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Research Article

ZINC PROTECTS AGAINST ARSENIC INDUCED NEUROTOXICITY AND REPRODUCTIVE DAMAGE IN NULLIPAROUS FEMALE RATS

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ABSTRACT

Arsenic contamination in drinking water poses serious risks during pregnancy, affecting both fetal development and maternal health. This study explored whether low-dose zinc supplementation could protect against arsenic-induced reproductive toxicity and oxidative stress in the maternal brain using a rat model. Pregnant Wistar rats (n=32, 8 per group) received normal water (control), 50 ppm sodium arsenite, 50 ppm arsenic plus 5 ppm zinc (as $ZnCl_2$), or zinc alone from gestation day 1 to 18. On day 18, dams were sacrificed to evaluate reproductive outcomes and oxidative stress markers in mitochondrial fractions of the cerebral cortex, cerebellum, and hippocampus. Arsenic exposure alone caused significant reproductive impairment, increasing post-implantation loss to 27.27 ± 3.85% (vs. 7.14 ± 1.20% in controls; $P<0.001$) and reducing live fetuses to 8.00 ± 0.69 (vs. 13.00 ± 0.82; $P<0.001$). It also triggered pronounced oxidative stress in the maternal brain, with lipid peroxidation rising sharply (e.g., 1.888 ± 0.046 vs. 1.112 ± 0.094 nmol MDA/g tissue in cerebral cortex; $P<0.001$) and antioxidant enzyme activities (Mn-SOD, Cu/Zn-SOD, catalase, GPx, GR, GST) dropping by 30-55% ($P<0.001$). Co-administration of zinc substantially reversed these effects: post-implantation loss fell to 16.67 ± 2.45% ($P<0.05$ vs. arsenic alone), lipid peroxidation decreased by 35-42%, and enzyme activities recovered 55-80% toward control values ($P<0.001$). These results indicate that gestational arsenic exposure induces marked reproductive toxicity and brain oxidative damage in dams, while low-dose zinc offers robust protection by enhancing antioxidant defenses and limiting lipid peroxidation. Zinc supplementation may represent a safe, affordable strategy to counteract arsenic toxicity in exposed pregnant populations.

Keywords: Arsenic toxicity, Zinc supplementation, Gestational exposure, Reproductive toxicity, Oxidative stress.

INTRODUCTION

Arsenic (As) is a ubiquitous environmental toxicant and one of the most hazardous substances known to humans, ranked first on the Agency for Toxic Substances and Disease Registry (ATSDR) Priority List of Hazardous Substances for many years (ATSDR, 2022). Chronic exposure to inorganic arsenic through contaminated drinking water, food, and occupational settings, and air affects millions of people worldwide, particularly in South and Southeast Asia, Latin America, and parts of the United States (Podgorski & Berg, 2020; Naujokas *et al*., 2013). Arsenic readily crosses the placental barrier and the blood-brain barrier, making the developing fetus and maternal brain highly vulnerable targets (Jin *et al*., 2020; Tolins *et al*., 2014). Reproductive toxicity is among the most sensitive non-cancer endpoints of arsenic exposure. Epidemiological and experimental studies have consistently demonstrated that gestational and perinatal arsenic exposure is associated with increased risks of spontaneous abortion, stillbirth, low birth weight, impaired fetal growth, and congenital malformations (Milton *et al*., 2017; Quansah *et al*., 2015).

In animal models, arsenic administration during pregnancy induces oxidative stress, disrupts steroidogenesis, alters placental morphology, and causes embryotoxicity and teratogenicity (Chattopadhyay *et al*., 2019; Souza *et al*., 2021). The maternal brain is also adversely affected by arsenic exposure during pregnancy.

