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Arsenic – Toxic to Female Reproductive Activity: A Review

Review Article

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Abstract

One common metalloid and heavy metal that contributes significantly to the global decline in human fertility is arsenic. Arsenic and its compounds are known to be extremely toxic and to pollute the environment. Humans are constantly exposed to arsenic from both biological and non-biological sources, especially when they eat or drink arsenic-contaminated food or water. Reproductive toxicity is one of the many detrimental health effects associated with such exposure. Arsenic exposure is still a problem worldwide, despite the known negative effects. Thus, the purpose of this study is to present a comprehensive analysis of the body of research on the impacts and processes through which arsenic affects female reproductive function.

Keywords: Arsenic; Infertility; Toxicity

Introduction

Metalloids and heavy metals, such as mercury, chromium, cadmium, lead, and arsenic, are commonly encountered by humans and pose a threat to the ecosystem because they are major contaminants of the air, water, food, and soil [1]. Arsenic is known to be the most potent environmental toxin among these heavy metals, affecting both plant and animal life [2]. Because of its pervasiveness and harmful health effects, arsenic has significant global health implications. Arsenic, which is found naturally in the crust of the Earth, can enter drinking water supplies through leaching, erosion, and mining operations. In Asia (Bangladesh, China, India, Inner Mongolia, and Taiwan), Europe (Hungary), and the Americas (Argentina, Chile, Mexico, and portions of the northeastern and western regions), elevated levels of arsenic in water have been reported. Arsenic is absorbed into the tissues of crops and vegetables that are grown in soil that contains arsenic or that are irrigated with water that contains arsenic. Arsenic is also used in the manufacturing of glass, pesticides, herbicides, semiconductors, medications, and wood preservatives.

As a result, exposure to arsenical pesticides and herbicides, eating food tainted with arsenic, and breathing in arsine in industrial settings can all raise intake of arsenic [3]. Since the bioavailability (the actual amount absorbed into the bloodstream) of arsenic from water is higher than that from grains or vegetables, drinking water is the main way that the general public is exposed to arsenic (NationalResearch Council,2001). This is a more dangerous exposure than food-based arsenic [3]. Furthermore, seafood primarily contains organic forms of arsenic, such as arsenobetaine, whereas drinking water primarily contains inorganic forms. In general, the organic forms of arsenic are thought to be less harmful than the inorganic ones [4].

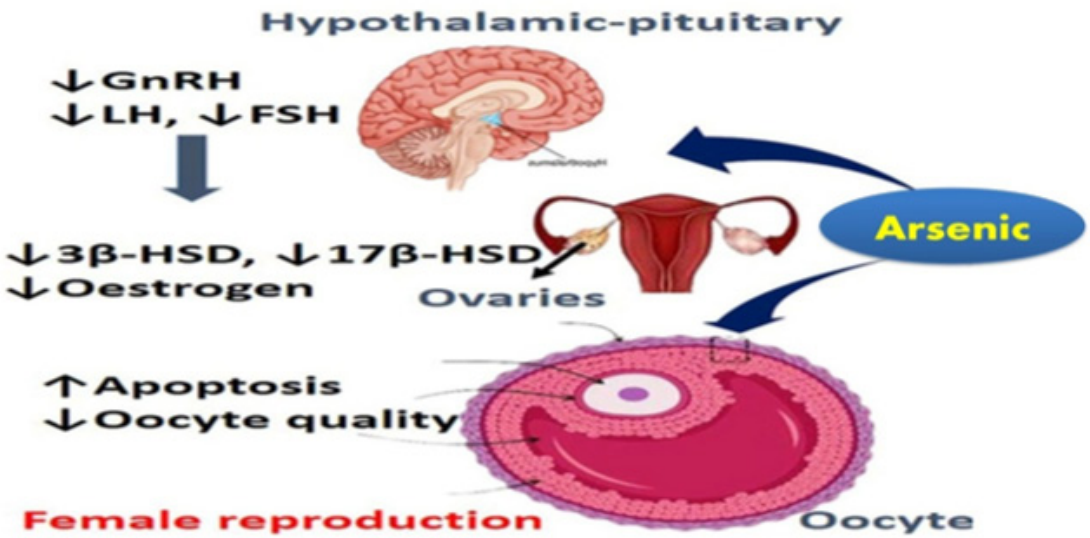
In early studies, arsenic administered intraperitoneally (i.p.) or intravenously (i.v.) during the early stages of pregnancy caused fetal malformations in rats and mice [5]. At levels that were either maternally toxic or nearly lethal, both inorganic and methylated forms of arsenic caused developmental toxicity. In contrast, neither mice nor rats showed appreciable fetal malformations as a result of a single or repeated oral exposure to inorganic arsenic [6]. In both species, repeated oral administration of dimethylarsinic acid was linked to decreased fetal weight and increased resorptions at toxic doses to the mother [7]. Rogers et al. (1981) reported a higher incidence of cleft palate in mice, but no significant abnormalities were observed in the rats [7]. Additionally, inhalation of inorganic arsenic or arsine did not result in developmental toxicity [8].

