Research Article

Ameliorative Potential of Selenium Against Arsenic-Induced Interrupted Reproductive Cycle and Pregnancy Loss of Swiss Albino Female Mice

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Abstract | Arsenic, a major environmental contaminant, is closely linked to female reproductive dysfunction due to its role as an endocrine disruptor, potentially affecting reproductive outcomes and offspring health later in life. Although the exact mechanisms remain unclear, sodium selenite (Na_2SeO_3), a known antioxidant, has shown promise in mitigating the toxicity induced by sodium arsenite ($NaAsO_2$). This study aimed to investigate the protective effect of Na_2SeO_3 on $NaAsO_2$-induced disruptions in reproductive cyclicity and early pregnancy outcomes in female mice. Initially, estrous cyclicity was assessed, and results indicated that Na_2SeO_3 effectively reduced the cycle disruptions caused by $NaAsO_2$. Subsequently, pregnancy initiation was evaluated on gestational day 12.5 by examining the presence of conceptuses and placental formation. Mice treated with Na_2SeO_3 displayed a significantly higher number of conceptuses ($p < 0.01$) compared to the $NaAsO_2$-only group, suggesting a protective effect against arsenic-induced pregnancy loss. Anatomical evaluation of conceptuses, placentas, and embryos revealed normal development across all groups, except for a rare occurrence of monochorionic-diamniotic twins in the Na_2SeO_3-treated group. These findings suggest that sodium selenite may serve as a potential therapeutic agent to counteract arsenic-induced reproductive toxicity.

Keywords | Sodium-arsenite, Sodium-selenite, Estrous cycle, Pregnancy, Placenta, Water pollution, Heavy metal

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INTRODUCTION

Arsenic pollution is a serious public health concern globally that severely affects Bangladesh (Flanagan *et al.*, 2012). Millions of people appear to be regularly exposed to arsenic due to arsenic-contaminated groundwater around the world, particularly in Bangladesh, Mexico, Taiwan, and India (Akter *et al.*, 2022). The primary source of water in Bangladesh comes from underground sources, primarily tube wells, and 50% of the water from those sources has been found to have arsenic levels over the permissible limit of 0.05 mg/L for Bangladesh

