Systematic Review

Exploring the Association between Arsenic Exposure and Sperm Quality: A Systematic Review and Meta-analysis

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Abstract

Background: Human beings are routinely exposed to arsenic, a ubiquitous environmental toxicant present in food, water, air and soil. Both acute and chronic exposure to this metalloid poses significant health risks, including negative impact on the male reproductive system, as evident from studies in humans and animals. **Objective:** The current systematic review evaluated the impact of arsenic exposure on semen quality in human populations to determine any association between decline in semen quality and arsenic exposure. **Materials and Methods:** A total of 361 studies were retrieved from systematic literature search in electronic databases, namely Scopus, PubMed and Cochrane central databases. Two step screening process was performed by two reviewers independently, and finally four studies were included in the review. **Results:** Two cross-sectional studies were included for meta-analysis. In cross-sectional studies, pooled mean semen volume (3.18 ml; 95% confidence interval [CI]: 2.34–4.02; I^2 = 86.5%), sperm concentration (78.69 × 10^6/mL; 95% CI: 66.01–91.37; I^2 = 0.0%) and sperm motility (52.13%; 95% CI: 29.88–74.37; I^2 = 95.0%) were within or above the World Health Organization reference values, although with high heterogeneity. The findings from two case–control studies could not be pooled due to a lack of appropriate non-exposure controls and are therefore described narratively. **Interpretation:** The meta-analysis suggests that arsenic exposure may negatively influence semen volume, with inconsistent effects on concentration and motility. Despite biological plausibility involving oxidative stress and endocrine disruption, the limited number of studies and methodological variability restrict definitive conclusions. Further large scale, longitudinal studies with standardised exposure and outcome assessments are essential to validate these findings. **Limitations:** The small number of eligible studies and high heterogeneity across designs and exposure assessments limit the generalizability of findings. In addition, the lack of longitudinal data restricts causal inference regarding arsenic's effect on semen quality. **PROSPERO Registration:** CRD42024529010.

Keywords: *Arsenic, male infertility, sperm concentration, sperm morphology, sperm motility*

Introduction

Infertility and sub-fecundity are global health concerns. Their prevalence is steadily increasing globally, for example one in every six couples experiences some fertility-associated challenges during their reproductive years.[1,2] In addition, literature analysis reveals that around 30% of infertility is accounted to male factors. While oxidative stress, generation of reactive oxygen species (ROS) and tissue damage are considered underlying mechanisms behind reproductive toxicity,

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lifestyle factors and exposure to environmental pollutants are also known to be detrimental factors affecting male reproductive health.[3] Exposure to endocrine-disrupting compounds in occupational settings, environment sources like contaminated water (pesticides and heavy metals) has been known to be associated with adverse outcomes in the male reproductive system, especially reductions in semen quality and quantity.[4,5] Furthermore, the general population residing in industrial and agricultural regions where pollutant discharge is prevalent also exhibits reproductive health issues.[6]

Arsenic is a naturally occurring element widely dispersed across the environment.[7] It enters water supplies mostly through geological or industrial processes and exhibits severe threat to human health on a global scale.[8,9] Arsenic can enter the human system by three major routes, namely ingestion, inhalation and/or skin contact via contaminated ground water, low levels in air and food products.[10,11] Literature demonstrates that millions of people, specifically in areas of South Asia, the United States of America and Latin America are exposed to high amount of arsenic.[12] The World Health Organization (WHO) recommends a maximum arsenic concentration of 10 μg/L in drinking water.[13] In normal human populationblood arsenic concentrations are usually below 5 μg/L, and urinary arsenic levels are generally <10 μg/L.[14] Heavy metals exert negative effect on sperm quality through multiple pathways, including interference with cellular signalling, modulation of gene expression, induction of oxidative stress, DNA damage and activation of apoptotic pathways.[15,16] These mechanisms collectively contribute to compromised reproductive function and highlight the pressing need for further investigation into environmental contaminants and reproductive health.[9] Inorganic arsenic is most toxic form that exhibits negative health effects on accumulation in the human body. Arsenic gains enter majorly through contaminated water, food, air and soil.[17] It thereafter gets absorbed through the gastrointestinal tract, respiratory system or skin.[18] It then crosses the blood-testis barrier and accumulates in reproductive organs such as testes, epididymis and seminal vesicles. It can exert deleterious effects on organs such as the brain, liver, kidneys and testicular tissues. The consequences of arsenic deposition are reduction in sperm concentration, low sperm motility, abnormal sperm morphology, testicular damage, germ cell apoptosis and Leydig cell dysfunction as well as hormonal imbalance (decrease in testosterone, LH and FSH levels).[19-21]