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Arsenic accumulates in brain tissue and triggers excessive generation of reactive oxygen species (ROS), lipid peroxidation, protein carbonylation, and depletion of endogenous antioxidants, ultimately leading to neuronal damage, neuroinflammation, and behavioral deficits in both mothers and offspring (Mochizuki, 2019; Chandravanshi *et al*., 2019; Tolins *et al*., 2014). These neurotoxic effects are largely mediated by arsenic-induced oxidative stress, which disrupts cellular redox homeostasis and mitochondrial function (Hu *et al*., 2020).

Zinc (Zn) is an essential trace element that plays a critical role in more than 300 enzymatic reactions, gene expression, immune function, and antioxidant defense (Roohani *et al*., 2013). Zinc is a key component of copper/zinc superoxide dismutase (Cu/Zn-SOD) and acts as a cofactor for numerous antioxidant enzymes. Several studies have shown that zinc supplementation can ameliorate heavy metal-induced oxidative damage in various organs, including liver, kidney, testis, and brain (Sousa *et al*., 2016; Kheradmand *et al*., 2017; Al-Attar, 2011). Importantly, zinc has been reported to antagonize arsenic toxicity by competing for binding sites on biomolecules, restoring antioxidant enzyme activities, and reducing ROS production (Ganger *et al*., 2016; Kumar & Sharma, 2020). Despite growing evidence of the protective role of zinc against arsenic toxicity in non-pregnant models, there is limited information on its efficacy against arsenic-induced reproductive toxicity and maternal brain oxidative damage during pregnancy. Therefore, the present study was designed to investigate whether zinc supplementation can mitigate arsenic-induced oxidative stress in the maternal brain and protect against reproductive toxicity in a rat model of gestational arsenic exposure.

MATERIALS AND METHODS

Procurement and Maintenance of Experimental Animals

Healthy young adult female and male Wistar albino rats (150-180 g) were procured from the Institutional Animal Breeding Facility, Indian Institute of Science (IISc), Bangalore, India. The animals were acclimatized and maintained in the registered animal house of Watson Life Sciences, Tirupati, India (CPCSEA Registration No. 1715/PO/Re/S/13/CPCSEA). Rats were housed in clean polypropylene cages with sterile paddy husk bedding under controlled environmental conditions (temperature 28 ± 2 °C, relative humidity 60 ± 10%, 12-h light/dark cycle). Standard rodent pellet diet (Sri Venkateswara Traders, Bangalore, India) and reverse-osmosis purified water were provided ad libitum. All experimental procedures were approved by the Institutional Animal Ethics Committee (IAEC) and followed the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India.

Chemicals

Sodium arsenite ($NaAsO_2$, purity ≥ 99%) and zinc chloride ($ZnCl_2$, purity ≥ 98%) were purchased from Sigma-Aldrich, St. Louis, MO, USA. Thiobarbituric acid, epinephrine, 1-chloro-2,4-dinitrobenzene (CDNB), reduced glutathione (GSH), NADPH, and bovine serum albumin were also obtained from Sigma-Aldrich. All other analytical-grade chemicals were procured from Qualigens (Thermo Fisher Scientific India Pvt. Ltd., Mumbai, India).

Experimental Design and Treatment Protocol

Nulliparous female rats exhibiting regular 4-5-day estrus cycles were selected. Vaginal smear examination was performed daily between 08:00-10:00 h following the method of Zarrow *et al*. (1964). Females in proestrus were paired overnight with proven fertile males (1:1 ratio). The presence of spermatozoa in the vaginal smear or a vaginal plug the next morning was taken as evidence of successful mating and designated as gestation day 0 (GD 0). Pregnant females were randomly allocated into four groups (n = 8 dams/group) and treated from GD 1 to GD 18 through drinking water as follows: Group I (Control): Normal drinking water. Group II (As): 50 mg/L (50 ppm) sodium arsenite. Group III (As + Zn): 50 mg/L sodium arsenite + 5 mg/L (5 ppm) zinc (as $ZnCl_2$). Group IV (Zn): 5 mg/L zinc (as $ZnCl_2$). Fresh solutions were prepared daily, and water consumption was monitored. On GD 18, dams were euthanized by cervical dislocation under mild CO_2 anesthesia. Uteri were excised to record the number of implantations, live fetuses, resorptions, and fetal body weight. Post-implantation loss (%) was calculated as:

Post-implantation loss (%) = [(Number of implantations − Number of live fetuses) / Number of implantations] × 100

Maternal brains were rapidly dissected on ice, washed with ice-cold saline, and stored at −80 °C until biochemical analysis.