(Ahmad *et al*., 2001). Continuing exposure and subsequent consumption of arsenic by food, inhalation, or skin contact causes arsenicosis and may ultimately result in poisoning (Orosun, 2021). Long-term exposure to arsenic is linked to an increased risk of several malignancies (Choudhury *et al*., 2018), including skin, lung, bladder, and kidney cancer, in addition to its cancer-causing effects, prolonged exposure to arsenic has also been linked to developmental problems, cardiovascular illness, neurotoxicity, diabetes, gastrointestinal problems, hormone disruption, ovarian and uterine disorders, and infertility (Basher *et al*., 2024; Chattopadhyay *et al*., 2003). Inorganic arsenic is considered an endocrine disruptor (Davey *et al*., 2008), thus exerting several deleterious effects on reproduction and development (Rami *et al*., 2022). Epidemiological studies showed that chronic exposure to inorganic arsenic gives rise to spontaneous abortion, stillbirth, pre-term birth, neonatal death, and infant mortality in the human placenta (Quansah *et al*., 2015), the multifunctional exchange of nutrients between mother and fetus is indispensable for the growth and survival of embryo (Wang and Wang, 2018) which further reflects on post-natal growth and development. The placenta is more susceptible to arsenic contamination, as it crosses the placenta (Milton *et al*., 2017). Additionally, disrupted placental development is associated with numerous pregnancy complications, namely miscarriage, preeclampsia, and intrauterine growth restriction (Norwitz, 2006). It is now apparent that chronic arsenic exposure disrupts placenta formation as well as fetal postnatal development (Rychlik *et al*., 2024), both in humans and animals. Arsenic is known to produce oxidative stress (Flora, 2011). According to several research fields (El-Demerdash *et al*., 2009), oxidative damage was a factor in arsenic poisoning (Flora, 2011). It has been shown that the primary cause of oxidative damage is the formation of too many reactive oxygen species (ROS), particularly superoxide anions and hydroxyl radicals (Kitchin and Ahmad, 2003; Liu *et al*., 2001). These reactive species generated by arsenic are responsible for increased cellular oxidative stress and result in oxidative DNA damage and apoptosis (Yedjou *et al*., 2010). To lessen the toxicity caused by arsenic, antioxidants have been suggested as having possible benefits. Selenium is a potent antioxidant, and its presence can help neutralize the harmful effects of reactive oxygen species (ROS) that arsenic exposure can induce (Zwolak, 2020). The antioxidant trace element selenium is necessary for human health. The fact that selenium is found near numerous antioxidant enzymes' active sites, including glutathione peroxidase (GPx) and thioredoxin reductase, in the cell, is the most compelling proof of its activity. Free radical damage is known to be reduced by GPx, and the number of reactive metabolites caused by arsenic is also known to be reduced. The toxicity carried on by arsenic may thus be mitigated by selenium. Numerous research has demonstrated that selenium is crucial in reducing liver cell damage caused by hepatotoxic agents like arsenic (Messarah *et al*., 2012). Though we have extensive knowledge of the antioxidative and protective effects of selenium, there is a lack of similar information available on the alleviation of arsenic-induced reproductive toxicity using selenium (Jalaludeen *et al*., 2014). There have been no studies on the potential of selenium to protect against arsenic-induced abnormal placental development as well as the abnormal cyclicity of estrous, which may apply to humans and animals. Based on prior studies, we hypothesize that sodium selenite may serve as a potential protective agent against arsenic-induced disruptions in the reproductive cycle and pregnancy loss in Swiss albino mice. The protective role of selenium against arsenic toxicity both in humans and animals is of ecological significance as arsenic and selenium commonly coexist in the environment and are often both present in anthropogenic discharges. Thus, the present study aimed to investigate the ameliorative effect of sodium selenite on sodium arsenite-induced reproductive cyclicity and placenta formation. To the best of our knowledge, this is the first study to examine the effects of inorganic arsenic on reproductive cyclicity and placental development in Swiss albino female mice. Furthermore, it explores the potential ameliorative role of selenium supplementation in mitigating these effects.

MATERIALS AND METHODS

Selection, housing, and care of the experimental animals

Female Swiss albino mice of 5-6 weeks of age were acquired from the International Center for Diarrheal Disease Research, Bangladesh (icddr, b), and they were acclimated to laboratory conditions at the laboratory animal facilities of the Department of Genetics and Animal Breeding at Hajee Mohammad Danesh Science and Technology University. The animals were maintained in polypropylene cages with wood-cob bedding at a temperature of 25±2°C with a regulated photoperiod (12 h cycles of light and dark) in a well-ventilated room with approximate humidity levels (e.g., 50–60%) (Ulfhake *et al*., 2022). Four mice were randomly assigned to each cage. Standard maintenance feed (purchased from the Animal Resources Facility of icddr, b) and filtered tap water were provided ad libitum. The volume of water consumed per day was noted. Every morning, a calming environment was created by transforming drinking water and bedding (wood cob). This study was performed in line with the principles of the animal handling ethics committee and prior approval and adhering to the guidelines established by the Institutional Ethical Committee (IEC) of the Institute of Research and Training (IRT), Hajee Mohammad Danesh Science and Technology University, Dinajpur-5200, Bangladesh (Resolution No. HSTU/VAS/GAB-22).

Breeding strategy

The phases of the estrous cycles in each mouse were determined by checking vaginal smear (daily morning at the same time). Female mice were randomly selected and mated with male mice from separate cages as soon as proestrus was confirmed to ensure pregnant females. The mating strategy was two females and one male for one night. The next morning, the female vulva was examined for the presence of a vaginal plug. The detection of a vaginal plug was designated embryonic day 0.5 (E0.5) of gestation. Plug-positive females were considered "pregnant" and immediately placed in separate cages for further treatment.

