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Systematic Review

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Unexplained Infertility in Women: Hidden Link between Mitochondrial Dysfunction and Heavy Metal Exposure- A Systematic Review

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ABSTRACT

Background: Among infertility cases, unexplained infertility (UI) remains a major clinical challenge. Increasing evidence suggests that environmental exposure to heavy metals (HMs), such as lead (Pb), cadmium (Cd), mercury (Hg), and arsenic (As), may contribute to UI by acting as endocrine-disrupting chemicals (EDCs). This systematic review aimed to evaluate the relationship between heavy metal exposure, mitochondrial dysfunction, mitochondrial DNA (mtDNA) copy number, and unexplained infertility in women.

Methods: A comprehensive literature search was conducted using peer-reviewed experimental, epidemiological, and clinical studies retrieved from major scientific databases, including PubMed, Scopus, Google Scholar, and Web of Science. Studies examining female infertility, heavy metal exposure, oxidative stress, mitochondrial dysfunction, and mtDNA copy number were included. The review methodology followed PRISMA 2000 guidelines.

Results: A total of 12 studies met the inclusion criteria. The findings indicate that heavy metals induce oxidative stress, reduce mtDNA copy number, and impair mitochondrial energy metabolism in oocytes. Cadmium and arsenic were found to aggravate oxidative damage and suppress mitochondrial biogenesis, while lead and mercury exposure were associated with decreased mtDNA content, impaired oocyte quality, and lower fertilization success. Long-term exposure to heavy metals may disrupt hormonal regulation, accelerate ovarian aging, reduce embryo viability, and increase the risk of infertility.

Conclusions: Heavy metal exposure may play an important role in unexplained infertility through mitochondrial dysfunction and altered mtDNA copy number. mtDNA copy number may serve as a potential biomarker for evaluating environmentally associated infertility. Improved understanding of these mechanisms may support preventive strategies, enhance assisted reproductive technologies, and guide public health policies aimed at reducing reproductive harm caused by environmental toxicants.

Key-words: Unexplained infertility; Mitochondrial dysfunction; Mitochondrial DNA; Heavy metals; Oxidative stress; Female fertility

INTRODUCTION

Infertility, as defined by the World Health Organization (WHO), is the inability of a couple to conceive after one year of regular unprotected intercourse [1,2].

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It is a major reproductive health problem affecting millions of people worldwide, particularly women of reproductive age. Globally, approximately 186 million people are affected by infertility, and the WHO estimates that one in six individuals will experience infertility at some point in their lives [3,4]. The lifetime prevalence of infertility in 2022 was estimated to be approximately 17.5%, and recent trends indicate a global decline in fertility rates accompanied by a rising burden of infertility [2,5].

The most common cause of infertility is ovulatory disorders, accounting for approximately 25% of cases.

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Another major category is unexplained infertility (UI), which affects nearly 30% of infertile couples [6,7]. UI is diagnosed when standard clinical evaluation reveals no obvious abnormalities in either partner's reproductive system. However, there is no universal consensus regarding the exact diagnostic criteria for UI, and the diagnosis often depends on the availability and scope of investigative methods. According to the International Committee for Monitoring Assisted Reproductive Technologies (ICMART), subfertility refers to reduced fertility in couples with normal reproductive anatomy and function who engage in adequate sexual intercourse frequency [8].

A key biological process related to female fertility is oogenesis—the development and maturation of oocytes within the ovaries. Disruption of oogenesis may impair fertility by producing poor-quality oocytes. Environmental factors, particularly exposure to pollutants, can interfere with this process and may induce chromosomal abnormalities in oocytes, thereby reducing the likelihood of conception [9]. In addition to ovarian dysfunction and tubal disease, male infertility also contributes significantly to overall infertility rates [5]. Lifestyle factors and environmental exposures further influence reproductive health outcomes.

A major environmental concern is exposure to heavy metals (HMs), including lead, cadmium, arsenic, and mercury. These naturally occurring elements have become widespread pollutants due to industrialization, agricultural practices, fossil fuel combustion, mining activities, and improper waste disposal [10,11]. The United States Environmental Protection Agency identifies cadmium, lead, and mercury among the most hazardous environmental toxicants posing serious public health risks [12]. These metals persist in the environment and accumulate in water, soil, air, and food chains, leading to chronic human exposure.

Heavy metal exposure adversely affects both male and female reproductive systems by disrupting hormone production, cellular signaling, and tissue function. Several studies have linked such exposure to infertility and other reproductive disorders in women [11]. Although the exact mechanisms underlying ovarian aging remain incompletely understood, mitochondrial dysfunction appears to play a central role [13]. Mitochondria are essential for cellular energy production, calcium homeostasis, and apoptosis regulation, while mitochondrial DNA (mtDNA) copy number is considered an important indicator of mitochondrial health and functional capacity.