To sum up, the studies mentioned above only found developmental toxicity caused by arsenic at levels that were harmful to the mother. Research on the toxicity of arsenic to reproduction and development has expanded over the last five years to include a wider range of endpoints and more human-relevant exposure scenarios. Notably, recent studies on arsenic used repeated or prolonged oral exposures, either through drinking water or gavage methods, in compliance with the US Food and Drug Administration's (US FDA) Guidelines for Develop-

mental Toxicity Studies [9]. In addition, the studies looked at non-gross developmental endpoints like brain development, behavioral outcomes, and molecular events as well as reproductive endpoints. Results showed that even at levels that are not harmful to the mother, prolonged exposure to arsenic may cause developmental toxicity. For example, it has been demonstrated that fetal brain development and newborn rat behaviors are affected when mothers are exposed to inorganic arsenic in drinking water during pregnancy [10].

Because of both natural and man-made processes, arsenic, a naturally occurring element in the earth's crust, is widely present in the environment [11]. According to recent research, arsenic exposure can seriously impair the reproductive system [12]. Furthermore, it is crucial to understand that arsenic affects the female reproductive system by altering specific steroidogenesis-related regulatory enzymes, including 3β-hydroxysteroid dehydrogenase (3-βHSD) and 17β-hydroxysteroid dehydrogenase (17βHSD), which is linked to lower gonadotropin levels [13]. Additionally, changes in neurotransmitter levels have been noted, including decreased gonadotropin secretion and decreases in luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol [14].

Graphical abstract



Methods

This research was founded on data obtained from the Scientific Literature, which was gathered through a search performed across the following databases: PubMed, EMBASE, Scopus, and Google Scholar.

Arsenic

It is unclear and has not been thoroughly investigated how arsenic (As) affects female reproductive function. Females exposed to arsenic through the air or drinking water had theirreproductive effectsexamined. They investigated the connection between oxidative damage during pregnancy andexposure to arsenic from a copper smelter area in Bulgaria [15]. Areas with the highest environmental contamination had the highest levels of arsenic in placental tissue, and pregnant women who were exposed were more likely to experience oxidative damage during pregnancy. They looked into the connection between spontaneous abortion and the quality of the drinking water in the community [16]. Regular analyses of the public tap water supplies in the areas where the pregnant women lived were used to determine the type and concentration of trace elements. High levels of arsenic were linked to a higher incidence of spontaneous abortion after controlling for potential confounders. The evaluation of environmental arsenic exposures and the examination of confounders, such as race, ethnicity, maternal age, median income, and parity, were part of a case-control study of stillbirths [17]. The group that was exposed to the most arsenic had a statistically significant higher risk of stillbirth. Subsequent investigation revealed that the increase was specific to Hispanic individuals, potentially due to a genetic deficit in the metabolism of folate.

Nevertheless, this study did not account for possible confounding exposures to other chemicals, had few cases in the high-exposure group, and lacked smoking data. The studies on the effects of arsenic on reproduction as a whole have drawn criticism for failing to measure exposure to arsenic and other metals sufficiently and failing to account for other possible confounding factors [18]. Schroeder and Mitchener's multigenerational experimental study found no evidence of reduced fertility in female rats exposed to drinking water containing arsenate on a regular basis [19]. In two additional studies, female rats gavaged with trivalent arsenic from 14 days prior to mating through gestation showed no change in reproductive functions (such as precoital interval, mating index, and fertility index) [20].

Female mice exposed to monomethyl arsenic acid before mating and during pregnancy showed some effects, such as producing fewer litters than usual; however, these effects were primarily caused by the males' decreased fertility [21]. Additionally, rats given daily gavages of arsenic (prior to mating and throughout pregnancy) had significantly higher skeletal malformations and significantly lower fetal body weights, which the researchers believed to be the results of growth retardation. The number of resorptions per litter and the mean fetal weight and number of live pups per litter were significantly reduced in mice treated with arsenic acid. However, at the same or lower doses as those causing developmental effects, overt maternal toxicity [including death] was discovered.