Experimental design

Swiss albino female mice (7-8 weeks of age, weighing 25–30g) were randomly assigned to four groups in each consisting of six (n= 6) animals, for this experiment. Each group of mice was housed individually throughout the experiment in polypropylene cages with four mice per cage. The various treatment groups are listed below:

- Group 1: Control
- Group 2: $NaAsO_2$ (Sodium arsenite)
- Group 3: $NaAsO_2$ + Na_2SeO_3 (Combined treatment of Sodium arsenite and Sodium selenite)
- Group 4: Na_2SeO_3 (Sodium selenite)

Treatments

Different animal groups received various treatments. Group 1 mice received nothing except regular drinking water. Group 2 and Group 4 mice received 10 micromolar each of sodium arsenite ($NaAsO_2$; Sigma-Aldrich, USA) and sodium selenite (Na_2SeO_3; Sigma-Aldrich, USA) dissolved in deionized distilled water (ddH_2O) for 60 days (Basher *et al.*, 2024), while Group 3 mice received a combination of sodium arsenite and sodium selenite. The doses of $NaAsO_2$ and Na_2SeO_3 were adjusted according to our previous research (Basher *et al.*, 2024) and other literature available, where 10 µM $NaAsO_2$ showed disrupted self-renewal and differentiation of mouse and human trophoblast stem cells. Treatments were initiated in each regimen portrayed in the experimental layout (Figure 1).

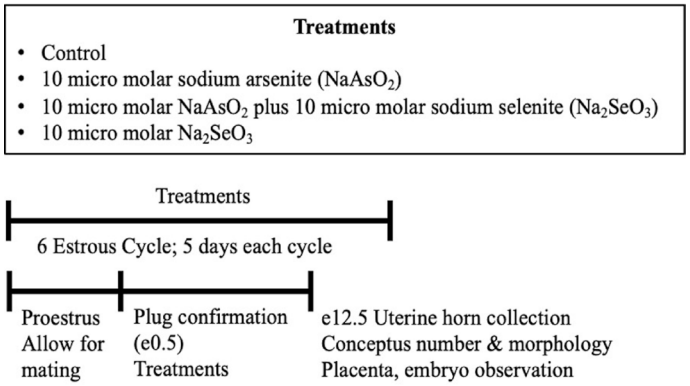

Figure 1: Experimental layout.

Observation of reproductive cyclicity (estrous cycle)

Reproductive cyclicity or estrous cycle was observed in mice of all experimental groups. Each cycle was considered 5 days, and 6 estrous cycles were observed. For observation of different stages of the estrous cycle, a vaginal swab was obtained using cotton-tipped swabs wetted with ambient temperature physiological saline and introduced into the vagina of the restrained mouse (Byers *et al.*, 2012). The swab was gently turned and rolled against the vaginal wall and then removed. Cells were collected and then transferred to a dry glass slide by moving the swab across the slide. The slide was air-dried, stained with Giemsa stain (Sigma-Aldrich, St. Louis, MO), and viewed under the microscope (Byers *et al.*, 2012). The stages of the estrous cycle were determined based on the presence or absence of leukocytes, cornified epithelial, and nucleated epithelial cells according to Felicio *et al.* (1984). The respective stages of the estrous cycle were identified based on- *Diestrus*- Stringy mucous in which are entangled many leucocytes and a few nucleated epithelial cells. *Proestrus*- Largely small, round, nucleated epithelial cells, singly or in sheets. None too few leucocytes. *Estrus*- Contains hundreds of large cornified cells (squames) with degenerate nuclei. Towards the end of estrus, the smear becomes "cheesy"- masses of adherent cornified cells. *Metestrus*- Many leucocytes and a few cornified cells. The estrous cycle has been estimated as the occurrence of several stages during 30 days of exposure.

$$\text{Incidence of a stage} = \frac{\text{No: of days a phase occurred during the course of the exposure period}}{\text{Total days of exposure}} \times 100$$

Evaluation of conceptus

To observe the ameliorative effect of Na_2SeO_3 on $NaAsO_2$-induced toxic effect on placenta formation and embryo development, conceptuses were evaluated based on number and gross morphology. Four different treatment groups, namely control, sodium arsenite ($NaAsO_2$), sodium arsenite ($NaAsO_2$) plus sodium selenite (Na_2SeO_3), and sodium selenite (Na_2SeO_3) treated conceptuses at E12.5 were evaluated to compare the toxic effects of $NaAsO_2$ and its amelioration using Na_2SeO_3. Briefly, after the confirmation of mating (plug formation), mice were treated with four different treatments and were continued up to E12.5 (Figure 1). Then treated E12.5 mice were euthanized by cervical dislocation, uterine horns and organs (liver, kidney, spleen, heart, and lungs) were collected and evaluated. Uterine horns were opened, and conceptuses were collected. The number of conceptuses and gross morphology were recorded and finally, images were taken. Then conceptuses were dissected to isolate embryos, yolk sacs, and placentae. All embryos, placentae, and organs were photographed for comparison purposes.

