GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 12 (369) Декабрь 2025

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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Содержание:

GEORGIAN MEDICAL NEWS
No 12 (369) 2025

HEAVY METAL TOXICITY VERSUS TRACE ELEMENT PROTECTION IN WOMEN'S REPRODUCTIVE HEALTH - A SYSTEMATIC REVIEW

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Abstract.

Background: Environmental exposures are increasingly linked to reproductive dysfunctions such as endometriosis, ovarian insufficiency, and polycystic ovary syndrome (PCOS). Through endocrine disruption, oxidative stress, and epigenetic pathways, heavy metals (such as cadmium [Cd], lead [Pb], mercury [Hg], and arsenic [As]) and trace elements (such as zinc [Zn], copper [Cu], and selenium [Se]) may affect female fertility. Nevertheless, there are still few integrated assessments that address their combined consequences.

The goal is to perform a critical evaluation and systematic analysis of epidemiological data about the link between reproductive health issues in women of reproductive age and exposure to heavy metals and trace elements.

Methods: A comprehensive literature search was carried out in PubMed, Scopus, Google Scholar, and Web of Science to locate articles published between 2010 and 2024. Included were observational human studies that looked at correlations between metal exposure and the reproductive results of females. The study's quality was assessed using the Newcastle–Ottawa Scale (NOS), and the review process adhered to PRISMA guidelines.

Findings: A total of twenty-three studies were included in the review: eleven case–control studies, eight cross-sectional studies, three cohort studies, and one analytical study. Cd, Pb, As, Hg, Cu, and Zn were the most frequently evaluated elements; these were usually detected in biological samples such blood, serum, or follicular fluid. While low Zn and Se levels were linked to endometrial diseases and a reduced ovarian reserve, elevated levels of Cd, Pb, and As were linked to an increased risk of PCOS and endometriosis. Inflammation and endocrine dysregulation were inversely correlated with protective trace elements, especially zinc and selenium. 17 studies had a high-quality rating (NOS score ≥ 7).

Conclusions: One important and controllable risk factor for the reproductive health of women is exposure to hazardous metals. It seems that preserving reproductive function depends on striking a balance between harmful and necessary components. To elucidate dose-response connections, synergistic effects, and possible therapeutic options, further prospective and mechanistic research is required.

Key words. Heavy metal, toxicity, women's reproductive health.

Introduction.

In addition to being a vital aspect of personal happiness, women's reproductive health plays a significant role in societal advancement and population sustainability. In recent decades, there has been a troubling increase in reproductive disorders, including infertility, ovarian insufficiency, gestational complications, and premature reproductive aging [1-6]. An increasing amount of data suggests that exposure to environmental chemicals, especially heavy metals and trace elements, may contribute to various disorders in addition to endogenous or hereditary causes. Because of their high toxicity, bioaccumulative characteristics, and resistance to biodegradation, several substances—such as lead (Pb), cadmium (Cd), mercury (Hg), arsenic (As), and nickel (Ni)—have raised special concerns [7-9].

These substances can enter a woman's body through tainted food, drink, or air, as well as through interaction with polluted environments at work or at home [7]. Remarkably, even subtoxic levels have the potential to harm reproductive organ tissues, cause epigenetic changes, and interfere with endocrine function [8-20].

On the other hand, trace minerals like magnesium (Mg), copper (Cu), zinc (Zn), and selenium (Se) are crucial for immunological response, DNA repair, antioxidant defense, and hormone regulation [10-12]. Maintaining ovarian reserve, corpus luteum function, and implantation processes all depend on the proper balance between essential and harmful substances [5,14,19].

PCOS, endometriosis, premature ovarian insufficiency, and decreased fertility have all been linked to this balance being upset. Additionally, the same transport proteins, receptors, and enzyme systems may be contested by hazardous metals and micronutrients, which could affect the hormonal and tissue-level regulation of reproductive function [6,17,22].

An integrated, multidisciplinary synthesis of toxicological, endocrinological, and nutritional evidence is still lacking, despite the fact that many studies have addressed different facets of this problem. The entire reproductive life cycle, from menarche to perimenopause, is not adequately covered by existing evaluations, which frequently concentrate on pregnant women or particular aspects [3,6,18]. By combining epidemiological, clinical, and laboratory data about the impact of heavy metals and trace elements on female reproductive health, this systematic review aims to close this knowledge gap. It encompasses a broad range of biological matrices (blood, serum, follicular fluid), exposures, analytical techniques, and diagnostic categories, such as PCOS, endometriosis, infertility, and decreased ovarian reserve [1,2,4,13,16].

