to improved sexual behavior (Besong et al. 2023b). Guvvala et al. (2017) investigated the effects of green tea extract on arsenic intoxicated in Swiss albino mice. Acute exposure to epigallocatechin-3-gallate restored deficits in testosterone levels and the following sperm parameters: sperm concentration, motility, structural membrane integrity, and mitochondrial membrane potential. It also restored lipid peroxidation changes and oxidative imbalance by scavenging free radicals with the abundance of hydroxyl bases (Guvvala et al. 2017). It also mediates antioxidant changes by inhibiting the generation of hydroxyl radicals, superoxide, and hydrogen peroxide (Guvvala et al. 2017).

Ogunlade et al. (2021) described the potentiating response of D-ribose-L-cyteine on sodium arsenic-induced endocrine alterations, spermatogenic deficits, and histomorphometric abnormalities in rats exposed to 30 mg/kg for 28 days. D-ribose-L-cysteine ameliorated the distortion of testicular morphology, oxidative stress, and impaired semen quality while increasing hormone concentrations (Ogunlade et al. 2021).

Fisetin is a bioactive flavonoid with strong antioxidant effects on rat testes. Treatment with FIS resulted in significant improvement in an arsenic-induced decrease in enzyme antioxidant defense while decreasing metabolic alterations evidenced by decreased cholesterol, low-density lipoprotein, and triglycerides and increased high-density lipoprotein. These have a stimulatory effect on the expression of steroidogenic enzymes 3B-HSD, 17B-HSD, STAR, CYP11A1, and CY17A1 to cause increased secretion of T, LH, and FSH and associated increase in sperm count, motility, and sperm morphology. This is characterized by attenuation of histoarchitectural degenerative changes and decreased caspase-3, Bax, and Bcl-2 (Ijaz et al. 2023).

Ellagic and ferulic acids exert protective effects on Swiss albino mice at 40 mg/kg after exposure for 40 days causing a decline of lipid peroxidation and protein carbonylation, with an associated increase in sperm kinematics and increased expression of StAR, Ppargc1a, and Nfe212 (Guvvala et al. 2019). Laboratory investigation of the effect of grape seed proanthocyanidin on arsenic-induced reproductive toxicity in male mice showed that administration of the extract improved oxidative stress, Nrf2, and NADPH. This suggests that the extract counteracts arsenic-induced reproductive toxicity by mitigating oxidative damage and inhibiting Nrf2 (Li et al. 2015).

Female reproduction

Vitamin B and folic acid have also been demonstrated to be protective agents against arsenic-induced reproductive toxicity in female rats. At doses 0.07 µg and 4.0 µg respectively/100 g b.wt./day, they mitigated the disorganization of uteroovarian histoarchitecture, disruption of female gonadal function, ROS generation, and DNA fragmentation (Deb et al., 2021). In another study, Peerveen et al. (2024) showed that pectic polysaccharide (CCPS) from *Momordica charantia* administered for 8 days at varying oral doses of 1.5, 2.0, and 2.5 mg/kg led to a decrease in uterine oxidative stress and lipid peroxidation evidenced by decreased MDA and increased activities of CAT and SOD (Perveen and Chattophadhayy 2024). The study demonstrated that CCPS has chelating properties which ameliorated arsenic-induced ovarian toxicity and damage (Perveen and Chattophadhayy 2024).

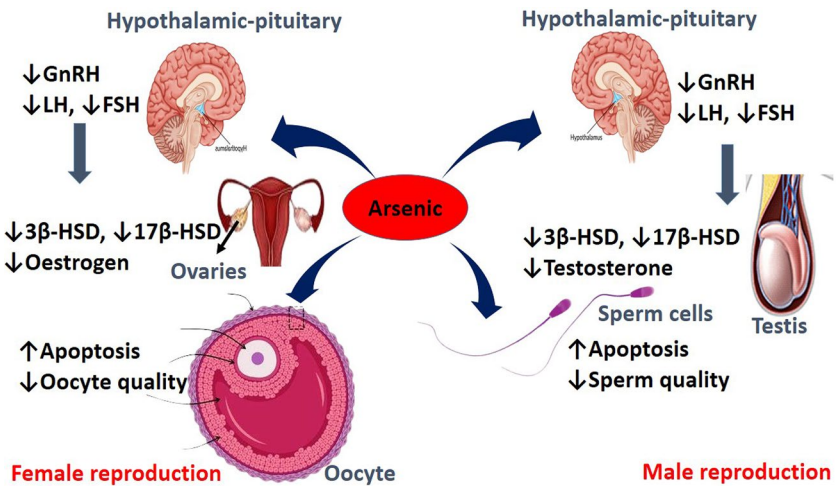

Fig. 1 Schematic illustration of the impact of arsenic exposure on male and female reproduction. Arsenic exposure promotes reactive oxygen species (ROS) generation and induces oxidative stress, which suppresses the hypothalamic-pituitary–gonadal axis and inactivates 3β-HSD and 17β-HSD. This leads to reduced gonadal steroidogenesis and apoptosis of oocytes and sperm cells, thus contributing to the development of infertility

Similarly, dietary N-acetyl cysteine (NAC) at 250 mg/kg has also been shown to demonstrate chelation properties in arsenic-induced reproductive dysfunction rat model (Dash 2021). NAC caused a decrease in the structural disintegration of ovarian-uterine tissues while increasing antioxidant enzymatic activities and gonadotropin's utility (rise in LH, FSH) significantly favoring ovarian steroidogenesis. It also inhibited the inflammatory condition following the arsenication inflammatory reaction to diminish the progression of ovarian-uterine apoptosis (Dash 2021).

Modal et al. (2013) demonstrated that a high protein diet prevents female reproductive toxicity and damage due to arsenic in a 30-day long exposure duration. Arsenic exposure led to a reduction in ovarian and uterine weight, utero-ovarian degeneration, ovarian DNA damage, and a decrease in ovarian activities of steroidogenic enzymes 3β-hydroxysteroid dehydrogenase and 17β-hydroxysteroid dehydrogenase leading to decreased serum estradiol level via an oxidative stress and lipid peroxidation. However, consumption of a high protein diet showed effective protection against these observations with associated optimum antioxidant defense.

Conclusion and future perspectives

Convincing data from the literature demonstrate that arsenic exposure promotes ROS generation and induces oxidative stress. This suppresses the hypothalamic-pituitary–gonadal axis and inactivates 3β-HSD and 17β-HSD, leading to reduced gonadal steroidogenesis and spermatogenesis. This cascade of events triggers the apoptosis of oocytes and sperm cells, thus contributing to the development of infertility (Fig. 1). More so, there are increasing data that reveal the benefits of antioxidants in ameliorating arsenic-induced reproductive toxicity. These molecules suppress ROS generation and maintain optimal activities of the hypothalamic-pituitary–gonadal axis, resulting in adequate steroidogenesis and gametogenesis as well as improved germ cells. However, more experimental studies exploring other possible pathways through which arsenic may mediate its reproductive toxicity is recommended. Also, clinical trials validating the therapeutic values of potential drug candidates in the management of arsenic-induced reproductive toxicity should be conducted.

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Data availability Data will be made available on request.

Declarations

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