Association between arsenic exposure and elevated oxidative stress, DNA damage and cell death has been established in several research articles, which ultimately affect the male reproductive system by impairing normal sperm function.[22,23] Exposure to arsenic has been correlated with alterations in sperm motility, morphology and concentration. Therefore, it is essential to understand the mechanisms behind these associations, particularly given the prevalent exposure to arsenic and increased infertility incidences.[24,25] Arsenic induces oxidative stress in testicular cells, resulting in ROS generation, affects spermatogenesis, sperm DNA and membrane integrity.[26-28] Genotoxic nature of arsenic is evident by its ability to destroy sperm DNA and chromatin structure.[21] In addition, inorganic arsenic can also decrease the concentration of gonadotrophins and testosterone.[21]

Given the widespread presence of arsenic and its potential to impair male reproductive function, it is crucial to assess the existing evidence urgently. Although several studies have explored arsenic's effects on male reproductive health, findings are often inconsistent. Therefore, a systematic review on this topic will provide a comprehensive analysis of arsenic's impact on sperm parameters (sperm count, viability, motility, morphology and sperm DNA integrity), clarify the extent of the risk and identify gaps in knowledge, ultimately aiding in formulating public health policies aimed at reducing arsenic exposure and safeguarding male fertility. In light of this, the objective of this systematic review was to scientifically evaluate the evidence underlying arsenic exposure to impaired sperm quality and male infertility, as well as understand the principle of biological mechanisms behind these associations and the implications for reproductive health. Through this analysis, we aim to inform clinical practices and public health guidelines for mitigating the adverse effects of arsenic on male reproductive health.

Materials and Methods

Protocol registration

This systematic review was written in compliance with PRISMA-P2020 guidelines.[29] Protocol has been registered with PROSPERO under ID CRD42024529010.

Data sources and search strategy

A compressive search in Scopus, PubMed and Cochrane central databases was performed on 01 March 2024. A combination of systematic methodological search terms related to arsenic, human, infertility and sperm parameters, along with their Medical Subject Headings terms, was used for search [Supplementary Table 1].

Inclusion/exclusion criteria for studies

The eligibility criteria for selecting studies for inclusion in this systematic review were formulated according to the PEOS approach.

Population

Studies conducted in human populations were included in the study. Studies conducted in animal models or cell lines were excluded from the study.

Exposure

Studies investigating exposure to arsenic from any source (e.g., in drinking water, air, food, occupational exposure) settings were included in the study. Further, for each included study, the quantitative exposure levels reported, the type of exposure (e.g., arsenic concentration in drinking water, blood, urine or air concentrations in μg/L), and the duration or frequency of exposure where available. Arsenic may exist in multiple forms such as Arsenic (As), inorganic arsenic (As_i), trivalent arsenic (As_i^{III}), pentavalent arsenic (As_i^{V}), monomethylarsonic Acid (MMA), dimethylarsinic acid (DMA) and arsenobetaine (AsB). Arsenic methylation indices can be calculated as primary (PMI = MMA/As_i) or secondary (SMI = DMA/MMA). Arsenic redox potential can be defined as As_i^{V}/As_i^{III}.

Outcome

Our primary outcome was critical sperm parameters. It included sperm count and functional parameters such as sperm motility, sperm morphology and sperm DNA integrity.

Study design

All the relevant cross-sectional, cohort and case–control studies were included in the study. However, comprehensive reviews, systematic reviews, abstracts and conference proceedings were not included in the study.

Language

Only studies written in English were included in the study.

Availability of full text

All the studies finally included were available on the journal website as open access.

Study selection and screening

All the studies retrieved after the database search were uploaded on RAYYAN blinded software and duplicate studies were removed.[30] Two authors did the primary screening independently of title and abstract as per the eligibility criteria and a third reviewer resolved the conflicts. Subsequently, the full-text articles for the selected studies were downloaded. Then, the full-text articles were screened for their eligibility to be included in the final study by two authors, independently.

Data extraction

The following data were collected: citation, study design, study location, sample size, exposure (Arsenic exposure), comparator, participant characteristics, reported outcomes, i.e. and sperm parameters (sperm count, viability, motility, volume and morphology). Data extraction was performed by two reviewers.

