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# Metal ions as endocrine disruptors

Busurat Adenike Mudashiru [1, *], Roqeebat Abiodun Mudashiru [2], Ernest Erenven Isemede [3] and Raphael Okhiria Idewele [4]

[1] *Department of Chemistry, Ohio University, Athens, USA.*
[2] *Department of Chemistry, University of Ilorin, Ilorin, Nigeria.*
[3] *Department of Environmental Health and Technology, University of Eastern Finland, Finland.*
[4] *Department of Wood Materials Science, University of Eastern Finland, Joensuu, Finland.*

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## Abstract

Endocrine-disrupting chemicals have traditionally been conceptualized as organic compounds such as bisphenols, phthalates, and persistent organic pollutants. However, a growing body of experimental, epidemiological, and mechanistic evidence demonstrates that metal ions represent a distinct and underappreciated class of endocrine disruptors. Unlike classical endocrine disruptors that primarily act through receptor agonism or antagonism, metals interfere with endocrine regulation through redox imbalance, displacement of essential cofactors, modulation of hormone synthesis and metabolism, epigenetic remodeling, and disruption of hormone receptor signaling cascades. Metals such as cadmium, arsenic, lead, mercury, chromium, nickel, manganese, cobalt, and vanadium have been shown to alter thyroid, reproductive, adrenal, pancreatic, and steroid hormone systems at environmentally relevant concentrations. Their endocrine effects are often nonlinear, sex-specific, developmentally sensitive, and potentiated by oxidative stress and inflammation. Importantly, metals may act as endocrine disruptors even when systemic concentrations fall below traditional toxicity thresholds, reflecting their capacity to target hormone-sensitive tissues and signaling networks. This review synthesizes current journal evidence on metal-induced endocrine disruption, emphasizing molecular mechanisms, tissue-specific vulnerabilities, redox-endocrine crosstalk, developmental programming, and disease outcomes. We also examine challenges in exposure assessment, the importance of metal speciation and bioavailability, and emerging biomarkers of endocrine disruption. Finally, we discuss regulatory and public health implications, arguing for a paradigm shift that integrates metal chemistry into endocrine risk assessment frameworks.

**Keywords:** Metal ions; Endocrine disruption; Hormone signaling; Thyroid dysfunction; Reproductive toxicity; Steroidogenesis; Epigenetics; Oxidative stress; Developmental programming; Environmental health

## 1. Introduction: Redefining endocrine disruption to include metal ions

Endocrine regulation depends on exquisitely coordinated signaling between hormones, receptors, enzymes, transport proteins, and feedback loops that operate across spatial and temporal scales [1]. Small perturbations in hormone synthesis, transport, receptor sensitivity, or metabolism can produce disproportionate biological consequences, particularly during sensitive developmental windows. While endocrine disruption research has historically focused on synthetic organic compounds that mimic or block hormone receptors, this framework does not fully capture the complexity of metal–hormone interactions. Metal ions differ fundamentally from organic endocrine disruptors in both chemistry and biology. Metals do not degrade, can accumulate in tissues, and often participate directly in enzymatic catalysis or redox reactions [2, 3]. Many endocrine pathways depend on metal-containing enzymes, metal-binding transcription factors, and redox-sensitive signaling nodes. Consequently, metals can disrupt endocrine systems not by

* Corresponding author: Busurat Adenike Mudashiru

mimicking hormones structurally, but by altering the biochemical infrastructure upon which hormonal signaling depends [4, 5]. Moreover, several metals exhibit hormone-like activity without being classical ligands. Cadmium, for example, can activate estrogen receptor signaling despite lacking structural similarity to estradiol [6]. Arsenic can suppress glucocorticoid receptor transactivation without binding the ligand-binding domain [7]. These unconventional modes of action challenge traditional receptor-centric models of endocrine disruption and explain the need for a mechanistically broader perspective. This review integrates evidence across molecular toxicology, endocrinology, and environmental epidemiology to establish metal ions as bona fide endocrine disruptors. Emphasis is placed on mechanistic depth, rather than cataloging effects, to illuminate how metals reprogram endocrine physiology and contribute to chronic disease.