Preparation of Brain Mitochondrial Fraction

Mitochondrial fractions from whole brain were isolated according to Lai and Clark (1979) with minor modifications. Brain tissue was homogenized (1:10 w/v) homogenized in ice-cold SET buffer (0.25 M sucrose, 10 mM Tris-HCl, 1 mM EDTA, pH 7.4). The homogenate was centrifuged at 800 × g for 10 min at 4 °C to remove nuclei and debris. The supernatant was further centrifuged at 10,000 × g for 20 min at 4 °C. The resulting mitochondrial pellet was resuspended in SET buffer and used for enzyme assays.

Estimation of Protein Content

Protein concentration was determined by the method of Lowry *et al*. (1951) using bovine serum albumin as standard.

Biochemical Assays in Maternal Brain Mitochondria

All assays were performed under zero-order kinetics at 25 °C. Superoxide dismutase (SOD) activity was measured by the method of Misra and Fridovich (1972) based on inhibition of epinephrine auto-oxidation at pH 10.2. Glutathione reductase (GR) activity was assayed according to Staal *et al*. (1969) by monitoring NADPH oxidation at

340 nm. Glutathione-S-transferase (GST) activity was determined using CDNB as substrate following Habig *et al*. (1974). Glutathione peroxidase (GPx) activity was measured by the method of Rotruck *et al*. (1973) using H_2O_2 and GSH as substrates. Remaining GSH was measured. Catalase activity was assayed by the method of Chance and Maehly (1955) by following the decomposition of H_2O_2. Lipid peroxidation (LPO) was estimated as thiobarbituric acid reactive substances (TBARS) according to Ohkawa *et al*. (1979).

Statistical Analysis

Data were expressed as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) was performed.

RESULTS AND DISCUSSION

All animals remained healthy throughout the experimental period with no mortality or overt clinical signs of toxicity in any group. Daily water consumption and body weight gain were comparable across groups. The effects of arsenic and zinc on reproductive performance are presented in Table 1.

Table 1. Effect of arsenic and zinc supplementation on reproductive parameters in Wistar rats (Mean ± SD, n = 8 dams/group).

Parameter	Control	Arsenic (50 ppm)	As + Zn (50 + 5 ppm)	Zinc (5 ppm)
Number of implantations/rats	14.00 ± 0.89	11.00 ± 0.57**	12.00 ± 0.59*	13.00 ± 0.45
Number of live fetuses/rats	13.00 ± 0.82	8.00 ± 0.69***	10.00 ± 1.00**	12.00 ± 1.52
Number of resorptions	0	3.00 ± 0.45	2.00 ± 0.32	0
Post-implantation loss (%)	7.14 ± 1.20	27.27 ± 3.85***	16.67 ± 2.45**†	7.69 ± 1.35

***p < 0.001, **p < 0.01 compared with control; †p < 0.05 compared with arsenic-alone group (one-way ANOVA followed by Tukey's post-hoc test).