Studies have provided insight into how oxidative stress—often triggered by heavy metal toxicity—can induce mitochondrial dysfunction and impair fertility [14]. These findings highlight the complex interplay among genetic susceptibility, environmental toxicants, and lifestyle factors in female infertility. The increasing prevalence of environmental pollutants has therefore raised growing concern regarding their impact on reproductive health worldwide [12].

Previous research has demonstrated associations between heavy metal exposure and infertility in women, as well as other reproductive disorders [15]. Although the precise mechanisms responsible for ovarian aging and unexplained infertility remain unclear, emerging evidence suggests that alterations in mitochondrial DNA may play an important role. Therefore, this systematic review aims to examine the potential relationship between unexplained infertility in women, exposure to heavy metals, and changes in mitochondrial DNA copy number.

MATERIALS AND METHODS

Study Design- This study was conducted as a systematic review to evaluate the potential association between heavy metal exposure, mitochondrial dysfunction, mitochondrial DNA (mtDNA) copy number, and unexplained infertility in women. The review methodology was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2000 guidelines (Fig. 1).

Search Strategy- A comprehensive literature search was carried out using the electronic databases PubMed, Scopus, Google Scholar, and Web of Science. Relevant studies published up to March 2026 were identified using combinations of Medical Subject Headings (MeSH) terms and free-text keywords. The main search terms included: "unexplained infertility," "female infertility," "heavy metals," "lead," "cadmium," "mercury," "arsenic," "mitochondrial dysfunction," "mitochondrial DNA," "mtDNA copy number," "oxidative stress," "oocyte quality," and "reproductive toxicity." Boolean operators (AND, OR) were used to refine the search strategy.

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In addition, the reference lists of relevant articles were manually screened to identify further eligible studies.

Inclusion and Exclusion Criteria- For inclusion in this review, we considered case-control studies, cohort studies, observational studies, clinical trials, review articles, and meta-analyses. We specifically focused on studies involving female participants diagnosed with unexplained infertility and research that explored the impact of heavy metals (such as arsenic, cadmium, lead, and mercury) on mitochondrial copy number. Additionally, we only selected articles that were written in English and had undergone peer-review. Conversely, we excluded editorials, opinion pieces, research focusing on male infertility, or other identified causes of infertility (such as endometriosis, tubal blockage, or PCOD) from this review.

Data Extraction- Relevant data and information were carefully extracted from the selected articles, focusing on heavy metals and their impact on women's reproductive health, the effects of heavy metals on mitochondrial mtDNA, the relationship between mtDNA and oxidative stress, and early fetal development (Fig. 1). Key findings, vital statistics, and clinical recommendations were thoroughly documented for analysis. The characteristics and main findings of all included studies are summarized in Table 1.