This study attempts to outline goals for future research in reproductive toxicology, explain risk thresholds, identify possible biomarkers, and advise preventative and therapeutic measures by combining current findings.

Methods.

Four significant international bibliographic databases—PubMed, Scopus, Google Scholar, and Web of Science—were thoroughly searched. All publications up to December 31, 2024, were included in the searches, which were conducted in both English.

The following search phrases and Boolean operators were used in the strategy. "heavy metals"[MeSH Terms] OR "trace elements"[MeSH Terms] OR cadmium OR lead OR arsenic OR mercury OR copper OR zinc OR nickel OR chromium) AND ("reproductive health"[MeSH Terms] OR "reproductive system"[MeSH Terms] OR ovarian OR fertility OR "polycystic ovary" OR endometriosis) AND (women OR female) was an example query for PubMed.

Humans, Filters, English, 2010–2024. The approach was modified to fit each database's syntax and indexing. Additionally, Google Scholar was used to screen grey literature, and a manual search was conducted utilizing the reference lists of important papers.

Original research using experimental or observational (cohort, case-control, or cross-sectional) designs is required for inclusion. examinations of correlations between the effects of trace elements or heavy metals on the female reproductive system; research papers released in English from 2010 to 2024; Human-centered studies that concentrate on women.

A systematic search following PRISMA guidelines across Web of Science, PubMed, Scopus, and Google Scholar yielded 1327 records. Following the removal of duplicates (n = 423) and the screening of titles, abstracts, and full texts (n = 835), a total of 69 full-text articles were evaluated for eligibility. A total of 23 studies satisfied the inclusion criteria and supplied adequate data for quality assessment (Tables 1 and 2).

Newcastle–Ottawa Scale methodological quality assessments were used for non-randomized studies. The NOS structure (Selection, Comparability, and Outcome/Exposure) was maintained, but cross-sectional studies were interpreted differently. Traditional NOS domains were used in cohort and case–control studies. Selection criteria include study population representativeness, metal concentration exposure assessment accuracy, case/control definition reliability, and explicit inclusion/exclusion. Comparison (up to 2 points): stratification, matching, or multivariable regression for major confounders (age, BMI, smoking, comorbidities, lifestyle factors). Statistical analysis (up to 3 points), reproductive outcome validity and objectivity (PCOS, endometriosis, DOR, etc.), and cohort study follow-up duration. A modified NOS with domain interpretation was used in cross-sectional research. Option (4 points max). Representative samples were reproductive-age women from hospitals, clinics, or ART programs with inclusion and exclusion criteria. A priori power estimates or logical sample adequacy determined sample size and justification. If the study documented refusals or exclusions and revealed no systematic differences between enrolled and excluded people, non-response and attrition were graded. Exposure assessment: ICP-MS, AAS, standardised pre-analytical sample processing, and known biospecimen collection methods scored points. Maximum 2 comparability points. This domain assessed how well the study handled key confounding variables. Multivariable models with age, BMI, smoking, metabolic, and endocrine disorders received one point. Multivariable regression, WQS, BKMR, or similar methods can establish a secondary point for lifestyle, occupational, dietary, and co-exposure to other environmental pollutants. Maximum 3 points for cross-sectional results. In cross-sectional designs, "outcome" covers reproductive status, including PCOS, endometriosis, infertility, endometrial abnormalities, and validated surrogate markers including hormone profiles and ovarian reserve. Clinical or international standards including Rotterdam criteria for PCOS, histological endometrial disease, and standardized ART regimens were scored. Objective lab tests including hormone panels, validated biomarkers, and blinded sample evaluations scored higher. A third point was provided for selecting statistical tests and models, verifying model assumptions, reporting confidence intervals and significance levels, and doing sensitivity analyses. High-quality research publications scored 7–9 on the NOS, moderate-quality 5–6, and low-quality below 5. Supplementary Table S1 lists operationalized criteria, including modified NOS for cross-sectional designs and point allocation situations. Methodological validation and in vitro or in vivo models without human clinical components were not examined by the NOS. Biological material source and representativeness, experimental settings, exposure design (dose, duration, and mode of administration), laboratory procedures, and repeatability were descriptively assessed for bias risk in these research.