Exposure to 50 ppm arsenic from GD 1 to GD 18 significantly reduced the number of implantations (by 21.4%) and live fetuses (by 38.5%) while markedly increasing post-implantation loss (3.8-fold) compared to the control group. Co-administration of 5 ppm zinc with arsenic significantly ameliorated these adverse effects: the number of live fetuses increased by 25%, and post-implantation loss was reduced by approximately 39% relative to the arsenic-only group. Zinc supplementation alone showed a slight improvement in implantation and fetal survival compared to control, although the differences were not statistically significant. Arsenic exposure induced significant oxidative stress in the maternal brain, evidenced by elevated lipid peroxidation and depletion of antioxidant enzyme activities in the cerebral cortex (Cc), cerebellum (Cbm), and hippocampus (Hip). Zinc co-treatment substantially reversed these alterations. Representative data from the cerebral cortex (the most affected and enzymatically active region) are shown in Tables 2 and 3; similar trends were observed in the cerebellum and hippocampus (data not shown for brevity).

Table 2. Effect of arsenic and zinc on lipid peroxidation (LPO) and catalase activity in maternal cerebral cortex (Mean ± SD, n = 8).

Parameter	Control	Arsenic (50 ppm)	As + Zn	Zinc (5 ppm)
LPO (nmol MDA/g tissue)	1.112 ± 0.094	1.888 ± 0.046***	1.230 ± 0.054†††	1.098 ± 0.082
Catalase (nmol H_2O_2 decomposed/mg protein/min)	2.45 ± 0.18	1.11 ± 0.04***	1.98 ± 0.12†††	2.62 ± 0.21

***p < 0.001 vs control; †††p < 0.001 vs arsenic group

Table 3. Effect of arsenic and zinc on superoxide dismutase and glutathione-related enzymes in maternal cerebral cortex (Mean ± SD, n = 8).

Enzyme (units/mg protein)	Control	Arsenic (50 ppm)	As + Zn	Zinc (5 ppm)
Mn-SOD	3.51 ± 0.14	2.41 ± 0.11***	2.92 ± 0.09†††	3.90 ± 0.04**
Cu/Zn-SOD	1.385 ± 0.028	0.895 ± 0.035***	1.160 ± 0.042†††	1.510 ± 0.049**
Glutathione-S-transferase (GST)	1.87 ± 0.08	1.19 ± 0.01***	1.39 ± 0.02†††	1.69 ± 0.09
Glutathione reductase (GR)	1.322 ± 0.094	0.708 ± 0.077***	1.074 ± 0.072†††	1.432 ± 0.623
Glutathione peroxidase (GPx)	1.768 ± 0.073	0.967 ± 0.006***	1.345 ± 0.064†††	1.870 ± 0.093**

***p < 0.001, **p < 0.01 vs control; †††p < 0.001 vs arsenic group (one-way ANOVA followed by Tukey's post-hoc test)

Post Implantation loss of the embryos of GD18 dissected rats

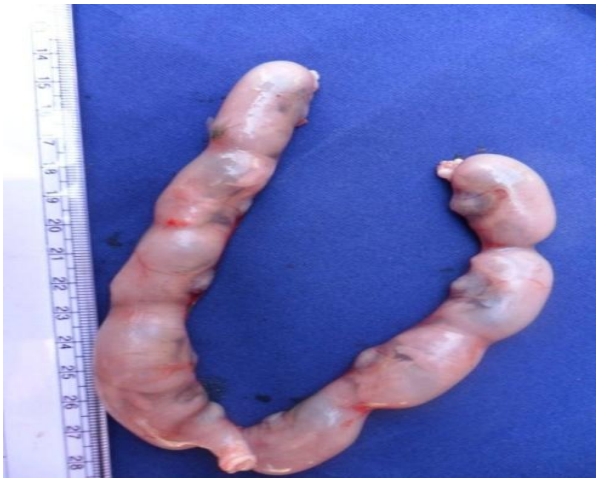

Figure 1. Number of implantations in control rats, dissected on GD18.