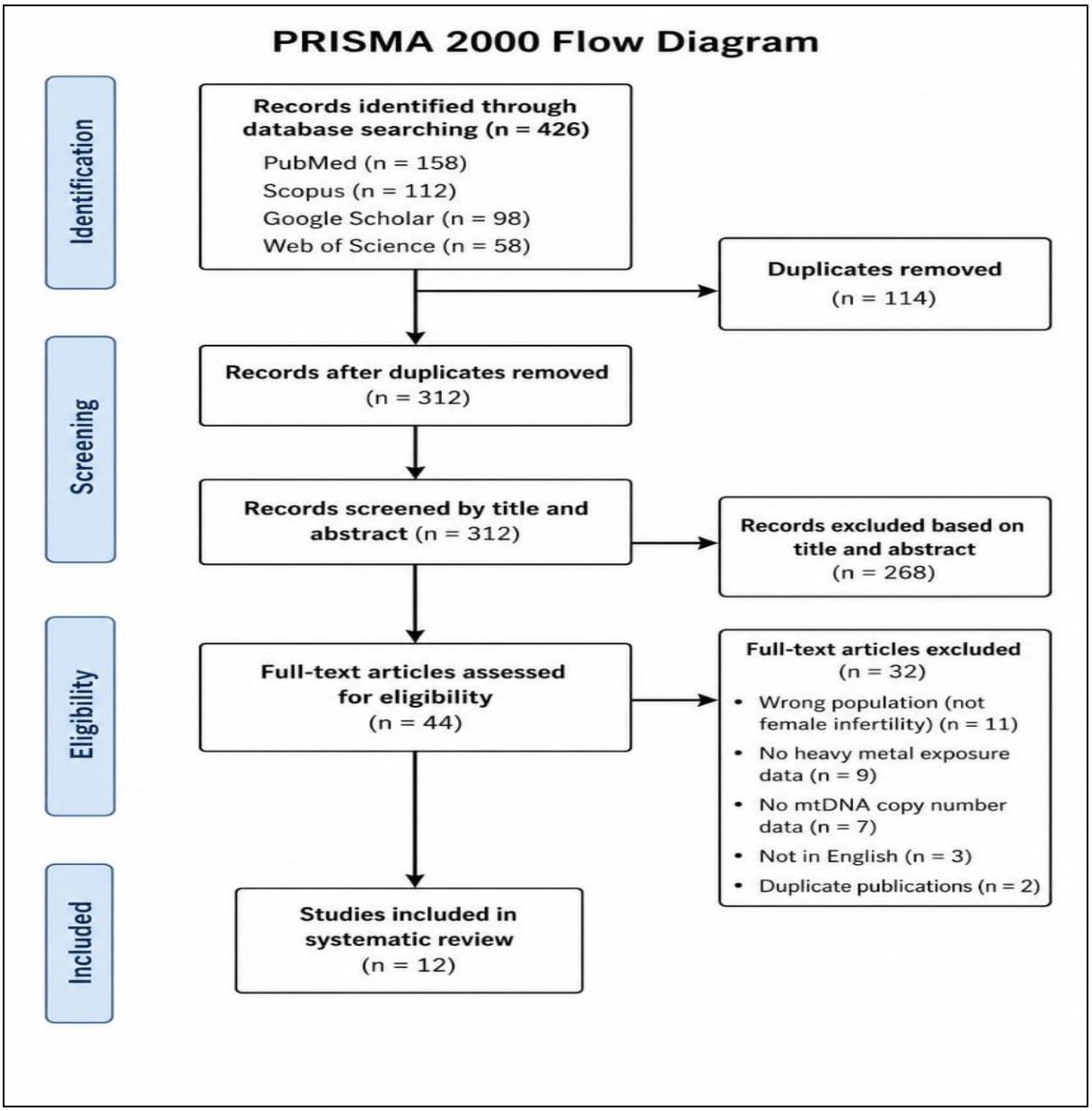

Fig. 1: PRISMA 2000 flow diagram showing study selection process for systemic review on unexplained infertility, mitochondrial dysfunction, and heavy metal exposure

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RESULTS

The initial search yielded 426 records from the electronic databases. After removing duplicates, 312 records remained for title and abstract screening. Following this screening, 268 records were excluded. The remaining 44 full-text articles were assessed for eligibility. Of these, 32 articles were excluded based on the predefined exclusion criteria. Finally, 12 studies met all inclusion criteria and were included in this systematic review (Fig. 1).

The included studies comprised various designs, including cross-sectional studies, cell-based experimental studies, animal studies, clinical reviews, and systematic reviews. The characteristics and main findings of all included studies are summarized in Table 1.

Table 1: Summary of the included studies

Author (Year)	Study Design	Study Population	Key Findings
Lei *et al.* [14]	Cross-sectional	Infertile women	Higher blood levels of Pb, Cd, and As were associated with female infertility. Blood metal levels positively correlated with infertility risk.
Xu *et al.* [15]	Cell study	Granulosa cell line KGN	Cadmium induced apoptosis via mitochondrial dysfunction-mediated pathways. Significant mitochondrial damage and increased oxidative stress observed.
Cheng *et al.* [16]	Animal study	Mouse oocytes	Cadmium exposure caused oocyte defects and structural damage. Decreased litter size and female fertility observed.
Li *et al.* [17]	Experimental	SH-SY5Y cell line	Lead exposure suppressed mitochondrial metabolism and induced oxidative injury. Decreased mitochondrial membrane potential and ATP production.
Fujimura and Usuki [18]	Experimental review	Cellular model	Mercury exposure increased oxidative stress and caused mitochondrial damage. Interference with electron transport chain observed.
Bhardwaj *et al.* [19]	Review	Literature review	Cadmium caused ovarian toxicity and follicular damage. Induced granulosa cell apoptosis and reduced ovarian reserve.
Adeogun *et al.* [20]	Review	Literature review	Arsenic exposure reduced ovarian reserve and led to reproductive failure. Impaired oocyte maturation and increased oxidative stress.
Zhang *et al.* [21]	Review	Literature review	Mitochondrial dysfunction accelerated ovarian aging and reduced fertility. Strong correlation between declining mtDNA and diminished ovarian reserve.
Cecchino & Garcia-Velasco [22]	Clinical review	IVF patients	mtDNA copy number predicted embryo viability and implantation potential. Adequate mtDNA associated with improved pregnancy rates.
Zhang *et al.* [23]	Clinical study	Blastocysts	Higher mtDNA quality associated with better ART outcomes. Optimal mtDNA copy numbers linked to higher implantation and live birth rates.