The research conducted by Miglietta et al. [20] integrates clinical observation of women receiving ART with TEM ultrastructural examination of human COCs. The clinical element satisfies NOS guidelines because it has clear criteria for choosing participants, groups with similar levels of exposure, and a reliable way to measure outcomes. The TEM analysis does not conform to the NOS framework and was thus assessed descriptively; standardized oocyte collection, fixation techniques, and uniform morphological criteria were validated. The ultrastructural changes seen—ER stress, mitochondrial malfunction, changes in the zona pellucida, and cumulus-cell apoptosis—are in line with clinical results that show a relationship between high levels of Cd/Pb and worse ART outcomes. Chen et al. [21] conducted a study employing a mixed design that integrated a clinical cohort of women with diminished ovarian reserve (DOR), in vitro granulosa cell tests, and a chronic arsenic-exposed rat model. The clinical aspect satisfied human-centered observational standards and was assessed utilizing the NOS: DOR was precisely delineated by hormonal and ultrasound criteria, groups were equilibrated using 1:1 propensity score matching, and follicular-fluid metals were measured using standardized ICP-MS. The in vitro and in vivo components are not subject to evaluation via NOS; rather, they function as mechanistic extensions of the clinical results. The study conducted by López-Botella et al. [19] is analytical rather than observational, rendering it ineligible for evaluation utilizing the NOS. Analytical-validity metrics (linearity, LOD/LOQ, internal standards, matrix-effect control, ICP-MS/MS) and appropriate biological sampling (laparoscopic collection, inclusion criteria, double-blinded processing, ethical

Table 1. *Data such as author(s), year of publication, country, study population and diagnosis, biological samples (e.g., blood, follicular fluid), metal concentrations, analytical techniques, statistical methodologies, and major findings were retrieved from the eligible studies.*

№	Authors (Year)	DOI	Type of research	Assessment tool	Quality assessment (NOS)
1	McClam et al., 2023	10.1186/s13690-023-01172-6	Cross-sectional	NOS	6/9 (moderate quality)
2	Geller et al., 2022	10.1038/s41370-022-00477-y	Cross-sectional	NOS	8/9 (high quality)
3	Jansen et al., 2018	10.1017/S2040174418000223	Cohort	NOS	8/9 (high quality)
4	Lei et al., 2015	10.1186/s12889-015-2564-x	Cross-sectional	NOS	7/9 (high quality)
5	Génard-Walton et al., 2023	10.1016/j.rbmo.2023.05.013	Case control	NOS	9/9 (high quality)
6	Yue et al., 2024	10.1016/j.ecoenv.2024.117144	Case control	NOS	9/9 (high quality)
7	Liang et al., 2022	10.1016/j.scitotenv.2022.157780	Case control	NOS	8/9 (high quality)
8	Liang et al., 2022 (ЭМ)	10.1016/j.scitotenv.2022.158882	Case control	NOS	9/9 (high quality)
9	Su et al., 2024	10.1016/j.ecoenv.2024.115932	Case control	NOS	9/9 (high quality)
10	Liu et al., 2023	10.3389/fnut.2023.1205748	Cohort	NOS	9/9 (high quality)
11	Michalczyk et al., 2023	10.3390/nu15163605	Cross-sectional	NOS	6/9 (moderate quality)
12	Kluza et al., 2024	10.3390/nu16010144	Case control	NOS	8/9 (high quality)
13	Kalkan Yilmaz et al., 2019	10.1080/01443615.2019.1634022	Case control	NOS	6/9 (moderate quality)
14	Li et al., 2023	10.1007/s12011-022-03328-x	Case control	NOS	8/9 (high quality)
15	Rabajdová et al., 2023	10.1002/2211-5463.13738	Cross-sectional	NOS	6/9 (moderate quality)
16	Das et al., 2024	10.7759/cureus.57393	Cross-sectional	NOS	7/9 (high quality)
17	Sharif et al., 2017	10.1007/s12011-017-1000-8	Case control	NOS	6/9 (moderate quality)
18	Kim et al., 2021	10.3390/ijerph18179077	Cohort	NOS	9/9 (high quality)
19	López-Botella et al., 2023	10.3390/toxics11050399	Analytical	no	N/A
20	Miglietta et al., 2023	10.3390/cells12212577	Cross-sectional	NOS	8/9 (high quality)
21	Chen et al., 2022	10.1016/j.ecoenv.2022.113816	Case–control	NOS	8/9 (high quality)
22	Mohsin et al., 2024	10.1016/j.envres.2024.118801	Cross-sectional	NOS	7/9 (high quality)
23	Atakul et al., 2019	10.1007/s12011-019-01844-x	Case control	NOS	7/9 (high quality)