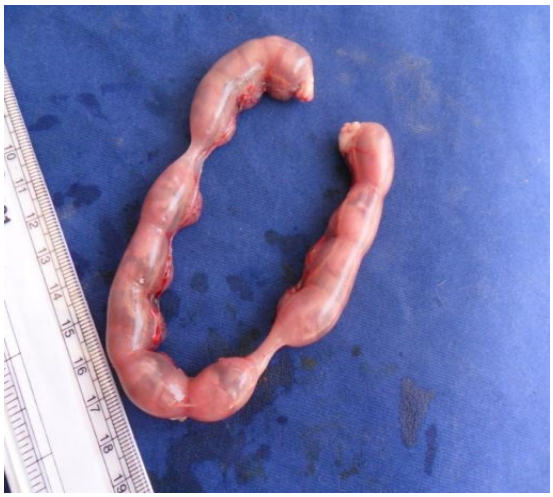

Figure 2. Number of implantations in Arsenic treated rats, dissected on GD18.

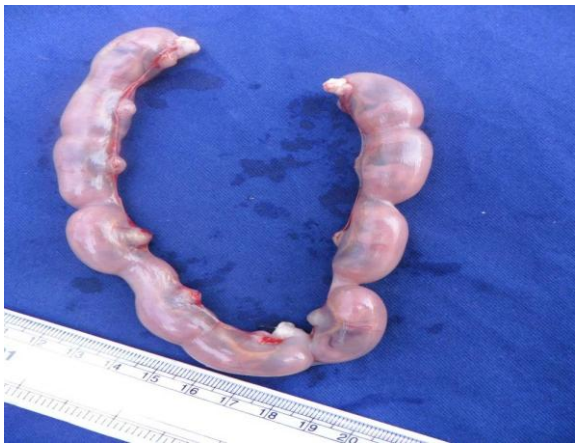

Figure 3. Number of implantations in As+Zn treated rats, dissected on GD18.

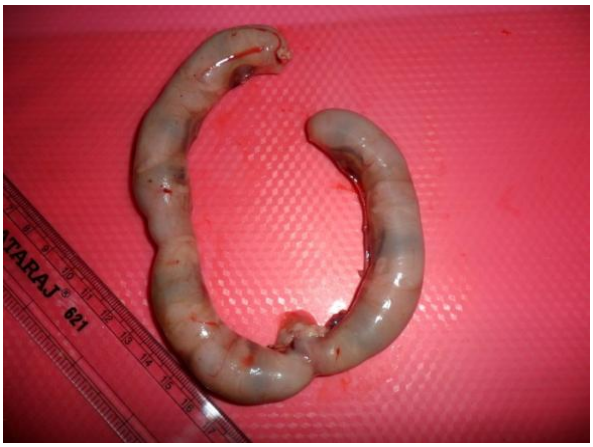

Figure 4. Number of implantations in treated rats, dissected on GD18.

Arsenic exposure produced a highly significant 70% increase in MDA levels in the cerebral cortex ($p < 0.001$), with similar elevations of 55-65% in the cerebellum and hippocampus. Zinc co-administration markedly attenuated arsenic-induced lipid peroxidation, reducing MDA levels by 35-42% compared to the arsenic-alone group ($p < 0.001$). Both Mn-SOD and Cu/Zn-SOD activities were significantly suppressed by arsenic (30-35% reduction, $p < 0.001$). Zinc supplementation restored Mn-SOD and Cu/Zn-SOD activities toward control values, with the most pronounced recovery observed for Cu/Zn-SOD, consistent with zinc being an essential cofactor. Arsenic caused 35-45% inhibition of GST, GR, and GPx activities across all brain regions ($p < 0.001$). Concurrent zinc treatment significantly reversed these inhibitions (recovery range 55-75% of lost activity), indicating improved glutathione regeneration and peroxide detoxification capacity. Catalase activity declined by approximately 55% in arsenic-exposed dams ($p < 0.001$). Zinc co-treatment restored catalase activity to near-control levels (80-85% recovery). Arsenic induced severe oxidative stress in maternal brain regions by increasing lipid peroxidation and depleting key antioxidant defenses. Zinc supplementation (5 ppm) exerted significant protection by (i) reducing lipid peroxidation, (ii) restoring activities of SOD (especially Cu/Zn-SOD), catalase, and glutathione-metabolizing enzymes, and (iii) partially preventing arsenic-induced post-implantation embryo loss. These findings demonstrate that low-dose zinc supplementation during gestation can effectively mitigate arsenic-induced reproductive toxicity and oxidative damage in the maternal brain.