Statistical analysis

Each experiment was repeated at least three times. The results were expressed as a ratio against each control as mean ± SEM. Single-factor analysis of variance (ANOVA) was used to analyze the statistical differences, where significances were considered at $p<0.05$. Furthermore, the Student-Newman-Keuls test was used to compare the two groups. Differences were considered significant at the level of $p<0.05$ (Zar, 1999).

RESULTS

Na-selenite (Na_2SeO_3) recovers Na-arsenite ($NaAsO_2$) induced estrous cycle abnormalities in Swiss albino female mice

In this study, Na_2SeO_3 ameliorates the toxic effect of $NaAsO_2$ on estrous cyclicity or reproductive cyclicity in adult female mice (Figure 2). Different stages of estrous cycles, proestrus (Figure 2A), estrus (Figure 2B), metestrus (Figure 2C), and diestrus (Figure 2D) were examined using the vaginal smear/cytology method. The results showed that among different stages percentage of estrus stages was significantly ($p<0.05$) influenced by $NaAsO_2$, and the toxic effect was minimized by Na_2SeO_3 treatment (Figure 2E). In the Na_2SeO_3 group, mice showed a higher rate of estrus stages than metestrus and diestrus. Contrary, $NaAsO_2$-treated mice showed a higher percentage of metestrus and diestrus than estrus stages which were minimized after Na_2SeO_3 treatment.

The potential of Na-selenite (Na_2SeO_3) to minimize Na-arsenite ($NaAsO_2$) induced pregnancy loss at E12.5 of adult female mice

In the control mice, conceptuses were observed (Figure 3C), whereas in $NaAsO_2$-induced mice, no conceptuses were found (Figure 3D) in the uterine horns. Conceptuses were observed in the uterine horn of $NaAsO_2$+Na_2SeO_3, and Na2SeO3-treated mice (Figure 3E, F). In addition, this study examined the number of conceptuses (Figure 3G), the morphology of conceptuses, and the placenta (Figure 4). Data revealed that Na_2SeO_3 significantly ($p<0.05$) minimizes the arsenic-induced pregnancy loss in terms of the number of conceptuses in the uterine horn (Figure 3G). Evaluation of conceptuses and placenta based on morphological features showed that conceptuses (Figure 4A, B, C) and placenta (Figure 4D, E, F) were morphologically normal, except in Na2SeO3-treated mice, where a rare phenomenon, monochorionic-diamniotic twins, was observed (Figure 4g, H).

DISCUSSION

Arsenic (As) is a well-known environmental endocrine disruptor whose pollution has been a worldwide public health concern (Meakin *et al.*, 2020). According to previous studies, the reproductive system is one of the most susceptible targets for arsenic (Kim and Kim, 2015). The metal is hazardous to female reproduction both during pregnancy and as adults (Tian *et al.*, 2021), and it crosses the placenta (Milton *et al.*, 2017). Additionally, disrupted placental development is associated with numerous pregnancy complications, namely miscarriage, preeclampsia, and intrauterine growth restriction (Norwitz, 2006). According to several previous studies, oxidative damage