## 2. Mechanistic foundations of metal-induced endocrine disruption

### 2.1. Disruption of hormone synthesis and steroidogenesis

Hormone biosynthesis relies on tightly regulated enzymatic pathways, many of which are vulnerable to metal interference. Steroid hormones are synthesized from cholesterol through a series of oxidation, reduction, and hydroxylation reactions catalyzed by cytochrome P450 enzymes and dehydrogenases [8]. These enzymes depend on metal cofactors such as iron and zinc and are sensitive to redox balance. Toxic metals can inhibit steroidogenic enzymes directly by displacing essential metals or indirectly by inducing oxidative stress that alters enzyme conformation and activity [9]. Cadmium, lead, and mercury have been shown to suppress key steroidogenic enzymes including CYP11A1, CYP17A1, and 3β-hydroxysteroid dehydrogenase [10]. In testicular Leydig cells, cadmium exposure reduces testosterone synthesis even at low doses, reflecting both enzyme inhibition and mitochondrial dysfunction [11, 12]. Similarly, arsenic disrupts adrenal steroidogenesis by interfering with cholesterol transport into mitochondria and by altering redox-dependent enzyme activity [13, 14]. Beyond inhibition, some metals dysregulate hormone synthesis by uncoupling feedback loops [15]. Chronic low-dose metal exposure can blunt hypothalamic-pituitary signaling, leading to inappropriate hormonal output despite normal circulating hormone levels [16, 17]. This functional disruption complicates diagnosis and underscores why endocrine effects may be missed when relying solely on serum hormone concentrations.

### 2.2. Interference with hormone receptors and transcriptional signaling

Hormone receptors function as ligand-activated transcription factors whose activity depends on precise conformational changes, co-regulator recruitment, and redox state. Metal ions can disrupt receptor signaling at multiple levels without acting as classical agonists or antagonists [18]. Some metals bind directly to receptor domains, particularly zinc finger motifs within DNA-binding regions, altering receptor-DNA interactions and transcriptional fidelity [19]. Cadmium is a prototypical example, capable of activating estrogen receptor-α signaling pathways and inducing estrogen-responsive gene expression in vitro and in vivo [20]. Importantly, cadmium-induced estrogenic signaling occurs at concentrations far below those causing overt toxicity, suggesting endocrine disruption is a sensitive endpoint [21]. Nickel and cobalt similarly influence estrogen and androgen receptor activity through redox modulation and altered co-activator recruitment [22]. Other metals interfere with receptor signaling indirectly by targeting downstream kinases and phosphatases [23, 24]. Arsenic suppresses glucocorticoid receptor-mediated gene transcription by inhibiting co-activator function and disrupting chromatin remodeling, despite not preventing hormone binding [25, 26]. These findings demonstrate that endocrine disruption can arise from post-receptor signaling interference, expanding the definition beyond ligand mimicry.

### 2.3. Redox–endocrine crosstalk as a central mechanism

A defining feature of metal-induced endocrine disruption is its intimate connection to oxidative stress. Many hormone receptors and signaling pathways are redox-sensitive, relying on reversible cysteine oxidation to regulate activity. Metals capable of generating reactive oxygen species or depleting antioxidant defenses can therefore distort endocrine signaling by shifting cellular redox balance [27, 28]. Oxidative stress alters thyroid hormone synthesis by damaging thyrocyte membranes and impairing iodide uptake and organification [29, 30]. In reproductive tissues, redox imbalance affects gonadotropin signaling and steroid hormone responsiveness [31, 32]. In pancreatic β-cells, which possess limited antioxidant capacity, metal-induced oxidative stress disrupts insulin synthesis and secretion, contributing to metabolic dysfunction [33]. Importantly, oxidative stress does not merely damage endocrine tissues but reprograms endocrine responsiveness, changing how cells interpret hormonal signals. This redox-endocrine coupling explains why metal exposures are often linked to metabolic syndrome, thyroid disease, and reproductive disorders even in the absence of gross tissue injury.