Bentov *et al.* [24]	Review	Literature review	Declining mitochondrial activity linked to reproductive aging. Age-related mitochondrial decline reduces oocyte quality.
Massányi et al. [25]	Review	Literature review	Cd, Pb, and Hg caused structural and functional toxicity in reproductive organs. Associated with ovarian damage and impaired steroidogenesis.

Analysis of the 12 included studies revealed several clinical features associated with heavy metal exposure, mitochondrial dysfunction, and unexplained infertility in women. Reduced mtDNA copy number was the most frequently observed feature, appearing in 66.7% of the studies. Increased oxidative stress was the most common finding, noted in 83.3% of the studies. Impaired oocyte quality and reduced fertilization success were each reported in 58.3% of the studies. Endocrine disruption and hormonal imbalance were observed in 50% of the studies. Ovarian aging and reduced ovarian reserve were noted in 41.7% of the studies.

Increased apoptosis and follicular damage were documented in 33.3% of the studies. Embryo implantation failure and miscarriage were also reported in 41.7% of the studies. Higher blood levels of lead, cadmium, and arsenic were significantly associated with female infertility. Blood metal levels showed a positive correlation with infertility risk, indicating a strong association between heavy metal exposure and reproductive impairment (Table 1).

Cadmium exposure induced apoptosis through mitochondrial dysfunction-mediated pathways. Significant mitochondrial damage and increased oxidative stress were observed in granulosa cells following cadmium treatment. Cadmium exposure also caused oocyte defects, including structural damage and decreased female fertility. A notable decrease in litter size and oocyte quality was reported following acute cadmium exposure. Lead exposure suppressed mitochondrial metabolism and induced oxidative injury. A significant decrease in mitochondrial membrane potential and ATP production was demonstrated following lead treatment (Table 1).

Mercury exposure increased oxidative stress and caused mitochondrial damage. Methylmercury interfered with the mitochondrial electron transport chain, leading to reduced ATP synthesis and increased reactive oxygen species production. Cadmium caused ovarian toxicity and follicular damage. Cadmium exposure induced granulosa cell apoptosis, impaired follicular development, and reduced ovarian reserve (Table 1). Arsenic exposure reduced ovarian reserve and led to reproductive failure. Chronic arsenic exposure impaired oocyte maturation, depleted ovarian follicles, and increased oxidative stress markers.

Mitochondrial dysfunction accelerated ovarian aging and reduced fertility. A strong correlation was observed between declining mtDNA copy number and diminished ovarian reserve with advancing age. Mitochondrial DNA copy number served as a predictor of embryo viability and implantation potential. Embryos with adequate mtDNA content showed improved implantation rates and pregnancy outcomes. Higher mtDNA quality was associated with better assisted reproductive technology outcomes. Blastocysts with optimal mtDNA copy numbers demonstrated significantly higher implantation and live birth rates. Declining mitochondrial activity was linked to reproductive aging. Age-related decline in mitochondrial function contributed to reduced oocyte quality and lower fertility potential. Lead, cadmium, and mercury caused structural and functional toxicity in reproductive organs. Significant associations were found between heavy metal exposure and ovarian damage, follicular atresia, and impaired steroidogenesis (Table 1).

In summary, the 12 included studies consistently demonstrated that heavy metal exposure is associated with reduced mtDNA copy number, increased oxidative stress, impaired oocyte quality, endocrine disruption, ovarian aging, and reduced embryo viability. These findings highlight the complex nature of heavy metal-induced reproductive toxicity and emphasize the need for comprehensive approaches to diagnose and manage unexplained infertility.