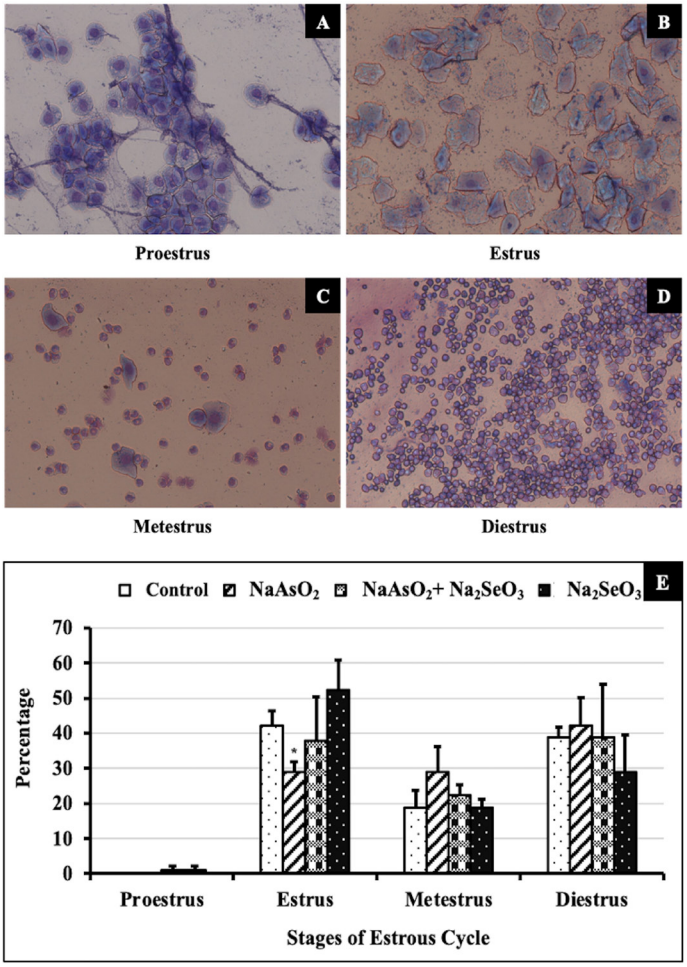

Figure 2: Na-selenite (Na_2SeO_3) minimizes the toxic effect of Na-arsenite ($NaAsO_2$) on reproductive cyclicity in adult female mice. The respective stages Proestrus (A), Estrus (B), Metestrus (C), and Diestrus (D) were evaluated based on the presence or absence of leukocytes, cornified epithelial, and nucleated epithelial cells. Proestrus- large, round, nucleated epithelial cells, singly or in sheets, and not too few leucocytes. Estrus- contains hundreds of large cornified cells (squames) with degenerate nuclei, Metestrus- many leucocytes, and a few cornified cells. Diestrus- stringy mucous in which are entangled many leucocytes and a few nucleated epithelial cells. Each stage's percentage was compared in control vs $NaAsO_2$ vs $NaAsO_2$+Na_2SeO_3 vs Na2SeO3-treated mice (E). Data expressed as mean ± SEM. *Significantly different ($p<0.05$) from the control mice.