The present study provides clear evidence that gestational exposure to inorganic arsenic (50 ppm in drinking water) induces significant reproductive toxicity and oxidative stress in the maternal brain of Wistar rats. Concurrent low-dose zinc supplementation (5 ppm) partially but significantly ameliorated both reproductive impairment and cerebral oxidative damage, reinforcing the therapeutic potential of zinc as a safe, inexpensive, and effective intervention against environmental arsenic toxicity. Gestational arsenic exposure markedly reduced the number of implantations and live fetuses while increasing post-implantation loss to 27.3% compared to 7.1% in controls. These findings are consistent with numerous epidemiological and experimental reports demonstrating that arsenic readily crosses the placental barrier, accumulates in embryonic tissues, and disrupts critical developmental processes (Jin *et al*., 2020; Souza *et al*., 2021; Milton *et al*., 2017). The observed increase in embryonic resorptions and post-implantation loss likely results from arsenic-induced oxidative damage to placental vasculature, impaired steroidogenesis, altered expression of angiogenic factors, and direct induction of apoptosis in trophoblast and embryonic cells (Chattopadhyay *et al*., 2019; Wang *et al*., 2022). Co-administration of zinc reduced post-implantation loss by ~39% and increased the number of live fetuses, indicating a protective role during early organogenesis. Zinc is essential for normal reproductive function, acting as a cofactor for numerous enzymes involved in DNA synthesis, cell division, and hormone regulation (Roohani *et al*., 2013; Uriu-Adams & Keen, 2010). Zinc modulates gonadotropin (FSH and LH) secretion, supports progesterone synthesis, and maintains follicular and luteal integrity (Bedwal & Bahuguna, 1994). Furthermore, zinc deficiency during pregnancy is teratogenic, whereas adequate zinc status protects against oxidative insult to rapidly proliferating embryonic tissues. The partial restoration of reproductive outcomes in the As+Zn group therefore likely reflects improved antioxidant defense, reduced placental oxidative stress, and stabilization of zinc-dependent reproductive hormones and enzymes.

The brain is particularly vulnerable to arsenic because inorganic arsenic and its methylated metabolites readily cross the blood-brain barrier (Rodríguez *et al*., 2005; Yadav *et al*., 2010). In the present study, arsenic exposure produced robust oxidative stress in all examined maternal brain regions, with the cerebral cortex showing the most pronounced changes. Lipid peroxidation increased by 70%, while activities of Mn-SOD, Cu/Zn-SOD, catalase, GPx, GR, and GST were significantly suppressed. These results align with earlier reports demonstrating that arsenic generates reactive oxygen species (ROS) through multiple pathways, including mitochondrial electron transport chain leakage, activation of NADPH oxidase, and formation of peroxyl radicals from dimethylarsine (Hu *et al*., 2020; Yamanaka *et al*., 1989, 1990). The marked decline in Cu/Zn-SOD activity is particularly noteworthy, as this isoform is highly sensitive to displacement of zinc or copper by arsenic at sulfhydryl sites (Flora *et al*., 2008). Reduced SOD activity leads to superoxide anion accumulation, which inactivates catalase and GPx and perpetuates a vicious cycle of oxidative damage (Kono & Fridovich, 1982). Depletion of glutathione-related enzymes further impairs H_2O_2 and lipid hydroperoxide detoxification, explaining the elevated malondialdehyde levels observed. Regional differences in vulnerability (cortex > hippocampus > cerebellum) correlate well with non-heme iron content and baseline metabolic rate, both of which facilitate Fenton-type reactions and ROS amplification (Hill & Switzer, 1984; Prakash *et al*., 2016).