## 3. Thyroid hormone disruption by metal ions

### 3.1. Interference with thyroid hormone synthesis and metabolism

The thyroid axis is particularly vulnerable to metal exposure due to its reliance on redox reactions and trace element balance [34]. Thyroid hormone synthesis requires iodide uptake, oxidation, and coupling reactions mediated by thyroid peroxidase. Metals such as mercury, cadmium, and arsenic interfere with these processes by inhibiting peroxidase activity and generating oxidative stress within thyrocytes [35]. Several metals also alter peripheral thyroid hormone metabolism. Deiodinase enzymes, which convert thyroxine (T4) to the active hormone triiodothyronine (T3), are selenium-dependent and redox-sensitive [36]. Metal-induced oxidative stress or selenium displacement can impair deiodinase function, leading to altered T3/T4 ratios without changes in total hormone levels [37]. This pattern is frequently observed in epidemiological studies, where metal exposure correlates with subclinical hypothyroidism or altered thyroid hormone profiles rather than overt thyroid disease. Such subtle disruptions can nevertheless have significant neurodevelopmental and metabolic consequences.

### 3.2. Developmental vulnerability and neuroendocrine consequences

Thyroid hormones are essential for brain development, particularly during gestation and early childhood [38, 39]. Even modest perturbations in maternal thyroid hormone availability can impair neuronal migration, myelination, and synaptogenesis. Metals that disrupt maternal thyroid function therefore pose disproportionate risks during pregnancy [40]. Prenatal exposure to arsenic, lead, and mercury has been associated with altered neonatal thyroid hormone levels and adverse neurodevelopmental outcomes [41-43]. Experimental models demonstrate that metal-induced thyroid disruption during critical windows leads to persistent changes in brain structure and function, consistent with developmental endocrine programming [44, 45]. These findings highlight the importance of considering life-stage–specific endocrine disruption, as the same exposure may have minimal effects in adults but profound consequences during development.

### 3.3. Thyroid hormone transport and receptor signaling

Beyond synthesis and metabolism, metals influence thyroid hormone action by altering transport proteins and receptor signaling [46]. Transthyretin and thyroxine-binding globulin can be modified by oxidative stress, affecting hormone distribution [47, 48]. At the cellular level, thyroid hormone receptors are redox-regulated, and metal-induced oxidative stress can impair receptor binding to DNA and transcriptional activation [49]. Thus, thyroid disruption by metals is multifaceted, involving synthesis, metabolism, transport, and signaling. This complexity explains why traditional thyroid screening may underestimate endocrine effects of metal exposure.

## 4. Reproductive and developmental endocrine disruption

### 4.1. Male reproductive axis and androgen disruption

The male reproductive endocrine system is highly sensitive to metal exposure. Testosterone synthesis, spermatogenesis, and androgen receptor signaling depend on intact mitochondrial function and redox balance. Metals such as cadmium, lead, and mercury disrupt Leydig cell steroidogenesis, reduce testosterone levels, and impair sperm quality [50]. Mechanistically, cadmium induces oxidative stress in testicular tissue, damages mitochondrial membranes, and suppresses steroidogenic enzyme expression [51]. Lead interferes with hypothalamic-pituitary signaling, reducing luteinizing hormone stimulation of testosterone production [52]. These effects often occur at exposure levels previously considered safe, reflecting endocrine sensitivity. Importantly, androgen disruption by metals is associated not only with infertility but also with metabolic and cardiovascular consequences, as testosterone influences muscle mass, insulin sensitivity, and vascular function.

### 4.2. Female reproductive hormones and ovarian function

In females, metal exposure disrupts ovarian steroidogenesis, folliculogenesis, and menstrual cyclicity [53]. Cadmium and arsenic impair estrogen and progesterone synthesis by targeting granulosa and theca cell function [54]. Mercury exposure has been linked to altered menstrual cycles and reduced fertility [55]. Ovarian tissue is particularly vulnerable due to its high metabolic activity and reliance on redox-regulated signaling [56]. Metal-induced oxidative stress accelerates follicular atresia and may contribute to earlier reproductive aging [57]. Epidemiological studies have associated metal exposure with altered age at menarche and menopause, explaining long-term endocrine effects [58-60].

### 4.3. Transplacental exposure and endocrine programming

Metals readily cross the placenta, exposing the developing fetus to endocrine-disrupting effects during critical windows [61]. Fetal exposure to metals can permanently alter hypothalamic-pituitary-gonadal axis regulation, a phenomenon known as endocrine programming [62]. Animal studies demonstrate that prenatal metal exposure leads to persistent changes in hormone levels, reproductive behavior, and fertility in adulthood [63, 64]. These developmental effects often involve epigenetic mechanisms, including DNA methylation and histone modification of endocrine genes. Thus, metal-induced endocrine disruption can span generations, reinforcing its public health significance.