Table 2. *The findings were methodically arranged in summary tables that included information on the target population, study methodology, place of origin, biological sample types, and the particular metals examined.*

№	Authors (Year)	Country	purpose of the study /diagnosis	Biomaterial sample	Valuable metals
1	McClam et al., 2023	USA	Fertility disorders	Blood	As, Cd, Pb, Hg, Cu и др.
2	Geller et al., 2022	USA	Reproductive status	Blood	Cd, Pb, Hg, Zn и др.
3	Jansen et al., 2018	USA	The age of menarche	Blood	Pb
4	Lei et al., 2015	China	Infertility/pregnancy	Blood	Pb, Cd, Hg, Se
5	Génard-Walton et al., 2023	France	DOR	Blood	Cd, Pb, Hg, Zn, Cu, Se, Mn
6	Yue et al., 2024	China	Endometriosis	Blood + follicular fluid	As, Cd, Pb, Hg
7	Liang et al., 2022	China	PCOS	Blood	Pb, As, Ba, Cd, Hg
8	Liang et al., 2022 (ЭМ)	China	Endometriosis	Blood + follicular fluid	As, Cd, Pb, Hg
9	Su et al., 2024	China	Endometriosis	follicular fluid	Zn, Se, Mo, Co, W
10	Liu et al., 2023	China	RPL, PTB	Blood	Cu, Zn
11	Michalczyk et al., 2023	Poland	Reproductive health	Blood	Zn, Cu, Fe, Mn
12	Kluza et al., 2024	Poland	Hyperplasia/EM cancer	Blood	Zn, Cu, Mo, Se
13	Kalkan Yilmaz et al., 2019	Türkiye	Endometrial polyp	Blood	Cu, Zn, Pb, Ni, Al
14	Li et al., 2023	China	Diseases of the endometrium	Blood	Zn, Cu, Se, Mo
15	Rabajdová et al., 2023	Slovakia	Endometriosis, РЭ	Blood	Cu, Zn + antiox. enzymes
16	Das et al., 2024	India	PCOS	Blood	Zn, Cu
17	Sharif et al., 2017	Sudan	PCOS	Blood	Zn, Cu
18	Kim et al., 2021	South Korea	Endometriosis	Exposition	Pb, Cd
19	López-Botella et al., 2023	Spain	Gynecological pathologies	Peritoneal fluid	Zn, Cu, Pb, Cd, Mn и др.
20	Miglietta et al., 2023	Italy	Cd/Pb exposure	follicular fluid	Cd, Pb
21	Chen et al., 2022	China	Low ovarian reserve	Blood	As
22	Mohsin et al., 2024	USA	IVF/oocyte reaction	follicular fluid	Cu, Co, Pb, Hg, Sr, As и др.
23	Atakul et al., 2019	Türkiye	Endometrial cancer	Blood	Zn, Cu

permission) were used to judge its quality. The limitations encompassed a limited sample size and the lack of a healthy control group. The analytical results served as a supplementary biomarker to human observational research.

Criteria for exclusion: editorials, reviews, meta-analyses, and commentary; research on animals that does not include clinical human participants; Studies that do not publish gender-specific results or include women.

Data such as author(s), year of publication, country, study population and diagnosis, biological samples (e.g., blood, follicular fluid), metal concentrations, analytical techniques, statistical methodologies, and major findings were retrieved from the eligible studies. Quality assessment according to NOS Table 1.

Data Analysis.

The findings were methodically arranged in summary tables that included information on the target population, study methodology, place of origin, biological sample types, and the particular metals examined. The most commonly studied toxic elements—cadmium, lead, mercury, and arsenic—as well as the main reproductive outcomes evaluated, such as polycystic ovarian syndrome (PCOS), endometriosis, and ovarian response, were identified by a quick quantitative and qualitative synthesis Table 2.

Seventeen of the reviewed studies scored 7 or higher on the NOS, with six scoring 9/9 and seven scoring 8/9. This shows good selection, confounder control, and reliable metal quantification (ICP-MS, AAS). Good quality was awarded to four studies (7/9) and moderate quality to five (6/9). They mainly didn't account for enough confounding variables or have a representative sample. One analytical study was deemed “not applicable” because its laboratory-based mechanistic approach violated the NOS framework.

Results.