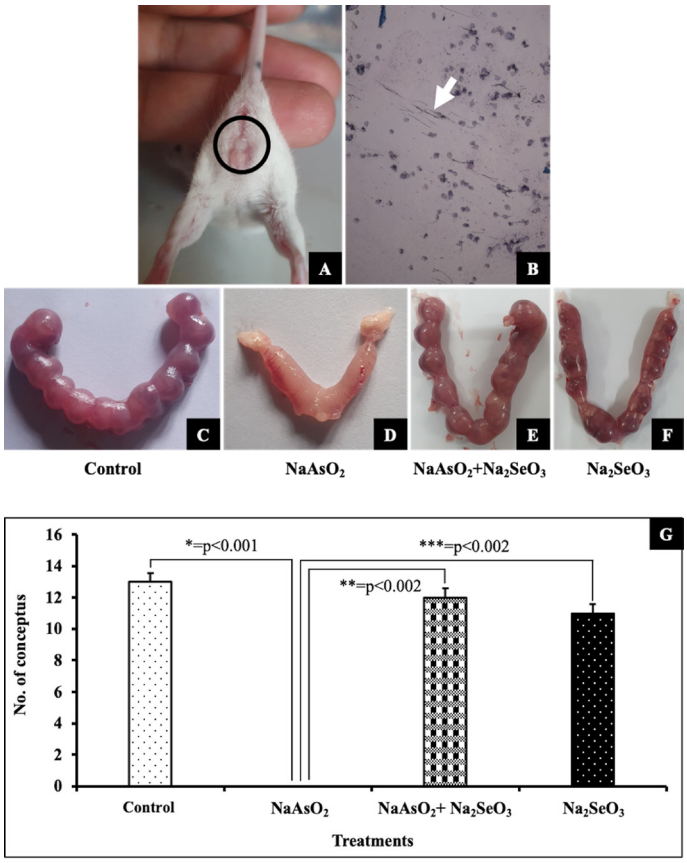

Figure 3: Na-selenite (Na_2SeO_3) rescues Na-arsenite ($NaAsO_2$) induced pregnancy loss at E12.5 of adult female mice the presence of semen plugs to confirm mating (A). Giemsa stain (Sigma-Aldrich, St. Louis, MO) was viewed under the microscope and photographed for sperm (B). Presence or absence of the conceptus in the uterine horns (control-C, $NaAsO_2$-D, $NaAsO_2$+Na_2SeO_3-E, Na_2SeO_3-F). Pregnancy output in terms of conceptus number was compared based on the average number of concepti in the uterine horns of each treatment (G). Data expressed as mean ± SEM. *Significantly different ($p<0.001$) from the control mice, **and***Significantly different ($p<0.002$) from the $NaAsO_2$ treated mice.

was a factor in arsenic poisoning (El-Demerdash *et al.*, 2009). Selenium is a well-recognized essential antioxidant that controls antioxidant defense processes and can lessen oxidative damage in various cells (Habibian *et al.*, 2015). In addition to promoting viral resistance and maintaining reproductive function, selenium supplementation has numerous beneficial impacts (Yu *et al.*, 2011). To ensure a beneficial impact on the target objects, arsenic and selenium combination therapy has recently gained scientific attention to cure illnesses, including malignancies and neurological disorders, among others (Hsueh *et al.*, 2017). Considering this, we conducted this study to learn how selenium protects against the harmful effects of arsenic on reproductive cyclicity and placental anomalies. The current study showed that among different stages, the percentage of estrus stages was significantly ($p < 0.05$) influenced by the $NaAsO_2$-treated group. $NaAsO_2$-treated mice showed higher percentages of metestrus and diestrus than estrus stages, which supports the previous research (Mehta and Hundal, 2016), and they depicted a prolonged diestrus phase in rats given sodium arsenite treatment. The protracted diestrus and metestrus states may be caused by an imbalance in progesterone and estradiol production, which primarily controls the phases of the estrous cycle and their interconversions. Any hormone imbalance causes irregularities in the ovary's function and alterations in the estrous cycle's length (Basher *et al.*, 2023; Mehta and Hundal, 2016). However, compared to the arsenic-alone exposure group, the mice treated with arsenic together with sodium selenite supplementation experienced a shorter met-estrous and diestrus phase, demonstrating the efficient ameliorative impact of selenium against arsenic-induced toxicity, which is comparable with the study of the regulation on hormonal level by selenium supplementation on lead toxicity (Shen *et al.*, 2016). Surprisingly, proestrus was almost absent during the study period in both control and NaAsO2-treated groups, but Na_2SeO_3 treatment could recover this condition. The possible reason might be the high environmental temperature. The major limitation of our study was the lack of controlled conditions, which might exert irregularities in estrous cycles in mice.