Arsenic and Female Reproductive Function

As a poisonous substance, arsenic can negatively impact a woman's ability to conceive by causing oxidative stress [23]. Since the ovary undergoes cyclic metabolic events during the mammalian reproduct-

ive period, elevated production and interaction of free radicals can impact ovarian functions [24]. It has previously been reported that oxidative damage occurs in the ovary of a mouse model after exposure to arsenic [25]. In that study, arsenic stimulated p66Shc, which catalyzes the production of free radicals from mitochondrial proteins [cytochrome C], causing follicular-mitochondrial dysfunction [26,27]. As the site of energy production, mitochondria play a critical role in follicle development and maturation, fertilization, and subsequent embryo growth [28].

Increased free radical concentrations induced follicular oxidative damage by forcing open transition pores on the follicular-mitochondrial membrane and penetrating the follicle cytosol[29]. Through ROS-antioxidant imbalance, arsenic caused oocytes to undergo apoptosis [30]. The surrounding granulosa cells support the maturing oocyte by secreting hyaluronic acid, which is necessary for fertilization, and by providing antioxidants to maintain ROS-antioxidant balance [31]. Anovulation has been shown in numerous human and animal model studies to impair the body's enzymatic antioxidant defense [32]. Through the enhanced ROS interaction, arsenic causes oxidative damage to the pre-antral follicle by downregulating ovarian glutathione levels [33]. By changing genes linked to granulosa cells (PTGS, TNFAIP6, and HAS2), arsenic has been shown to suppress the growth of nearby granulosa cells. Meiosis abruption and a lack of hyaluronic acid reduce the likelihood of fertilization and embryonic growth in both natural conception and IVF. When produced free radicals enter the nucleus of the oocyte and interact with DNA, they can cause the paired strands of DNA to break, which can lead to ovarian toxicity and infertility [34].

By disrupting the hypothalamo-pituitary-ovarian axis, arsenic has been shown to cause an abrupt ovarian steroidogenesis [35,36]. In the hypothalamic pre-optic region (POA), arsenic elevates serotonergic neurotransmission. The release of gonadotropins (folliclestimulating hormone and luteinizing hormone) is negatively impacted by serotonin elevation, which suppresses the growth of GnRH neurons in the hypothalamus. The ovarian steroidogenic enzymes 3β-HSD and 17β-HSD are subsequently inhibited by suppressions of FSH and LH [37].

Furthermore, excessive glucocorticoid and catecholamine secretion from the adrenal cortex, which has been shown to have an impact on gonadotropic cell resistance to GnRH, may also be the cause of arsenic-induced gonadotropin suppression [38]. Since the expression of estrogen-regulated genes in an ovary or uterus depends on the sensitivity of estrogen receptors to estrogen, arsenic has been shown to disrupt the estrogenic signaling pathway by changing the expression of genes related to estrogen, which leads to infertility [39]. By deactivating the cell growth proteins that promote the proliferation of endometrial cells, estrogen receptor resistance in the uterus disrupts the estrogen signaling pathway [39]. Unconstrained miscarriages may result from arsenic's downregulation of the expression of vascular endothelial growth factor (VEGF) genes that are regulated by estradiol and that start cyclical angiogenesis in the uterus [40].

Furthermore, arsenic methylation rather than DNA may change the expression of steroidogenic factor-1 (SF-1), which is required for the synthesis of ovarian steroid hormones, affecting follicular development and ovarian steroidogenesis [35,36]. Additionally, it has been documented that exposure to arsenic causes spontaneous miscarriages in humans as well as estrogen-dependent illnesses like uterine and breast cancer [39]. Although the exact mechanisms underlying the disruption of the hypothalamo-pituitary-ovarian axis caused by arsenic are still unknown, it was thought to have an opposing effect on the ovary that could change the levels of LH and FSH and impair oocyte function [40]. The disruption of the hypothalamo-pituitary-ovarian axis and the ensuing hormonal imbalance, which can be brought on by arsenic toxicity, may cause infertility in women [41].

Furthermore, by interfering with the regulation and release of gonadotropins (FSH and LH), which are necessary for ovarian follicular development, ovulation, and the synthesis of sex hormones like estrogen and progesterone, exposure to arsenic can significantly disturb the hypothalamo-pituitary-ovarian (HPO) axis. By changing the expression of genes involved in this pathway, including the estrogen signaling that is crucial for different reproductive processes, arsenic also affects estrogen signaling [40]. By altering the expression of genes regulated by estrogen, arsenic has been demonstrated to induce estrogen receptor (ER) resistance, especially in the uterus. Cell growth proteins necessary for endometrial cell proliferation and vascularization are rendered inactive as a result of this resistance's disruption of the regular estrogen signaling pathway.