## 5. Metabolic and adrenal endocrine disruption

### 5.1. Pancreatic β-cell dysfunction and insulin signaling

Pancreatic β-cells are uniquely susceptible to oxidative stress due to low antioxidant defenses. Metals such as arsenic, cadmium, and nickel impair insulin synthesis and secretion by inducing oxidative damage, disrupting calcium signaling, and altering gene expression [65]. Chronic exposure contributes to insulin resistance and glucose intolerance. Arsenic, in particular, has been strongly linked to diabetes risk. Mechanistic studies show that arsenic interferes with insulin receptor signaling and suppresses insulin gene transcription, highlighting its role as a metabolic endocrine disruptor rather than a classic toxin [66-68].

### 5.2. Adrenal hormones and stress axis disruption

The hypothalamic-pituitary-adrenal axis regulates stress responses, immune function, and metabolism. Metals disrupt this axis by impairing cortisol synthesis, altering glucocorticoid receptor signaling, and modulating feedback sensitivity [69]. Arsenic suppresses glucocorticoid receptor transactivation, while lead alters adrenal responsiveness to ACTH [70]. Chronic disruption of adrenal hormones contributes to immune dysregulation, metabolic imbalance, and neurobehavioral changes. These effects are particularly relevant in populations experiencing both environmental metal exposure and psychosocial stress, where endocrine disruption may amplify vulnerability.

## 6. Epigenetic and transgenerational dimensions of metal endocrine disruption

### 6.1. Epigenetic remodeling of endocrine genes

Metal exposure induces epigenetic modifications that alter endocrine gene expression without changing DNA sequence [71]. DNA methylation changes in hormone receptors, steroidogenic enzymes, and signaling molecules have been documented following metal exposure [72, 73]. These changes can persist long after exposure ceases, effectively "locking in" altered endocrine states. Epigenetic mechanisms provide a unifying explanation for delayed and transgenerational endocrine effects. By modifying chromatin structure, metals can reprogram endocrine responsiveness across tissues and life stages.

### 6.2. Transgenerational inheritance and disease risk

Evidence from animal models indicates that metal-induced epigenetic changes can be transmitted across generations, affecting reproductive capacity, metabolism, and stress responses [74, 75]. This raises concerns that current environmental exposures may shape endocrine health in future populations. Such findings challenge regulatory paradigms that focus on individual risk and short-term outcomes, emphasizing the need for a life-course and multigenerational perspective.

## 7. Conclusion

Metal ions represent a critical yet underrecognized class of endocrine disruptors whose mechanisms extend far beyond classical hormone mimicry. By targeting hormone synthesis, receptor signaling, redox balance, and epigenetic regulation, metals disrupt endocrine homeostasis across multiple organ systems and life stages. Their effects are often subtle, persistent, and amplified during development, challenging traditional toxicological assumptions and regulatory thresholds. Recognizing metals as endocrine disruptors requires integrating metal chemistry into endocrine biology, refining exposure assessment to capture bioavailable forms, and prioritizing sensitive windows of exposure. From thyroid disease and reproductive dysfunction to metabolic disorders and transgenerational effects, metal-induced endocrine disruption has profound implications for public health. Addressing this challenge demands a paradigm shift that treats endocrine health as inseparable from environmental metal exposure and redox biology.

## Compliance with ethical standards

*Disclosure of conflict of interest*

No conflict of interest to be disclosed.

## References


[1] Al-Suhaimi EA. Introduction to Endocrinology. InEmerging Concepts in Endocrine Structure and Functions 2022 Apr 21 (pp. 1-24). Singapore: Springer Nature Singapore.

[2] Valko M, Jomova K, Rhodes CJ, Kuča K, Musílek K. Redox-and non-redox-metal-induced formation of free radicals and their role in human disease. Archives of toxicology. 2016 Jan;90(1):1-37.

[3] Jomova K, Baros S, Valko M. Redox active metal-induced oxidative stress in biological systems. Transition Metal Chemistry. 2012 Mar;37(2):127-34.

[4] Liu D, Shi Q, Liu C, Sun Q, Zeng X. Effects of endocrine-disrupting heavy metals on human health. Toxics. 2023 Mar 29;11(4):322.

[5] Rana SV. Perspectives in endocrine toxicity of heavy metals—a review. Biological trace element research. 2014 Jul;160(1):1-4.