Zinc supplementation substantially reversed arsenic-induced oxidative damage in the maternal brain. Key protective mechanisms include: Direct antioxidant action: Zinc stabilizes sulfhydryl groups, inhibits NADPH oxidase, and scavenges hydroxyl radicals (Bray & Bettger, 1990; Powell, 2000). Metalloenzyme stabilization: As a structural component of Cu/Zn-SOD and cofactor for numerous antioxidant enzymes, zinc restores enzymatic activity lost due to arsenic binding (O'Dell, 2000). Induction of metallothionein: Zinc upregulates metallothionein synthesis, which sequesters arsenic and other toxic metals, reducing their bioavailability (Klaassen *et al*., 1999; Majumdar *et al*., 2021). Nrf2-ARE pathway activation: Zinc activates the transcription factor Nrf2, enhancing expression of antioxidant and phase-II detoxifying enzymes (Cortese *et al*., 2008). The most dramatic recovery was observed for Cu/Zn-SOD and GPx activities, consistent

with zinc's known role in stabilizing these enzymes and competing with arsenic for sulfhydryl binding sites (Ganger *et al*., 2016; Kumar & Sharma, 2020). Gestational arsenic exposure induces significant reproductive toxicity and oxidative stress in the maternal brain through excessive ROS generation and depletion of antioxidant defenses. Low-dose zinc supplementation during pregnancy offers substantial protection by restoring antioxidant enzyme activities, reducing lipid peroxidation, and partially preventing embryonic loss. These findings support the use of zinc as a safe nutritional intervention in arsenic-endemic regions to mitigate maternal and developmental toxicity. Future studies should explore dose-response relationships, long-term neurobehavioral outcomes in offspring, and translational relevance to human populations.

CONCLUSION

The present investigation clearly demonstrates that gestational exposure to inorganic arsenic at environmentally relevant doses induces severe reproductive toxicity and oxidative stress in the maternal brain of Wistar rats. Arsenic significantly impaired reproductive success by reducing the number of implantations and live fetuses while increasing post-implantation embryonic loss from 7.14% in controls to 27.27% in arsenic-exposed dams. Concurrently, arsenic triggered profound oxidative damage across all examined maternal brain regions (cerebral cortex, cerebellum, and hippocampus), as evidenced by markedly elevated lipid peroxidation and substantial depletion of key antioxidant enzymes, including Mn-SOD, Cu/Zn-SOD, catalase, glutathione peroxidase, glutathione reductase, and glutathione-S-transferase. Low-dose zinc supplementation (5 ppm in drinking water) provided significant protection against both endpoints. Zinc co-administration notably attenuated arsenic-induced post-implantation loss (reduced to 16.67%), increased the number of viable fetuses, markedly lowered lipid peroxidation, and substantially restored the activities of antioxidant enzymes, with particularly prominent recovery of Cu/Zn-SOD and glutathione-dependent systems. These protective effects are attributable to zinc's multifaceted roles: direct ROS scavenging, stabilization of sulfhydryl-containing enzymes, competitive inhibition of arsenic binding, induction of metallothionein, and activation of Nrf2-mediated antioxidant response pathways. Taken together, the results strongly suggest that zinc supplementation during pregnancy can serve as an effective, safe, and low-cost nutritional strategy to mitigate arsenic-induced reproductive toxicity and maternal brain oxidative stress in arsenic-endemic regions. Although derived from a rodent model, these findings provide a solid mechanistic foundation and scientific rationale for future clinical and community-based intervention trials aimed at reducing the transgenerational impact of chronic arsenic exposure in affected human populations. Further translational research is warranted to establish optimal zinc dosing regimens and long-term neurodevelopmental outcomes in offspring.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

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AI TOOL DECLARATION

The authors declare that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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