Assessment of risk of biases

All the included studies were appraised for the risk of bias by two authors, independently. The case–control studies were assessed on the basis of 'The Newcastle–Ottawa Scale'.[31] The cross-sectional studies, however, were assessed in accordance with 'JBICritical Appraisal Checklist for Analytical Cross-sectional Studies'.[32]

Meta-analysis

The meta-analysis was performed for two cross-sectional studies using random effect model as there was high heterogeneity. It was focused on outcomes such as semen volume, sperm concentration and motility.

Results

Study selection and description of included studies

We retrieved a total of 233 studies from Scopus, 124 studies from PubMed and 4 studies from Cochrane databases. Out of the total 361 studies, 100 were removed due to duplicity. During the primary screening of the title and abstracts, 256 studies were further removed. Full-text articles were retrieved for the five selected studies, screened and ultimately, two studies were included in the review for meta-analysis. In addition, two studies cross sectional were also included, but they do not have non-exposed controls; therefore, meta-analysis was not performed. The selection process used is outlined briefly in Figure 1. Detailed characteristics of the included studies are mentioned in Table 1.

Meta-analysis results for cross sectional studies

The meta-analysis of the two included cross-sectional studies (Xu *et al*., 2012; Oguri *et al*., 2016) was conducted to quantitatively evaluate the effect of arsenic exposure on semen quality parameters, including semen volume, sperm concentration and sperm motility [Figure 2]. Normal reference value for sperm parameters is considered per the WHO 2010 guidelines, i.e., semen volume (≥1.5 mL), sperm concentration (≥15 × 10^6/mL), sperm motility (≥40%) and sperm morphology (≥4%). Here, the WHO 2021 was not considered because all the included studies were conducted from 2010 to 2020.[38]

Semen volume

The pooled mean was estimated at 3.18 ml (95% confidence interval [CI]: 2.34–4.02; $P < 0.001$), with a wide prediction interval ranging from − 5.85 to 12.21. A high degree of heterogeneity was observed across studies (I^2 = 86.5%, P = 0.0065), indicating substantial variability likely attributable to differences in arsenic exposure levels, participant characteristics or assessment methods.

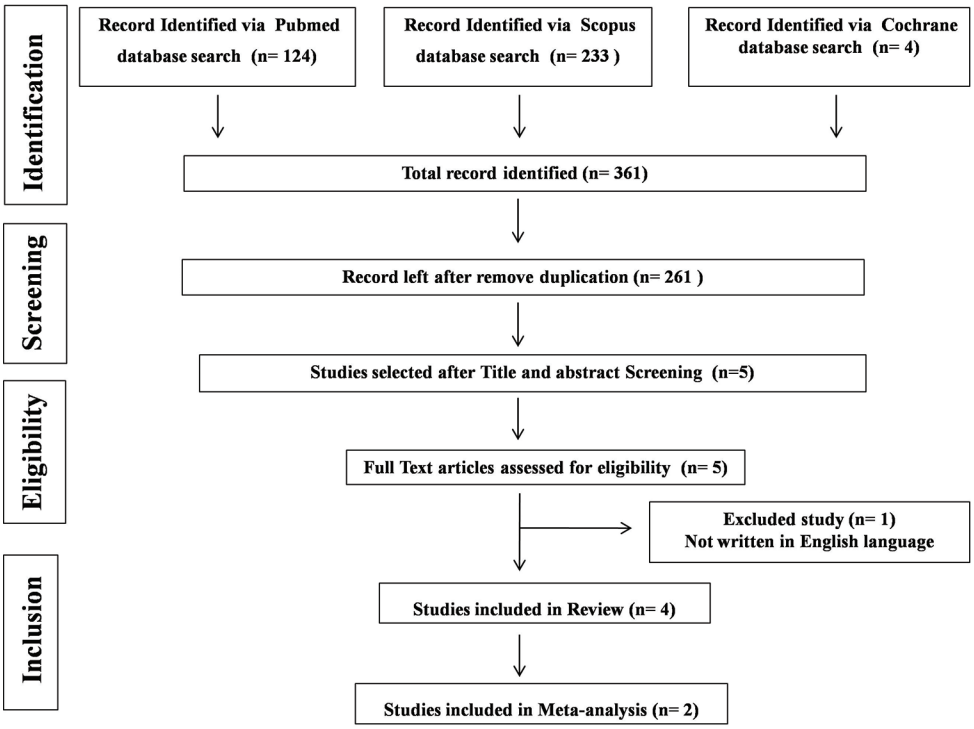

Figure 1: PRISMA flowchart for identification, screening and selection of eligible studies to assess the impact of arsenic exposure on human sperm quality