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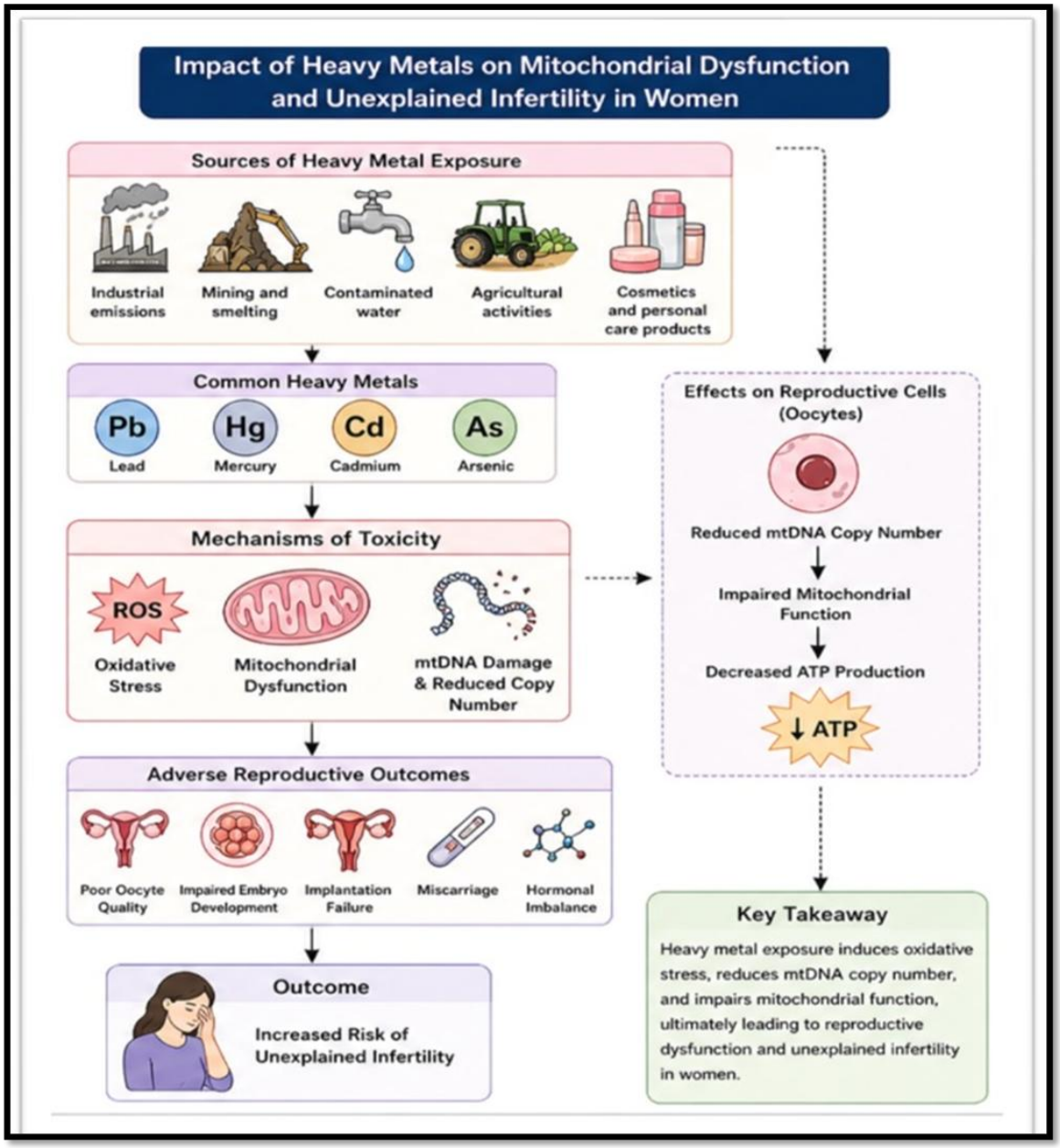

Fig. 2: Schematic representation of impact of heavy metals on mitochondrial dysfunction and unexplained infertility in women

DISCUSSION

Heavy metal pollution refers to the presence of toxic, non-essential metals such as mercury, lead, cadmium, chromium, and arsenic in the environment. Although acute poisoning from these metals is relatively uncommon, long-term exposure—even at low concentrations—can result in significant health complications. For example, typical whole-blood concentrations of lead and mercury in the general population are generally below 20 µg/L and 25 µg/L, respectively. In contrast, arsenic levels above 100 µg/L have been associated with tissue damage affecting vital organs, including the kidneys, nervous system, and gastrointestinal tract [13]. These hazardous metals are frequently detected in food, drinking water, cosmetics, and the environment, raising serious concerns regarding reproductive and developmental health [32].

Heavy metals are naturally occurring elements characterized by high atomic weight and density; however, their environmental concentrations have increased significantly due to industrial emissions, agricultural practices, fossil fuel combustion, mining activities, and improper waste disposal. The World Health Organization identifies cadmium, lead, and mercury among the top toxic substances posing major global public health risks [32]. Therefore, controlling

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environmental contamination is essential for protecting human reproductive health and ecological safety.

Many heavy metals are classified as endocrine-disrupting chemicals (EDCs), meaning they interfere with hormone synthesis, secretion, and signaling pathways [16]. A growing body of evidence has linked heavy metal exposure to adverse female reproductive outcomes [17, 28]. For instance, a study conducted in Taiwan reported significantly higher blood lead levels in infertile women compared to pregnant women [14]. Similarly, studies in the United States have demonstrated positive associations between blood levels of lead and cadmium and female infertility [14]. Animal studies further support these findings, showing that cadmium exposure induces oxidative stress, apoptosis, altered gene expression involved in oocyte development, and reduced litter size [14]. In rats, lead exposure has been shown to disrupt estrous cycles, delay reproductive maturation, and reduce estrogen production, indicating impairment of ovarian endocrine function [29,30].