This comprehensive systematic review examined original papers on heavy metals and trace elements' impacts on women's reproductive health. The Newcastle–Ottawa Scale (NOS) was used to evaluate non-randomized research, while PRISMA 2020-compliant NOS variants were used for cross-sectional designs. Methodological validation studies and in vitro/in vivo experimental models without a human clinical component were not evaluated using the NOS. All included studies were assessed for quality in Table 1 and Figure S1. The Newcastle-Ottawa Scale removed one research due to in vitro experiments, scored five studies as moderate, and rated seventeen studies as good (Table 1). Several case–control and cohort studies scored 9/9 because they had clear participation criteria, reliable metal level measurement methods (ICP-MS, AAS), validated reproductive outcome diagnostic criteria (PCOS, endometriosis, DOR), and strong multivariable statistical adjustment. The majority of studies were conducted in China (n = 12) and the United States (n = 4), while the remaining research was sourced from European countries (Poland, France, Slovakia, Spain, Italy, Turkey) and Asia (India, South Korea, Sudan), as detailed in Table 2. The predominant study design identified was case–control (n = 11), succeeded by cross-sectional studies (n = 8), cohort studies (n = 3), and a single analytical study (n = 1) (Table 1). Table 2 indicates that the elements most frequently analyzed include arsenic (As, n = 9 studies), copper (Cu, n = 13), zinc (Zn, n = 14), mercury (Hg, n = 12), cadmium (Cd, n = 15), and lead (Pb, n = 17). Multiple studies also assessed manganese (Mn), molybdenum (Mo), cobalt (Co), strontium (Sr), barium (Ba), and various other trace elements. Metals were primarily quantified in blood/serum and follicular fluid, with fewer studies examining peritoneal fluid and tissue samples (Table 2). Table 2 systematically presents diagnostic categories along with their corresponding exposure profiles. The primary reproductive outcomes identified were: polycystic ovary syndrome (PCOS, n = 6); endometriosis (n = 7); diminished ovarian reserve and ovarian response in ART (DOR/ovarian response, n = 3–4); endometrial hyperplasia, polyps, and endometrial cancer (n = 4); and general reproductive disorders, encompassing infertility, recurrent pregnancy loss (RPL),

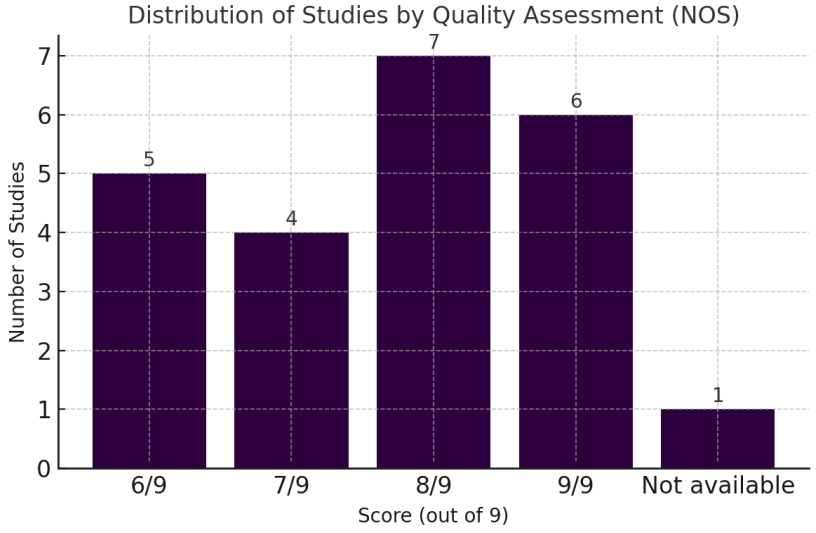

Figure 1. *Distribution of studies according to Newcastle–Ottawa Scale (NOS) quality assessment.*