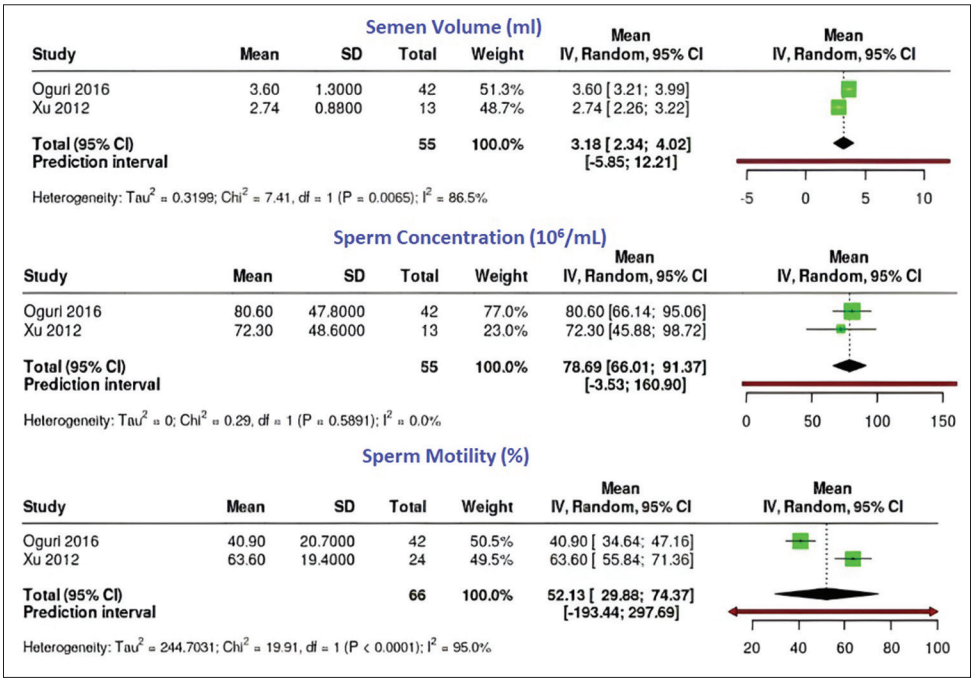

Figure 2: Quantitative analysis of sperm parameters of cross sectional studies using Random effect model. Note: Normal reference value for sperm parameters are considered as per World Health Organization (WHO) 2010 guidelines, i.e. semen volume (≥1.5 mL), sperm concentration (≥15 × 10^6/mL), sperm motility (≥40%) and sperm morphology (≥4%.) WHO 2021 guidelines, i.e. semen volume (≥1.4 mL), sperm concentration (≥16 × 10^6/mL), sperm motility (≥42%) and sperm morphology (≥4%)[37]

Sperm concentration

The pooled mean was 78.69 × 10^6/mL (95% CI: 66.01–91.37; $P < 0.0001$), with a prediction interval of − 3.53–160.90. Notably, no statistical heterogeneity was detected ($I^2 = 0.0\%$, $P = 0.5891$), suggesting consistent findings across both studies and supporting the reliability of this estimate.

Sperm motility

The pooled mean was 52.13% (95% CI: 29.88–74.37; $P < 0.0001$), with an exceptionally wide prediction