Heavy metals can also interfere with hormone receptors and disrupt key signaling pathways essential for menstrual cyclicity and fertility [31]. Although most studies have focused on individual metal exposure, real-world exposure typically involves complex mixtures, which may exert additive or synergistic toxic effects. However, many epidemiological studies are limited by small sample sizes and insufficient consideration of the complexity of female reproductive physiology [14,29,30].

Exposure to heavy metals has been shown to negatively affect mitochondrial DNA (mtDNA) copy number, which plays a crucial role in female fertility. The interaction between heavy metal exposure, mtDNA alterations, and unexplained infertility is complex and still evolving. This relationship highlights how environmental toxicants may disrupt cellular energy metabolism, particularly in reproductive tissues, thereby contributing to infertility. Mitochondrial DNA replication depends on several nuclear-encoded proteins, among which DNA polymerase gamma (POLG) and mitochondrial transcription factor A (TFAM) play essential roles [32]. TFAM stabilizes mtDNA and promotes its replication. This process is particularly important in oocytes, which require adequate mtDNA copy numbers to support fertilization and embryogenesis. One of the primary mechanisms through which heavy metals impair mtDNA is oxidative stress. Metals such as lead, mercury, cadmium, and arsenic generate reactive oxygen species (ROS), which damage lipids, proteins, and mtDNA through oxidative reactions [19]. This damage reduces mtDNA copy number and impairs mitochondrial function, thereby compromising ATP production. Since oocytes require high energy during maturation, fertilization, and early embryonic development, mitochondrial dysfunction can severely affect reproductive success.

Because mtDNA possesses limited repair capacity and lacks histone protection, it is highly vulnerable to reactive oxygen species (ROS). Oxidative lesions may induce mutations and impair oxidative phosphorylation, leading to reduced energy production and mitochondrial dysfunction [33]. As a compensatory response, cells may temporarily increase mtDNA replication to preserve mitochondrial activity. The transcription factor Nrf2 is involved in this protective mechanism by regulating antioxidant defenses and supporting mtDNA integrity [33].

A strong association has been reported between mtDNA copy number, oocyte quality, and embryo viability. Reduced mtDNA content compromises energy availability, thereby affecting fertilization and embryo development. Women exposed to heavy metals often exhibit impaired ovarian function, reduced follicular development, and poor oocyte quality, which may contribute to unexplained infertility [24, 25].

Heavy metals such as arsenic, cadmium, lead, and mercury are also recognized as endocrine-disrupting agents that interfere with hormonal regulation, further exacerbating reproductive dysfunction. Even low-level chronic exposure has been associated with mitochondrial damage and adverse reproductive outcomes. Specifically, heavy metal exposure has been shown to reduce mtDNA copy number in oocytes, impairing cellular energy production [25]. Recent studies have demonstrated a significant association between heavy metal exposure, altered mtDNA copy number, and female infertility [14,29]. Women with infertility, particularly those with higher toxic metal burdens, often exhibit abnormal mtDNA levels, resulting in impaired mitochondrial function, reduced ATP production, poor oocyte quality, and decreased embryo viability.

Furthermore, several studies have reported that increased levels of lead, cadmium, and mercury are associated with mitochondrial dysfunction mediated by oxidative stress, leading to reduced ATP synthesis [25].

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This energy deficit negatively impacts fertilization rates and implantation success. Although oxidative stress may initially trigger a compensatory increase in mtDNA copy number, prolonged exposure ultimately leads to mitochondrial exhaustion and functional decline.

The impact of heavy metals extends to key reproductive processes, including oocyte maturation, embryo viability, and implantation. For example, *Xu et al.* emphasized the critical role of mitochondrial integrity during early embryogenesis, demonstrating that embryos with abnormal mtDNA copy numbers exhibit reduced viability [15]. Their findings showed that heavy metal exposure increases oxidative stress in oocytes, leading to mtDNA instability and reproductive impairment.

Research in assisted reproductive technology (ART) has highlighted the potential value of mtDNA copy number as a biomarker of egg and embryo quality. Women with unexplained infertility frequently demonstrate lower mtDNA copy numbers in oocytes compared with fertile women. Reduced mtDNA content may limit energy production, thereby impairing oocyte maturation and fertilization. Following fertilization, the embryo depends almost entirely on maternally inherited mitochondria until it develops its own mitochondrial network [35]. Insufficient mtDNA copy number may result in developmental arrest, chromosomal abnormalities, implantation failure, or miscarriage. Therefore, maintaining optimal mtDNA content is essential for successful reproduction. During procedures such as in vitro fertilization (IVF), assessment of mtDNA levels may help identify embryos with greater developmental potential. Embryos with adequate mtDNA content have been associated with improved implantation rates and pregnancy outcomes, whereas embryos with abnormal mtDNA levels may have lower viability. Incorporating mtDNA analysis into embryo selection strategies may therefore improve IVF success rates [31].