preterm birth (PTB), and hormonal imbalance (n = 6). Before meta-analytic pooling, descriptive synthesis links metals and diseases. Table 2 reveals that PCOS is associated with raised blood levels of Pb, As, Cd, Hg, and Ba (Liang et al., 2022 — case–control design, ICP-MS) and changed Cu and Zn status, including an increased Cu/Zn ratio. Research links PCOS to harmful metal accumulation and trace element imbalance. In Table 2, As, Cd, Pb, and Hg are repeatedly implicated in blood and follicular fluid as endometriosis risk indicators. These findings recommend researchers weigh endometriosis' hazards and advantages (Table 2). Table 2 reveals ART-related reduced ovarian reserve and response (Génard-Walton, 2023; Chen, 2022; Mohsin, 2024): Chen et al. measured arsenic (As) in the blood of patients with inadequate ovarian reserve, while Mohsin et al. measured Cu, Co, Pb, Hg, Sr, As, and other elements in follicular fluid about IVF ovarian response. These results show that As, Cd, Pb, Hg, Cu/Zn, and Sr impact ovarian reserve and recovered oocytes. Table 2 shows that Kluza et al. measured Zn, Cu, Mo, and Se in blood from women with endometrial hyperplasia and cancer; Kalkan Yilmaz examined Cu, Zn, Pb, Ni, and Al from endometrial polyps; Li measured Zn, Cu, Se, and Mo from various endometrial disorders; and Atakul examined Zn and Cu from endometrial cancer. The most constant finding across research is the changing Cu/Zn ratio, which may suggest endometrial growth and cancer. Table 2 demonstrates how women with infertility or altered reproductive status had their blood tested for As, Cd, Pb, Hg, Cu, Zn, and other elements. The effects of Cu and Zn on RPL and PTB were also examined. Tables 1 and 2 reveal that toxic metals (Cd, Pb, Hg, As) cause endometriosis, PCOS, ovarian reserve loss, and negative response. Essential elements (Zn, Cu, Se, and partially Mo and Mn) can be protective or pathogenic depending on their absolute levels and relative balance, especially the Cu/Zn ratio.

Table 2's organized overview shows how biological matrix type (blood, serum, follicular fluid, or peritoneal fluid) affects data analysis. More thorough research using multivariable regression models and complex statistical approaches including Bayesian kernel machine regression (BKMR), weighted quantile sum (WQS) analysis, and propensity score matching has higher NOS values in Table 1. These studies used serum, follicular fluid, and peritoneal fluid and confirmed metal measurement by AAS or ICP-MS/MS. To understand how toxic and required factors affect women's reproductive health, including PCOS, endometriosis, endometrial pathology, and ovarian response to assisted reproductive technologies, see Tables 1 and 2.

Discussion.

The results of this systematic review show that the effects of trace elements and heavy metals on female reproductive function are gaining attention from scientists. 23 studies in all, mostly from high- and middle-income nations, were examined; they included case-control, cross-sectional, and cohort designs and were published within the last ten years. All of the evidence suggests that mercury (Hg), copper (Cu), zinc (Zn), lead (Pb), arsenic (As), cadmium (Cd), and lead (Pb) play a major role in the pathophysiology of hormone-related reproductive disorders, such as endometriosis, ovarian dysfunction, polycystic ovary syndrome (PCOS), hormonal imbalance, and infertility.

Numerous excellent research have confirmed the link between PCOS and exposure to heavy metals. In a case-control research using Bayesian kernel machine regression (BKMR) and logistic regression, Liang et al. [7] discovered a strong positive correlation between the risk of PCOS and blood levels of Pb, As, and Ba. Based on investigations of both blood and follicular fluid, Yue et al. [6] also revealed substantial effects of Cd, Hg, Pb, and As on the likelihood of PCOS and endometriosis. The importance of zinc deficiency in the pathogenesis of PCOS was emphasized by Das et al. [16] and Sharif et al. [17], especially in low-resource environments like Sudan and India.

The development of endometriosis has been consistently linked to the buildup of arsenic, mercury, and cadmium, according to three separate investigations [8,9,14]. Strong evidence for the synergistic effects of metal combinations, especially As and Hg, in both blood and follicular fluid was presented by Liang et al. [8]. Using weighted quantile sum (WQS) regression, Su et al. [9] verified that a combination of Zn, Se, Co, Mo, and W in follicular fluid could be a biomarker for the risk of endometriosis. Studies by Rabajdová et al. [15] and Kim et al. [18] also highlight the roles of Pb and Cd in proliferative and inflammatory disorders of the female reproductive system.

Follicle fluid is an important biological matrix that indicates localized metal buildup, according to several studies. According to Mohsin et al. [22], Pb levels were inversely connected with greater estradiol levels and mature oocyte counts, while elevated Cu and Hg in follicular fluid were linked to both. In the meantime, reduced ovarian reserve (DOR) was associated with co-exposure to Cd, Pb, Hg, and Zn by Génard-Walton et al. [5]. A crucial window of sensitivity was highlighted by Jansen et al. [3], who were among the first to show that prolonged exposure to lead throughout puberty may postpone menarche.