Table 1: Characteristics features of the eligible studies included

Author and year	Country	Study design	Participant characteristics	Sample size	Duration of sample	Urinary arsenic concentration (µg/g creatinine)	Reproductive parameters	Reference
Xu *et al.*, 2012	China	Cross-sectional observational study	Age=32±4.8 years BMI=23.5±3.3 kg/m^2 Male partner of infertile couple	*n*=96	July 2009–August 2010	As_i=4.03±3.67 AsB=7.49±24.8 MMA=2.77±3.33 DMA=20.9±13.7	DMA concentration above the median associated with below reference sperm concentration (*P*=0.02)	[33]
Oguri *et al.*, 2016	Japan	Cross-sectional observational study	Age=36.8±5.4 years BMI=23.4±2.6 kg/m^2 Male partner of infertile couple	*n*=42	January 2010–June 2010	As^V=0.549±0.834 As^{III}=0.8±0.515 MMA=1.15±0.516 DMA=20.6±14.1 As_i±MMA=2.50±1.30 PMI=1.13±0.72	No correlation found	[34]
Shen *et al.*, 2013	China	Case-Control observationalstudy	Cases Age=29.7±4.6 years BMI=23.4±3.2 kg/m^2 Infertile male (unknown cause of infertility) Control Age=29.2±5.2 years BMI=24.7±3.2 kg/m^2 Fertile male	Cases=150 Control=151	April 2007–September 2010	Cases AsiV=19.6±343.3 AsiIII=3.5±7.9 AsB=9.8±44.6 Asi=36.7±344.2 As=95.6±355.7 MMA=3.1±3.4 DMA=20.5±21.3 PMI=0.08±0.6 SMI=6.6±25.9 Redox Potential=5.6±102.8 Controls AsiV=2.4±165.0 AsiIII=3.4±3.1 AsB=8.1±16.9 Asi=10.8±165.8 As=49.6±172.5 MMA=2.8±2.5 DMA=18.2±15.4 PMI=0.3±0.4 SMI=6.5±15.6 Redox Potential=0.7±29.8	Increase urinary concentrations of As_i^V from general As exposure is significantly associated with male infertility	[35]

Contd...

Table 1: Contd...

Author and year	Country	Study design	Participant characteristics	Sample size	Duration of sample	Urinary arsenic concentration (µg/g creatinine)	Reproductive parameters	Reference
Wang *et al.*, 2016	China	Case-control observational study	Cases Age=28.7±3.9 years BMI=23.1±2.9 kg/m^2 Infertile males (unexplained infertility) Controls Age=28.5±5.3 years BMI=25.3±3.1 kg/m^2 Fertile males	Cases=101 Control=61	April 2007–September 2010	Cases As_i^{III}=2.70±4.22 As_i^{V}=41.37±293.81 AsB=10.27±34.19 MMA^{V}=3.70±4.57 DMA^{V}=22.78±34.78 As_i=50.71±294.51 As=108.45±317.76 Redox Index=15.34±1000.52 PMI=0.07±0.38 Controls As_i^{III}=3.32±2.63 As_i^{V}=1.79±101.27 AsB=7.89±7.27 MMA^{V}=2.83±2.53 DMA^{V}=18.12±14.27 As_i=9.49±102.07 As=47.21±105.56 Redox Index=0.54±16.26 PMI=0.30±0.41	No significant differences observed between cases and controls in semen parameters As_i^{V}, AsB, MMA^{V}, DMA^{V}, As, As_i and redox potential were significantly high and PMI were significantly lower in infertile male group as compared to control group	[36]

As_i^{V}/As_i^{III}=Arsenic redox potential, AsB=Arsenobetaine, BMI=Body mass index, DMA=Dimethylarsinic acid, MMA=Monomethylarsonic Acid, As_i^{V}=Pentavalent arsenic, PMI=Primary methylation indices, SMI=Secondary methylation indices, AS=Total Arsenic, As_i=Total Inorganic arsenic, As_i^{III}=Trivalent arsenic, PMI=MMA/Asi, SMI=DMA/MMA, As=As_i^{III} + As_i^{V} + A sB + MMA + DMA, As_i=As_i^{III} + As_i^{V}

interval (−193.44–297.69), reflecting substantial uncertainty. Heterogeneity was considerable (I^2 = 95.0%, P < 0.0001), indicating significant inconsistencies between studies, potentially due to methodological differences or population-specific factors.

Sperm morphology

Xu *et al*. 2012 highlighted abnormal morphology in 47% of participants with infertility issues. However, Oguri *et al*. 2016 did not assess the sperm morphology; therefore, meta-analysis was not possible for this outcome.

Association of arsenic exposure with sperm parameter

Xu *et al*., 2012, reported that DMA concentration above the median was associated with reduced sperm concentration (P = 0.02) in Chinese men of reproductive age. However, Oguri *et al*., 2016, could not establish any correlation amongst arsenic exposure and sperm parameters, which might be due to low level of arsenic exposure (0.5 $mg^{-1\ kg}\ day^{-1}$).

Narrative result for case control studies

Shen *et al*., 2013-Findings from this case–control study amongst Han Chinese men showed increased urinary arsenate (AsV) levels were strongly associated with idiopathic male infertility in a dose-dependent manner. Further urinary metabolic biomarkers, including reduced acylcarnitines and aspartic acid and elevated uridine and methylxanthine levels were linked to poor semen quality. These findings suggest arsenic may impair male fertility through oxidative stress and hormone disruption pathways.