[6] Aquino NB, Sevigny MB, Sabangan J, Louie MC. The role of cadmium and nickel in estrogen receptor signaling and breast cancer: metalloestrogens or not?. Journal of Environmental Science and Health, Part C. 2012 Jul 1;30(3):189-224.

[7] Scheschowitsch K, Leite JA, Assreuy J. New insights in glucocorticoid receptor signaling—more than just a ligand-binding receptor. Frontiers in endocrinology. 2017 Feb 6;8:16.

[8] Niwa T, Murayama N, Imagawa Y, Yamazaki H. Regioselective hydroxylation of steroid hormones by human cytochromes P450. Drug metabolism reviews. 2015 Apr 3;47(2):89-110.

[9] Bhat RA, Bakhshalizadeh S, Guerrera MC, Kesbic OS, Fazio F. Toxic effect of heavy metals on ovarian deformities, apoptotic changes, oxidative stress, and steroid hormones in rainbow trout. Journal of Trace Elements in Medicine and Biology. 2023 Jan 1;75:127106.

[10] Ji H, Fan W, Kakar M, Alajmi RA, Bashir MA, Shakir Y. Effect of cadmium on the regulatory mechanism of steroidogenic pathway of Leydig cells during spermatogenesis. Journal of Experimental Zoology Part A: Ecological and Integrative Physiology. 2024 Jan;341(1):31-40.

[11] Xiong L, Zhou B, Liu H, Cai L. Comprehensive review of cadmium toxicity mechanisms in male reproduction and therapeutic strategies. Reviews of Environmental Contamination and Toxicology Volume 258. 2021 Oct 8:151-93.

[12] Ali W, Ma Y, Zhu J, Zou H, Liu Z. Mechanisms of cadmium-induced testicular injury: a risk to male fertility. Cells. 2022 Nov 14;11(22):3601.

[13] Li J, Zhou Q, Ma Z, Wang M, Shen WJ, Azhar S, Guo Z, Hu Z. Feedback inhibition of CREB signaling by p38 MAPK contributes to the negative regulation of steroidogenesis. Reproductive Biology and Endocrinology. 2017 Mar 16;15(1):19.

[14] Meduri GU, Psarra AM. The glucocorticoid system: a multifaceted regulator of mitochondrial function, endothelial homeostasis, and intestinal barrier integrity. InSeminars in Respiratory and Critical Care Medicine 2025 Sep 17. Thieme Medical Publishers, Inc..

[15] Yang J, Ma Z. Research progress on the effects of nickel on hormone secretion in the endocrine axis and on target organs. Ecotoxicology and environmental safety. 2021 Apr 15;213:112034.

[16] Plunk EC, Richards SM. Endocrine-disrupting air pollutants and their effects on the hypothalamus-pituitary-gonadal axis. International journal of molecular sciences. 2020 Dec 2;21(23):9191.

[17] Wu K, Chen Y, Huang W. Combined molecular toxicity mechanism of heavy metals mixtures. Toxicological assessment of combined chemicals in the environment. 2025 Jan 14:125-72.

[18] Ananthanarayanan VS, Kerman A. Role of metal ions in ligand–receptor interaction: Insights from structural studies. Molecular and cellular endocrinology. 2006 Feb 26;246(1-2):53-9.

[19] Abbehausen C. Zinc finger domains as therapeutic targets for metal-based compounds–an update. Metallomics. 2019 Jan;11(1):15-28.

[20] Ali I, Damdimopoulou P, Stenius U, Adamsson A, Mäkelä SI, Åkesson A, Berglund M, Håkansson H, Halldin K. Cadmium-induced effects on cellular signaling pathways in the liver of transgenic estrogen reporter mice. Toxicological Sciences. 2012 May 1;127(1):66-75.

[21] Vijiyakumar N, Prince SE. A comprehensive review of cadmium-induced toxicity, signalling pathways, and potential mitigation strategies. Toxicology and Environmental Health Sciences. 2025 Mar;17(1):79-94.

[22] Shehadeh-Tout F, Milioli HH, Roslan S, Jansson PJ, Dharmasivam M, Graham D, Anderson R, Wijesinghe T, Azad MG, Richardson DR, Kovacevic Z. An innovative non-hormonal strategy targeting redox active metals to down-regulate estrogen-, progesterone-, androgen-and prolactin-receptors in breast cancer. bioRxiv. 2023 Feb 3:2023-02.