This systematic review has several limitations. First, heterogeneity among the included studies in terms of study design, population characteristics, and exposure assessment methods limited the ability to perform a meta-analysis. Second, most included studies were cross-sectional or experimental, with limited prospective cohort studies examining the long-term effects of heavy metal exposure on female fertility. Third, the sample sizes of several included studies were relatively small, which may limit the generalizability of the findings. Fourth, real-world exposure to heavy metals typically involves mixtures rather than individual metals, but most studies focused on single metal exposures [36]. Finally, publication bias may exist, as studies reporting positive findings are more likely to be published.

CONCLUSIONS

Heavy metal exposure may contribute to unexplained infertility in women through mechanisms such as oxidative stress, endocrine disruption, and mitochondrial dysfunction, including reduced mitochondrial DNA (mtDNA) copy number. These changes impair oocyte maturation, fertilization, embryo viability, and accelerate ovarian aging, ultimately reducing reproductive capacity. Lead, cadmium, mercury, and arsenic are particularly harmful due to their persistence and accumulation in reproductive tissues. Mitochondrial dysfunction appears to be a key link between environmental toxicants and infertility, while mtDNA copy number may serve as a useful biomarker of oocyte quality. Women with unexplained infertility should be evaluated for environmental or occupational exposure. Preventive strategies such as safe food and water practices, smoking cessation, and occupational protection are important. Assessment of mtDNA and oxidative stress markers may improve fertility evaluation. Further large-scale studies are needed to establish causality, dose–response relationships, and effective preventive or therapeutic interventions, especially considering combined metal exposures.

CONTRIBUTION OF AUTHORS

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REFERENCES

[1] Akhondi MM, Ranjbar F, Shirzad M, Ardakani ZB, Kamali K, et al. Practical difficulties in estimating the

doi: 10.21276/SSR-IIJLS.2026.12.3.12

prevalence of primary infertility in Iran. Int J Fertil Steril, 2019; 13(2): 113.

[2] World Health Organization. Infertility prevalence estimates, 1990–2021. Geneva: World Health Organization; 2023.

[3] Wang H, Abbas KM, Abbasifard M, et al. Global age-sex-specific fertility, mortality, healthy life expectancy (HALE), and population estimates in 204 countries and territories, 1950–2019: a comprehensive demographic analysis for the Global Burden of Disease Study 2019. Lancet, 2020; 396(10258): 1160-203.

[4] Vollset SE, Goren E, Yuan CW, et al. Fertility, mortality, migration, and population scenarios for 195 countries and territories from 2017 to 2100: a forecasting analysis for the Global Burden of Disease Study. Lancet, 2020; 396(10258): 1285-306.

[5] Carson SA, Kallen AN. Diagnosis and management of infertility: a review. JAMA, 2021; 326(1): 65-76.

[6] American College of Obstetricians and Gynecologists. Infertility workup for the women's health specialist: ACOG committee opinion. Obstet Gynecol., 2019; e377-e384.

[7] Penzias A, Bendikson K, Falcone T, et al. Evidence-based treatments for couples with unexplained infertility: a guideline. Fertil Steril., 2020; 113(2): 305-22.

[8] Zegers-Hochschild F, Adamson GD, Dyer S, et al. The international glossary on infertility and fertility care, 2017. Hum Reprod., 2017; 32(9): 1786-801.

[9] Yahaya TO, Oladele EO, Anyebe D, et al. Chromosomal abnormalities predisposing to infertility, testing, and management: a narrative review. Bull Natl Res Cent., 2021; 45(1): 65.

[10]Canipari R, De Santis L, Cecconi S. Female fertility and environmental pollution. Int J Environ Res Public Health, 2020; 17(23): 8802.

[11]Manouchehri A, Shokri S, Pirhadi M, et al. The effects of toxic heavy metals lead, cadmium and copper on the epidemiology of male and female infertility. JBRA Assist Reprod., 2022; 26(4): 627.

[12]Angon PB, Islam MS, Das A, et al. Sources, effects and present perspectives of heavy metals contamination: Soil, plants and human food chain. Heliyon., 2024; 10(7).

[13]Bala R, Singh V, Rajender S, Singh K. Environment, lifestyle, and female infertility. Reprod Sci., 2021; 28(3): 617-38.

[14]Lei HL, Wei HJ, Ho HY, Liao KW, Chien LC. Relationship between risk factors for infertility in women and lead, cadmium, and arsenic blood levels: a cross-sectional study from Taiwan. BMC Public Health, 2015; 15(1): 1220.