Wang *et al*., 2016-In this case–control study 101 men with unexplained infertility and 61 fertile controls were involved, and urinary concentrations of arsenate (AsV), AsB, MMAV and DMAV were measured. Result showed arsenic and their metabolite levels were significantly elevated in the infertile group compared with fertile controls. These findings suggest that even low-level environmental arsenic exposure may substantially increase susceptibility to unexplained male infertility through impaired arsenic metabolism.

Risk of bias

Cross-sectional study

Xu *et al*., 2012: Despite the identification and management of confounding factors, causal conclusions are limited by the study's basic design. Self-reported data were used for the exposure measurement, which could lead to reporting bias.

Oguri *et al*., 2016: This study lacked a sample size justification, power description or effect estimates, which could undermine the statistical validity. The details has been presented in Supplementary Table 2.

Case–control study

Shen *et al*., 2013: In this study, selection criteria achieved a moderate score, but exposure comparability was insufficiently robust, suggesting a risk of selection bias. Further, the study's inability to ensure comprehensive matching or control for confounders introduces uncertainty in the associations.

Wang *et al*., 2016: The study adjusted for major confounding factors such as age, BMI, smoking, and drinking habits. Exposure to arsenic was measured using reliable and validated laboratory techniques. Both groups were assessed using the same methods, minimising measurement bias. Overall, the study design and analysis were methodologically sound and well-executed [Supplementary Table 3].

Discussion

In this study, we assessed the effects of arsenic exposure on critical semen parameters such as concentration, motility, volume and morphology, The results from the two cross-sectional studies included investigations offer important insights into the effects of arsenic exposure on sperm quality.[33-35] In brief, Xu *et al*. analysed arsenic metabolites in a reproductive-age cohort using a cross-sectional approach, Oguri *et al*. utilised a cross-sectional design with low arsenic exposure levels. By contrast, the two case–control studies could not be included in the meta-analysis due to the absence of appropriate control (non-exposure) groups. Shen *et al*. studied infertile men in a high-exposure area, and Wang *et al*. analysed the impact of low-level environmental arsenic exposure in non-occupational settings. Their findings showed that arsenic exposure, especially at higher levels, was associated with reductions in sperm concentration, motility and morphology.

To quantitatively amalgamate the findings, a meta-analysis of data extracted from the included studies was performed. The meta-analysis included two cross-sectional studies that provided an estimation of semen parameters, including semen volume, concentration and motility. In cross-sectional studies, the pooled mean sperm volume, concentration and motility were mostly within WHO reference limits. Briefly, in low-exposure cohorts, Oguri *et al*. (2016) stated no significant correlation between arsenic exposure and sperm motility or volume, emphasising the possible dose-dependent effects. Wang *et al*., 2016, observed a positive correlation between non-occupational arsenic exposure and male infertility parameters. While in high-exposure populations, Shen *et al*. (2013) and Xu *et al*. (2012) showed substantial decreases in sperm concentration, motility and morphology, suggesting

exposure to high arsenic concentration causes noticeable effects. It can hence be inferred that exposure to arsenic results in an alteration in the quality of semen, especially volume, whereas the extent of impact differs based on study design and measurement consistency. This heterogeneity in results underscores how essential parameters such as exposure duration, metabolites produced from arsenic and individual susceptibility affect the resultant toxicity. However, the complexity that arsenic exhibits on reproductive health was evident by the disparities between these studies, and therefore large-scale studies are necessary for reducing heterogeneity and ascertaining the obtained trends.

The findings from these studies are consistent with many studies that associate exposure to heavy metals like arsenic with toxicity in male reproduction.[39,40] Research has repeatedly demonstrated that arsenic exposure causes oxidative damage and hormonal disturbance, which lowers sperm count, motility, and morphology in humans.[41,42] More specifically, oxidative stress results in elevated ROS impairing spermatogenesis, disruption of mitochondrial and membrane integrity and DNA damage in spermatozoa.[3] This mechanistic insight was highlighted by Shen *et al*., who correlated urinary metabolomics biomarkers with an increase in the oxidative stress pathway. Moreover, the dose-response trends in individuals exposed to low arsenic levels in non-occupational settings were correlated with infertility risks. This signifies that even background exposure can result in arsenic-induced male infertility risks and affect several semen parameters.[36]