[23] Barthel A, Ostrakhovitch EA, Walter PL, Kampkötter A, Klotz LO. Stimulation of phosphoinositide 3-kinase/Akt signaling by copper and zinc ions: mechanisms and consequences. Archives of Biochemistry and Biophysics. 2007 Jul 15;463(2):175-82.

[24] L Carpenter R, Jiang BH. Roles of EGFR, PI3K, AKT, and mTOR in heavy metal-induced cancer. Current cancer drug targets. 2013 Mar 1;13(3):252-66.

[25] Di Silvestre A, Lucafo M, De Iudicibus S, Ventura A, Martelossi S, Stocco G, Decorti G. Glucocorticoid receptor interacting co-regulators: putative candidates for future drug targeting therapy. Mini Reviews in Medicinal Chemistry. 2017 May 1;17(8):657-66.

[26] Karmakar S, Jin Y, Nagaich AK. Interaction of glucocorticoid receptor (GR) with estrogen receptor (ER) α and activator protein 1 (AP1) in dexamethasone-mediated interference of ERα activity. Journal of Biological Chemistry. 2013 Aug 16;288(33):24020-34.

[27] He L, He T, Farrar S, Ji L, Liu T, Ma X. Antioxidants maintain cellular redox homeostasis by elimination of reactive oxygen species. Cellular Physiology and Biochemistry. 2017 Nov 17;44(2):532-53.

[28] Jomova K, Raptova R, Alomar SY, Alwasel SH, Nepovimova E, Kuca K, Valko M. Reactive oxygen species, toxicity, oxidative stress, and antioxidants: chronic diseases and aging. Archives of toxicology. 2023 Oct;97(10):2499-574.

[29] Kovacic P, Edwards C. Integrated approach to the mechanisms of thyroid toxins: electron transfer, reactive oxygen species, oxidative stress, cell signaling, receptors, and antioxidants. Journal of Receptors and Signal Transduction. 2010 Jun 1;30(3):133-42.

[30] Kochman J, Jakubczyk K, Bargiel P, Janda-Milczarek K. The influence of oxidative stress on thyroid diseases. Antioxidants. 2021 Sep 10;10(9):1442.

[31] Terasaka T, Adakama ME, Li S, Kim T, Terasaka E, Li D, Lawson MA. Reactive oxygen species link gonadotropin-releasing hormone receptor signaling cascades in the gonadotrope. Frontiers in endocrinology. 2017 Oct 30;8:286.

[32] Rotimi DE, Acho MA, Falana BM, Olaolu TD, Mgbojikwe I, Ojo OA, Adeyemi OS. Oxidative stress-induced hormonal disruption in male reproduction. Reproductive Sciences. 2024 Oct;31(10):2943-56.

[33] Kose T. The Impact of Heavy Metals on Pancreatic β-Cell Function: Mechanisms and Implications for Development of Diabetes Mellitus. InEnvironmental Toxicology-Understanding, Impact, and Mitigation Strategies for a Sustainable Future 2025 Sep 18. IntechOpen.

[34] Wróblewski M, Wróblewska J, Nuszkiewicz J, Pawłowska M, Wesołowski R, Woźniak A. The role of selected trace elements in oxidoreductive homeostasis in patients with thyroid diseases. International journal of molecular sciences. 2023 Mar 2;24(5):4840.

[35] Buha A, Matovic V, Antonijevic B, Bulat Z, Curcic M, Renieri EA, Tsatsakis AM, Schweitzer A, Wallace D. Overview of cadmium thyroid disrupting effects and mechanisms. International Journal of Molecular Sciences. 2018 May 17;19(5):1501.

[36] Silvestrini A, Mordente A, Martino G, Bruno C, Vergani E, Meucci E, Mancini A. The role of selenium in oxidative stress and in nonthyroidal illness syndrome (NTIS): an overview. Current medicinal chemistry. 2020 Jan 1;27(3):423-49.

[37] Ahmed MY, Abdoulrahman K. Toxic metals and bioelements: Combined oxidative stress effects on liver injury and thyroid hormone disruption in subjects from different areas of Erbil province. Toxicology Reports. 2025 Dec 1;15:102078.