Vascular endothelial growth factor (VEGF) genes, which are essential for angiogenesis during the menstrual cycle and pregnancy, are among the specific genes impacted by arsenic [40]. Arsenic also changes the expression of other estrogen-related genes that are involved in granulosa cell function, cumulus expansion, and hyaluronic acid production, including PTGS2, TNFAIP6, and HAS2. These changes may further contribute to infertility by affecting follicular development, ovulation embryo implantation, gonadotropin and ovarian steroidogenesis suppression, and poor endometrial receptivity [39]. All things considered, arsenic's effects on the HPO axis and estrogen signaling pathways highlight how critical it is to address environmental exposures in reproductive health in order to enhance fertility and lower the risk of reproductive disorders.

The gonadotropin-releasing hormone (GnRH) is rhythmically released into the bloodstream by the hypothalamus, which is the primary regulator of gonadal steroid synthesis. Gonadotropin-secreting cells block pulsatile excitatory impulses for the release of FSH and LH, and arsernic-induced ROS hyperproduction can disrupt connections between GnRH-secreting neurons at the hypothalamic arcuate nucleus [42]. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which control ovarian function, are not synthesized or secreted when excitatory impulses are not available to the anterior pituitary's gonadotropic cells. In order to preserve the typical cyclical reproductive event, ovarian steroids (progesterone and estrogen) naturally decrease during folliculogenesis and are continuously restored by negative feedback on the anterior pituitary and hypothalamus [43].

Additionally, estrogen maintains a reproductive level of estrogen by acting as a self-stimulating steroid through a positive feedback effect on granulose cells. Arsenic-induced changes in follicular development and maturation are caused by disrupted GnRH release, decreased serum levels of LH and FH, and a resulting decrease in estrogen [44]. Low LH concentrations brought on by arsenic may be the cause of decreased ovarian estrogen [45]. Additionally, excessive exposure to arsenic activates the pituitary-adrenocortical axis, which in turn causes an increase in the secretion of ACTH [46]. A higher blood level of glucocorticoids makes gonadotropic cells resistant to GnRH, which in turn prevents the production and release of LH and FSH [47]. Ovulation and the estrus cycle are inhibited, and the number and functions of oocytes are decreased when LH release is downregulated [48]. After being exposed to arsenic, a study found that women experienced an extended menstrual cycle and infrequent menstrual flow [49].

When exposed to arsenic, oogenesis-the process by which females form gametes, or ovums-can be hampered. Naturally, before developing into mature oocytes, oogonia [germ cells] go through a number of developmental stages [50]. As has been previously documented after arsenic exposure, oogenesis can be inhibited by disrupting the H-P-O axis, altering genes related to estrogen, and disrupting estrogen signaling pathways by polychlorinated biphenyls [51]. Reduced primordial germ cells after arsenic exposure implies that pregnancy-related exposure may prevent primordial germ cells from forming from primitive steak and further impede their migration into the growing gonads [52]. The development, maturation, and ovulatory function of oocytes can all be negatively impacted by arsenic toxicity, which can have an adverse effect on female fertility [53].

When ROS are introduced into the follicular cytoplasm by arsenic, the follicular cells enlarge and interact with the cytoplasmic components, causing oxidative damage to the follicles and preventing ovulation [54]. Additionally, aberrant methylation of histone H3 lysine 4, a marker for DNA transcription, is induced by arsenic toxicity, indicating that arsenic inhibits meiosis during oocyte maturation following puberty [26,27]. Furthermore, a study conducted on mice exposed to arsenic revealed that fertilization of arsenic-induced oxidatively stressed oocytes results in impaired meiosis and embryo development, blastocyst apoptosis, and compromised blastocyst implantation [55] (Table 1).

Table 1: Arsenic mediated toxicity in the female reproductive system.

Animal model	Treatment	Observation	Reference
Sprague-Dawley rats	50, 100, and 200 ppm of arsenic were 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.	[56]
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.	[57]
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.	[58]
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.	[59]
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.	[60]
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.	[61]

Conclusion

Arsenic and its compounds are known to be toxic, as evidenced by compelling data from the literature. To illustrate the chemical's toxicological effects, this review focuses on research on the harmful effects of arsenic and its compounds on various animal models with a human reference. The types and severity of arsenic-induced reproductive toxicity are significantly influenced by the forms of arsenic and the routes of administration.

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Author contribution

PVR Conceptualization, design, Investigation: Methodology, Writing-original draft and Validation. MSR Supervision, Writing-review

and editing and final approval. All authors reviewed and approved the final draft.

Conflict of interest

The authors declared no conflicts of interest.

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Data availability

Data will be made available on request.

Consent to participate

N/A.

Consent for publication

All authors consented to the submission and publication of the manuscript.

Conflict of interest

The authors declare no competing interests.

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