These findings also corroborate with animal models that revealed that arsenic exposure leads to bioaccumulation, testicular damage, alteration of spermatogenesis, low testosterone level and sperm DNA damage, etc.[43-45] The mechanism/biological pathway via which arsenic exerts its deleterious effect on male reproductive system is oxidative stress, hormonal dysregulation and direct germ cell damage.[46,47] Exposure to elevated levels of arsenic induces the generation of ROS that causes lipid peroxidation, DNA damage, germ cell death and denaturation of proteins in testicular tissues.[48,49] DNA integrity is also affected by ROS which is a vital factor for fertilization and generation of healthy progeny.[50] At hormonal level, arsenic can modulate hypothalamic–pituitary axis, alter gene expressions (luteinizing hormone receptor, steroidogenic acute regulatory protein) and disrupts the LH and FSH hormones, which lead to reduced testosterone levels and ultimately affecting the spermatogenesis process.[51,52] In addition, impairment arsenic exposure cause cellular toxicity in Leydig and Sertoli cells that impairs sperm production and maturation.[46,47,53,54] When arsenic accumulates in reproductive organ tissues, it leads to genotoxicity. Thereby accumulation of arsenic in reproductive tissues leads to genotoxic effects that alter chromatin structure as well as damages DNA, and germ cells ultimately leading to cell death.[55,56]

This review quantitatively integrates stated evidence and also highlights that at an individual level, statistical validation is limited. Further, the review helps in the identification of key parameters that can provide evidence for future research and accordingly prepare policy-making in environment and reproductive health domains. Long-term research focusing on evaluating dose-response associations between sperm quality and arsenic exposure needs to be undertaken; genetic and epigenetic variables that increases an individual's vulnerability to arsenic has to be analysed and examining the combined impact of arsenic and other environmental pollutants is equally essential. The review thus emphasises the need for multidisciplinary approaches that integrate toxicology, epidemiology and public health.

Limitations of the study

A major limitation of this systematic review and meta-analysis study is that only limited studies met the inclusion criteria, that too with different study design, that considerably restricts the statistical and meta-analysis results. The sample size was considerably small in the studies, especially Oguri *et al*., thereby further diminishing statistical robustness. The cross-sectional study designs restrict causal interpretation and chronological relationship. The confounding factors (such as lifestyle, nutrition, co-exposure and smoking) are not uniform; occupational exposure, co-exposures were not specific across all the included studies. Further, the absence of cohort and longitudinal study limits the prediction of long-term reproductive effect of arsenic exposure. In the last, included studies are concentrated to specific geographical region limiting its generalisability to global population.

Future perspective

This systematic review and meta-analysis offer insights into the impact of arsenic exposure on humans based on epidemiological data, thereby providing important insights into public health concerns related to arsenic exposure and toxicity. Minimising arsenic-induced reproductive damage requires a multipronged approach focusing on individual-level interventions, technological advancements and large-scale public health initiatives. However, contaminated drinking water contains high levels of arsenic and therefore water remediation strategies such as reverse osmosis, activated alumina

adsorption filters and ion-exchange systems can be used. Apart from this, sustainable and cost-effective filtration technologies can be used. In addition, promoting dietary diversity and antioxidant supplements can limit the risks after exposure.[56,57] At an individual level, apart from antioxidant supplementation, modification in diet, such as sulphur-rich diet (garlic and onions) can enhance detoxification of arsenic as these compounds promote excretion of arsenic.[57] Taking antioxidant-based dietary supplements rich in Vitamin C, E and selenium can help combat arsenic-induced oxidative stress.[58,59] Supplementation of folic acid in diet causes methylation of arsenic, thereby facilitating its excretion from the body. Further, community awareness efforts to inform people about the dangers of arsenic and protective practices are also a crucial step. The WHO's recommended 10 μg/L threshold as for acceptable levels of arsenic in drinking water, and this should be strictly enforced by governments.[60] Organising frequent public awareness programmes, focusing on dangers of arsenic exposure and protective actions, can be beneficial at the community level. Enforcement of strict regulations on permissible arsenic levels in water and food, awareness campaigns and regular health screening for early detection of arsenic toxicity can assist in timely medical interventions. Besides, regular monitoring of high-risk areas, implementation of resilient water quality regulations would help in long-term mitigation and accordingly policy measures can be made. Research focusing on understanding the genetic and epigenetics of susceptible population can assist in the creation of intensive protection plans for susceptible groups. These activities can significantly reduce the harm that arsenic poisoning does to reproductive health.