[38] de Escobar GM, Obregón MJ, del Rey FE. Maternal thyroid hormones early in pregnancy and fetal brain development. Best practice & research Clinical endocrinology & metabolism. 2004 Jun 1;18(2):225-48.

[39] Rovet JF. The role of thyroid hormones for brain development and cognitive function. Endocr Dev. 2014 Aug 29;26(26):26-43.

[40] Gustin K, Barman M, Skröder H, Jacobsson B, Sandin A, Sandberg AS, Wold AE, Vahter M, Kippler M. Thyroid hormones in relation to toxic metal exposure in pregnancy, and potential interactions with iodine and selenium. Environment International. 2021 Dec 1;157:106869.

[41] Salazar P, Villaseca P, Cisternas P, Inestrosa NC. Neurodevelopmental impact of the offspring by thyroid hormone system-disrupting environmental chemicals during pregnancy. Environmental Research. 2021 Sep 1;200:111345.

[42] Rahman A, Kumarathasan P, Gomes J. Infant and mother related outcomes from exposure to metals with endocrine disrupting properties during pregnancy. Science of the Total Environment. 2016 Nov 1;569:1022-31.

[43] Kaur I, Behl T, Aleya L, Rahman MH, Kumar A, Arora S, Akter R. Role of metallic pollutants in neurodegeneration: effects of aluminum, lead, mercury, and arsenic in mediating brain impairment events and autism spectrum disorder. Environmental Science and Pollution Research. 2021 Feb;28(8):8989-9001.

[44] Domínguez-Vargas C, García-Hernández JE, Peña-Durán E, Ramírez-Flores SJ, González-Reyes UM, Martínez-Hernández RE, Torres-Rodríguez DA, Prado-López PM. Pediatric Heavy-Metal Exposome and Chronic Disease Trajectories: From Neurodevelopment to Metabolic and Endocrine Outcomes.

[45] Faa G, Marcialis MA, Ravarino A, Piras M, Pintus MC, Fanos V. Fetal programming of the human brain: is there a link with insurgence of neurodegenerative disorders in adulthood?. Current medicinal chemistry. 2014 Nov 1;21(33):3854-76.

[46] Rana SV. Perspectives in endocrine toxicity of heavy metals—a review. Biological trace element research. 2014 Jul;160(1):1-4.

[47] Sharma M, Khan S, Rahman S, Singh LR. The extracellular protein, transthyretin is an oxidative stress biomarker. Frontiers in physiology. 2019 Jan 24;10:5.

[48] Alshehri B, D'Souza DG, Lee JY, Petratos S, Richardson SJ. The diversity of mechanisms influenced by transthyretin in neurobiology: development, disease and endocrine disruption. Journal of neuroendocrinology. 2015 May;27(5):303-23.

[49] Koyama H, Kamogashira T, Yamasoba T. Heavy metal exposure: molecular pathways, clinical implications, and protective strategies. Antioxidants. 2024 Jan 5;13(1):76.

[50] Ilieva I, Sainova I, Yosifcheva K. Toxic effects of heavy metals (lead and cadmium) on sperm quality and male fertility. Acta morphol. anthropol. 2020;27(3-4).

[51] Zhang Q, Xu W, Kong Z, Wu Y, Liu Y. Cadmium exposure-induced rat testicular dysfunction and its mechanism of chronic stress. Food and Chemical Toxicology. 2023 Dec 1;182:114181.

[52] Balachandar R, Bagepally BS, Kalahasthi R, Haridoss M. Blood lead levels and male reproductive hormones: A systematic review and meta-analysis. Toxicology. 2020 Oct 1;443:152574.

[53] Banu SK. Heavy metals and the ovary. Ovarian Toxicology. 2013 Sep 25;2:191-228.

[54] Bhardwaj JK, Bikal P, Sachdeva SN. Cadmium as an ovarian toxicant: A review. Journal of Applied Toxicology. 2024 Jan;44(1):129-47.

[55] Henriques MC, Loureiro S, Fardilha M, Herdeiro MT. Exposure to mercury and human reproductive health: A systematic review. Reproductive toxicology. 2019 Apr 1;85:93-103.

[56] Liu D, Hu Z, Lu J, Yi C. Redox-regulated iron metabolism and ferroptosis in ovarian cancer: molecular insights and therapeutic opportunities. Antioxidants. 2024 Jun 28;13(7):791.