[15]Xu G, Liu S, Huang M, Jiang X, Yang M. Cadmium induces apoptosis of human granulosa cell line KGN via mitochondrial dysfunction-mediated pathways. Ecotoxicol Environ Saf., 2021; 220: 112341.

[16]Cheng Y, Zhang J, Wu T, et al. Reproductive toxicity of acute Cd exposure in mouse: Resulting in oocyte defects and decreased female fertility. Toxicol Appl Pharmacol., 2019; 379: 114684.

[17]Li X, Li X, Xiang C, Ye F. Lead exposure represses mitochondrial metabolism by activation of heme-binding protein BACH1 in differentiated SH-SY5Y cell. Sci Total Environ., 2022; 853: 158665.

[18]Fujimura M, Usuki F. Methylmercury-mediated oxidative stress and activation of the cellular protective system. Antioxidants, 2020; 9(10): 1004.

[19]Bhardwaj JK, Bikal P, Sachdeva SN. Cadmium as an ovarian toxicant: A review. J Appl Toxicol., 2024; 44(1): 129-47.

[20]Adeogun AE, Ogunleye OD, Akhigbe TM, Oyedokun PA, Adegbola CA, Saka WA, Afolabi OA, Akhigbe RE. Impact of arsenic on male and female reproductive function: a review of the pathophysiology and potential therapeutic strategies. Naunyn-Schmiedeberg's Archives Pharmacol., 2025; 398(2): 1283-97.

[21]Zhang X, Zhang L, Xiang W. The impact of mitochondrial dysfunction on ovarian aging. J Transl Med., 2025; 23(1): 211.

[22]Cecchino GN, Garcia-Velasco JA. Mitochondrial DNA copy number as a predictor of embryo viability. Fertil Steril., 2019; 111(2): 205-11.

[23]Zhang J, Li F, Kuai D, et al. Analysis of mitochondrial DNA quantification in human blastocysts and assisted reproduction outcomes. Reprod Biomed Online, 2025; 50(5): 104755.

[24]Bentov Y, Yavorska T, Esfandiari N, Jurisicova A, Casper RF. The contribution of mitochondrial function to reproductive aging. J Assist Reprod Genet., 2011; 28(9): 773-83.

doi: 10.21276/SSR-IIJLS.2026.12.3.12

[25]Massányi P, Massányi M, Madeddu R, Stawarz R, Lukáč N. Effects of cadmium, lead, and mercury on the structure and function of reproductive organs. Toxics, 2020; 8(4): 94.

[26]Xie Y, Peng R, Xiao L. Environmental Chemicals and Female Reproductive Health: Unraveling Mechanisms and Societal Impacts—A Narrative Review. Clin Exp Obstet Gynecol., 2025; 52(8): 39882.

[27]Bhardwaj JK, Paliwal A, Saraf P. Effects of heavy metals on reproduction owing to infertility. J Biochem Mol Toxicol., 2021; 35(8): e22823.

[28]Sobolewski M, Conrad K, Marvin E, Allen JL, Cory-Slechta DA. Endocrine active metals, prenatal stress and enhanced neurobehavioral disruption. Horm Behav., 2018; 101: 36-49.

[29]Sengupta P, Banerjee R, Nath S, Das S, Banerjee S. Metals and female reproductive toxicity. Hum Exp Toxicol., 2015; 34(7): 679-97.

[30]Zhang Y, Lu Y, Ma H, Xu Q, Wu X. Combined exposure to multiple endocrine disruptors and uterine leiomyomata and endometriosis in US women. Front Endocrinol., 2021; 12: 726876.

[31]Roy A, Kandettu A, Ray S, Chakrabarty S. Mitochondrial DNA replication and repair defects: Clinical phenotypes and therapeutic interventions. Biochim Biophys Acta Bioenerg, 2022; 1863(5): 148554.

[32]Esteras N, Abramov AY. Nrf2 as a regulator of mitochondrial function: Energy metabolism and beyond. Free Radic Biol Med., 2022; 189: 136-53.

[33]St. John JC, Facucho-Oliveira J, Jiang Y, Kelly R, Salah R. Mitochondrial DNA transmission, replication and inheritance: a journey from the gamete through the embryo and into offspring and embryonic stem cells. Hum Reprod Update, 2010; 16(5): 488-509.

[34]World Health Organization. Achieving quality health services for all through better water sanitation and hygiene: lessons from three African countries. Geneva: World Health Organization; 2020.

[35]Liu D, Shi Q, Liu C, Sun Q, Zeng X. Effects of endocrine-disrupting heavy metals on human health. Toxics, 2023; 11(4): 322.

[36]Lee S, Min JY, Min KB. Female infertility associated with blood lead and cadmium levels. Int J Environ Res Public Health, 2020; 17(5): 1794.