Miglietta et al. [20] used human material for TEM ultrastructural COC studies, which fits our review's human-centered paradigm. Reproductive-age women taking infertility treatment had their blood and follicular fluid checked for Pb and Cd and their oocytes and cumulus cells investigated for ultrastructural alterations. Thus, the study is not a "auxiliary" experimental model but a key relationship between biomonitoring heavy metals in infertile women, clinical ART findings (pregnancy, early pregnancy loss, implantation failure), and direct morphological gamete damage. High blood and follicular fluid Cd and Pb levels, endoplasmic reticulum stress, mitochondrial dysfunction, zona pellucida modifications, and cumulus cell apoptosis in human cumulus oocyte complexes (COCs) suggest that exposure levels at or slightly above reference ranges disrupt oocyte and somatic cell microstructure.

Chen et al. [21] used a clinical human cohort with strong in vitro and in vivo experimental components, which suits our human-centered evaluation. The case–control study examined women with decreased ovarian reserve (DOR) and a matched age and reproductive history control group. Clinicians agree that As, Mo, and Sr are DOR risk factors and Cu and Mg may protect. Human granulosa cells and rats communicate clinical data, not distinct models. Follicular-fluid As, altered AMH/FSH levels, and lower ovarian reserve are linked to disrupted steroidogenesis and folliculogenesis in women. The human–

cell–animal translational method complements clinical findings in women (follicular metal levels, DOR, hormonal profiles, NRO) with consistent mechanistic data from cellular and animal models.

According to studies by Kluza et al. [12], Kalkan Yilmaz et al. [13], Li et al. [14], and Atakul et al. [23], changed copper-to-zinc ratios (Cu/Zn) could be indicators of endometrial proliferative dysfunction and oxidative stress. The incidence of endometrial polyps, hyperplasia, and cancer was positively correlated with a high Cu/Zn ratio, which is frequently caused by decreased Zn levels.

Due to their functions in cell cycle regulation and antioxidant defense, zinc and selenium have been repeatedly demonstrated to have protective effects. According to research by Michalczyk et al. [11], Liu et al. [10], Chen et al. [21], and López-Botella et al. [19], ovulatory dysfunction and increased inflammatory markers were linked to deficiencies in these components. Furthermore, disturbed ovarian response and hormonal homeostasis were associated with Se insufficiency and Cu/Fe overload [14, 20].

This systematic review focuses on clinical studies on women, however López-Botella et al. [19]'s analytical research is suitably included. Quantifying important trace elements and potentially hazardous metallic elements in peritoneal fluid from gynecological patients improves blood- and follicular-fluid-based data and helps assess local metal accumulation near reproductive organs. This study found that peritoneal fluid contains both necessary elements (Zn, Fe, Cu, etc.) and potentially toxic metals (Cd, Pb, Ni, Ba, etc.) at concentrations and detection frequencies different from blood and follicular fluid. It also highlights the pelvic microenvironment's importance. López-Botella et al. [19] link epidemiological findings to pathophysiological processes, not to present autonomous “element concentration–risk” relationships.

Although the studies were generally of excellent quality causal inference is limited by the prevalence of observational designs. Just one study included longitudinal assessments of metal concentrations, and only three research used cohort designs [3,10,18]. Variability in results was brought about by variations in biological matrices (blood, serum, follicular fluid), analytical techniques (ICP-MS, AAS), and demographic heterogeneity. Interpretation was made more difficult by the fact that many research lacked controls for environmental contaminants, occupational exposure, and food intake.

Many of the studies mentioned suggest that Pb, Cd, Hg, and As are still changeable factors that affect reproductive health, thus they must be prevented. Practical methods generally reduce environmental and workplace dangers. The most important steps in industrially polluted areas are to regularly check drinking water for arsenic, lead, and cadmium; screen high-risk foods like rice, fish, seafood, and vegetables grown in contaminated soils; and strictly follow safety rules in the metallurgy, mining, battery production, tanning, and pesticide industries. Women of reproductive age can significantly reduce their exposure by choosing verified safe water sources, not eating mercury-contaminated fish, limiting rice and imported grains from polluted areas, and using certified PPE when working with hazardous materials. Growing biomonitoring data shows that environmental controls reduce blood and follicular-fluid metal contents. So, being around toxic metals is a risk factor that can be modified, but reproductive toxicity-prone persons still need specific environmental health precautions [6,7,9,14,22].