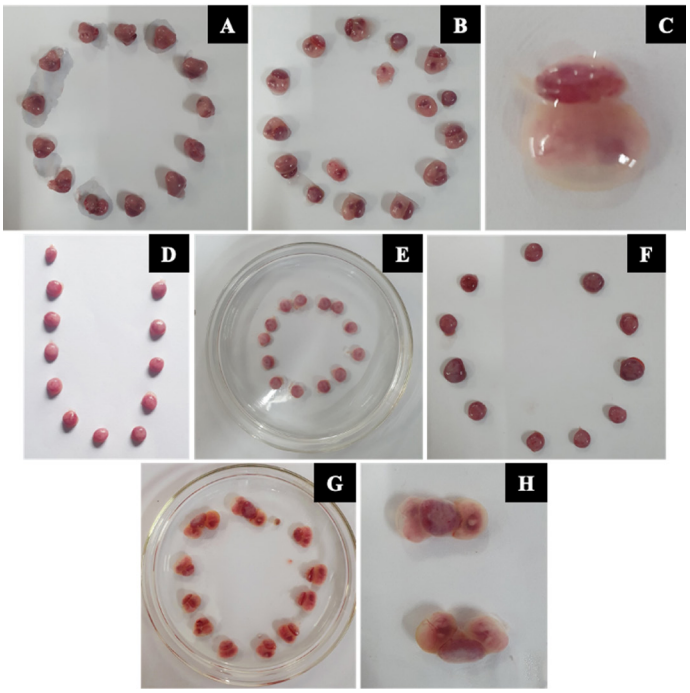

Figure 4: Morphological features of the conceptus (A, B, C), and placenta (D, E, F) at E12.5 of adult female mice. A rare phenomenon, monochorionic-diamniotic twins were observed (G, H) in Na_2SeO_3-treated mice.

The present study revealed the toxic effect of arsenic-induced pregnancy loss at E12.5 (Figure 3 and 4), which is analogous to earlier research on oxidative damage in trophoblast cells (Watson *et al.*, 2012). Arsenic exposure

impairs placental vasculogenesis (He *et al*., 2007) and causes uterine dysfunction (Chatterjee and Chatterji, 2010). Possibly it alters the estrogen and progesterone levels as well as disrupts endometrial stroma due to arsenic intoxication may affect the growth and differentiation of endometrial glands, thereby decreasing the nutritional needs of the early embryo, which results in early pregnancy loss (Mehta and Hundal, 2016). In addition, this study examined the number of conceptuses (Figure 3G), the morphology of conceptuses (Figure 4A, B,C), and the placenta (Figure 4). Our observations indicated that there were no conceptuses in the sodium arsenic exposure group significantly ($P<0.001$) compared to the control. Interestingly, Na-selenite (Na_2SeO_3) as a potential antioxidant minimizes Na-arsenite ($NaAsO_2$) induced pregnancy loss as well as significantly ($p < 0.002$) in terms of the number of conceptuses. It has been reported that the potential effect of selenium in the reproductive system (Shen *et al*., 2016), against cadmium-induced testicular toxicity in cocks (Li *et al*., 2010). According to the morphological features shown, conceptuses (Figure 4A, B, C) and placenta (Figure 4D, E, F) were morphologically normal. Unexpectedly, monochorionic-diamniotic twins (Figure 4G, H) appeared in Na_2SeO_3-treated mice. Due to the rarity of monozygotic twins in the animal kingdom, the specific reason for embryonic splitting is still unknown (Blickstein and Keith, 2007). Thus, further study is necessary (histological examination, functional analysis) to examine the toxic effect of $NaAsO_2$ and its amelioration after Na_2SeO_3 treatment.

CONCLUSION

The protective effects of selenium were assessed for the first time against the toxic effects on reproductive cyclicity/estrous cyclicity, placenta, and embryo during pregnancy induced by arsenic in female mice. Our findings demonstrated that Na_2SeO_3 not only improves reproductive (estrous) cyclicity but also mitigates $NaAsO_2$-induced pregnancy loss in adult female mice. However, a key limitation of our study was the absence of a highly controlled environment and the lack of molecular-level investigations. Therefore, further research is warranted, particularly at the molecular level, to elucidate the mechanisms by which Na_2SeO_3 exerts its protective effects against $NaAsO_2$-induced disruptions in estrous cyclicity and pregnancy outcomes.

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AUTHOR'S CONTRIBUTION

MRI and SS: Conceptualization and design of the research.
MRI: Methodology, sample resources, supervision and project administration.
MKB, SS, SS, and MRI: Experimental investigation,
MKB, SS, and MRI: Writing-original draft preparation and writing-review and editing.
All authors have read and agreed to the published version of the manuscript.

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Ethical statement

This article does not contain any studies with human participants performed by any of the authors.

Generative AI and AI-assisted technology statement

No generative artificial intelligence (AI) tools were used in the conception, analysis, or interpretation of this work. Grammarly was used solely for grammar correction and language refinement. All scientific content, interpretations, and conclusions are the original work of the authors.

Conflict of interest

The authors have declared no conflict of interest.

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