Conclusion

This systematic review highlights the detrimental consequences of arsenic exposure on male reproductive health, particularly critical semen parameters. The evidence obtained from the four studies suggests that exposure to environmental inorganic arsenic may lead to male infertility mediated through oxidative stress, hormonal imbalance and cellular damage. However, the generalisation of this fact is limited because of the cross-sectional design, methodological variation and small study sample. These findings demand the need for a prospective cohort study and vivid dose-response analysis for better clarity and framing of definitive policies for generalisation of threshold levels of arsenic. Further studies should focus on analysing the genetic vulnerability, dose-response and mitigation techniques to address this emerging urgent global health concern.

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Author contributions

R. G., P. M. and E. P. were responsible for conceptualization, investigation, formal analysis, and writing-original draft and review and editing. V. B. and T. A. were in charge of supervision, review and editing. All authors critically read and approved the manuscript.

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Conflicts of interest

There are no conflicts of interest.

Data availability statement

Not Applicable.

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Supplementary Table 1: Search Strategy

Database	Search Strategy	Results
Pubmed	((Human OR Men) AND (Arsenic OR "Inorganic arsenic" OR "Sodium arsenate")) AND ((("Male infertility" OR Infertility) OR (Semen OR "Semen parameters" OR "Semen quality" OR "Semen volume" OR "Semen analysis")) OR ("Sperm parameters" OR "Sperm quality" OR "Sperm analysis, Sperm count" OR "Sperm concentration" OR "Sperm morphology" OR "Sperm viability" OR "Sperm motility" OR "Sperm abnormality" OR "Sperm viscosity" OR "Sperm DNA" OR "Sperm DNA integrity" OR "Sperm DNA fragmentation"))	124
Scopus	((Human OR Men) AND (Arsenic OR "Inorganic arsenic" OR "Sodium arsenate")) AND ((("Male infertility" OR Infertility) OR (Semen OR "Semen parameters" OR "Semen quality" OR "Semen volume" OR "Semen analysis")) OR ("Sperm parameters" OR "Sperm quality" OR "Sperm analysis, Sperm count" OR "Sperm concentration" OR "Sperm morphology" OR "Sperm viability" OR "Sperm motility" OR "Sperm abnormality" OR "Sperm viscosity" OR "Sperm DNA" OR "Sperm DNA integrity" OR "Sperm DNA fragmentation"))	233
Cochrane	((Human OR Men) AND (Arsenic OR "Inorganic arsenic" OR "Sodium arsenate")) AND ((("Male infertility" OR Infertility) OR (Semen OR "Semen parameters" OR "Semen quality" OR "Semen volume" OR "Semen analysis")) OR ("Sperm parameters" OR "Sperm quality" OR "Sperm analysis, Sperm count" OR "Sperm concentration" OR "Sperm morphology" OR "Sperm viability" OR "Sperm motility" OR "Sperm abnormality" OR "Sperm viscosity" OR "Sperm DNA" OR "Sperm DNA integrity" OR "Sperm DNA fragmentation"))	4

Supplementary Table 2: Risk of biased for cross sectional study using JBI critical appraisal checklist

Criteria	Xu *et al*., 2012	Oguri *et al*., 2016
Were the criteria for inclusion in the sample clearly defined?	1	1
Were the study subjects and the setting described in detail?	1	1
Was the exposure measured in a valid and reliable way?	1	1
Were objective, standard criteria used for measurement of the condition?	1	1
Were confounding factors identified?	1	1
Were strategies to deal with confounding factors stated?	1	1
Were the outcomes measured in a valid and reliable way?	1	1
Was appropriate statistical analysis used?	1	1
Overall Score	8/8	8/8

Supplementary Table 3: Risk of biased for case control study using the Newcastle-Ottawa Scale		
Criteria	**Shen *et al*., 2013**	**Wang *et al*., 2016**
Selection		
Representativeness of the exposed cohort	0	0
Selection of the non-exposed cohort	0	0
Ascertainment of exposure	1	1
Demonstration that outcome of interest was not present at start of study	0	0
Comparability		
Comparability of cohorts on the basis of the design or analysis	1	1
Others		
Exposure		
Assessment of outcome	1	1
Was follow-up long enough for outcomes to occur	0	0
Adequacy of follow up of cohorts	0	0
Total score	3	3