Along with reducing dangerous exposures, maintaining critical elements is another dynamic area relevant to therapeutic therapy. This review of multiple studies reveals that low Zn and Se and high Cu and Fe induce oxidative stress, steroidogenesis, and folliculogenesis issues. Personalized micronutrient optimization should be used in clinical practice. This may include nutritional counseling to ensure adequate consumption of Zn- and Se-rich foods (whole grains, legumes, nuts, marine products), reduced Cu and Fe intake in biochemical overload, and organized supplementation for women with PCOS, endometriosis, DOR, or RPL/PTB. Laboratory examinations of Zn, Se, Cu, Fe, and dangerous metals may show women with an unfavorable "elemental profile" who may benefit from rectification. Infertility and ART assessment using elemental status helps clinicians discover poor nutritional balance and evaluate therapy response. Metal-related reproductive dangers can be reduced mechanistically with this clinical-nutritional method [10,11,15,16,21].

Conclusion.

A woman's reproductive function depends on hazardous-essential element equilibrium, not metal concentrations, says this review. High cadmium, lead, mercury, and arsenic levels are connected to oxidative stress, mitochondrial dysfunction, epigenetic alterations, and steroidogenesis issues in PCOS, endometriosis, low ovarian reserve, and poor ovarian response in many studies. Zinc and selenium deficits, Cu/Zn and Cu/Fe ratio abnormalities affect DNA repair, antioxidant defenses, and endometrial and folliculogenesis hormone control. Complex multivariate models like weighted quantile sum (WQS) analysis and Bayesian kernel machine regression exhibit scientifically meaningful metal combination synergy findings. Localized exposure evaluation using follicular fluid, a highly specialized biological matrix, improves reproductive toxicology risk assessment. The included research are scientifically sound, however study design, sampling, and analytical method variance require standardized protocols and longitudinal monitoring. In the presence of environmental stresses, heavy metal exposure is a modifiable risk factor for women's reproductive health. Prevention, clinical biomonitoring, and elemental balancing nutritional therapy should be studied in the future.

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Аннотация.

Введение: Всё больше данных указывает на связь воздействия факторов окружающей среды с нарушениями репродуктивной функции, такими как эндометриоз, овариальная недостаточность и синдром поликистозных яичников (СПКЯ). Посредством эндокринных нарушений, окислительного стресса и эпигенетических механизмов тяжёлые металлы (например, кадмий [Cd], свинец [Pb], ртуть [Hg] и мышьяк [As]) и микроэлементы (такие как цинк [Zn], медь [Cu] и селен [Se]) могут влиять на женскую фертильность. Тем не менее, интегрированных оценок их совокупного воздействия по-прежнему немного. Целью данного исследования является критическая оценка и систематический анализ эпидемиологических данных о связи между нарушениями репродуктивного здоровья у женщин репродуктивного возраста и воздействием тяжёлых металлов и микроэлементов.

Методы. Был проведён комплексный поиск литературы в базах данных PubMed, Scopus, Google Scholar и Web of Science для выявления статей, опубликованных в 2010–2024 годах. Включались наблюдательные исследования на людях, в которых рассматривались корреляции между воздействием металлов и репродуктивными исходами у женщин. Качество исследований оценивалось с использованием шкалы Ньюкасл–Оттава (Newcastle–Ottawa Scale, NOS), а процесс обзора соответствовал руководству PRISMA.

Результаты. В обзор были включены двадцать три исследования: одинадцать исследований типа «случай–контроль», восемь поперечных и три когортных и один аналитечиский. Наиболее часто изучались Cd, Pb, As, Hg, Cu и Zn, которые обычно определялись в биологических образцах — крови, сыворотке или фолликулярной жидкости. Низкие уровни Zn и Se были связаны с эндометриальными заболеваниями и сниженным овариальным резервом, тогда как повышенные концентрации Cd, Pb и As ассоциировались с повышенным риском СПКЯ и эндометриоза. Защитные микроэлементы, особенно цинк и селен, демонстрировали обратную корреляцию с воспалением и эндокринной дисфункцией. Семнадцать исследований имели высокое качество (оценка по NOS ≥ 7).

Выводы. Воздействие токсичных металлов является важным и потенциально контролируемым фактором риска для репродуктивного здоровья женщин. Сохранение репродуктивной функции, по-видимому, зависит от поддержания баланса между вредными и необходимыми элементами. Для уточнения дозозависимых связей, синергетических эффектов и возможных терапевтических стратегий требуются дальнейшие проспективные и механистические исследования.