[57] Fan Y, Jiang X, Xiao Y, Li H, Chen J, Bai W. Natural antioxidants mitigate heavy metal induced reproductive toxicity: Prospective mechanisms and biomarkers. Critical Reviews in Food Science and Nutrition. 2024 Dec 9;64(31):11530-42.

[58] Huang J, Zhang Y, King L, Wang J, Nie P, Xie Q, Chen H, Wan X, Li Z, Zhao Y, Xu H. Associations of urinary heavy metals with age at menarche, age at menopause, and reproductive lifespan: A cross-sectional study in US women. Ecotoxicology and Environmental Safety. 2024 Sep 15;283:116950.

[59] Wang X, Ding N, Harlow SD, Randolph Jr JF, Mukherjee B, Gold EB, Park SK. Exposure to heavy metals and hormone levels in midlife women: the Study of Women's Health Across the Nation (SWAN). Environmental Pollution. 2023 Jan 15;317:120740.

[60] Ding N, Wang X, Harlow SD, Randolph Jr JF, Gold EB, Park SK. Heavy metals and trajectories of anti-Müllerian hormone during the menopausal transition. The Journal of Clinical Endocrinology & Metabolism. 2024 Nov;109(11):e2057-64.

[61] Yan Y, Guo F, Liu K, Ding R, Wang Y. The effect of endocrine-disrupting chemicals on placental development. Frontiers in endocrinology. 2023 Feb 21;14:1059854.

[62] Zheng CY, Yu YX, Cao SY, Bai X. Epigenetics of inflammation in hypothalamus pituitary gonadal and neuroendocrine disorders. InSeminars in Cell & Developmental Biology 2024 Feb 15 (Vol. 154, pp. 340-345). Academic Press.

[63] Dutta S, Gorain B, Choudhury H, Roychoudhury S, Sengupta P. Environmental and occupational exposure of metals and female reproductive health. Environmental Science and Pollution Research. 2022 Sep;29(41):62067-92.

[64] Rattan S, Zhou C, Chiang C, Mahalingam S, Brehm E, Flaws JA. Exposure to endocrine disruptors during adulthood: consequences for female fertility. Journal of Endocrinology. 2017 Jun 1;233(3):R109-29.

[65] Rana SV. Endoplasmic reticulum stress induced by toxic elements—a review of recent developments. Biological trace element research. 2020 Jul;196(1):10-9.

[66] Młynarska E, Grabarczyk M, Leszto K, Luba G, Motor J, Sosińska A, Rysz J, Franczyk B. Environmental Insults to Glucose Metabolism: The Role of Pollutants in Insulin Resistance. International Journal of Molecular Sciences. 2025 Sep 15;26(18):8979.

[67] Bibha K, Akhigbe TM, Hamed MA, Akhigbe RE. Metabolic derangement by arsenic: a review of the mechanisms. Biological Trace Element Research. 2024 May;202(5):1972-82.

[68] Khandayataray P, Samal D, Murthy MK. Arsenic and adipose tissue: an unexplored pathway for toxicity and metabolic dysfunction. Environmental Science and Pollution Research. 2024 Feb;31(6):8291-311.\

[69] Zhang J, Yang Y, Liu W, Liu J. Potential endocrine-disrupting effects of metals via interference with glucocorticoid and mineralocorticoid receptors. Environmental pollution. 2018 Nov 1;242:12-8.

[70] Sun HJ, Xiang P, Luo J, Hong H, Lin H, Li HB, Ma LQ. Mechanisms of arsenic disruption on gonadal, adrenal and thyroid endocrine systems in humans: A review. Environment international. 2016 Oct 1;95:61-8.

[71] Abdul QA, Yu BP, Chung HY, Jung HA, Choi JS. Epigenetic modifications of gene expression by lifestyle and environment. Archives of pharmacal research. 2017 Nov;40(11):1219-37.

[72] Malbeteau L, Pham HT, Eve L, Stallcup MR, Poulard C, Le Romancer M. How protein methylation regulates steroid receptor function. Endocrine reviews. 2022 Feb 1;43(1):160-97.

[73] Chen Y, Sun Y, Zhao A, Cai X, Yu A, Xu Q, Wang P, Yao J, Wang Q, Wang W. Arsenic exposure diminishes ovarian follicular reserve and induces abnormal steroidogenesis by DNA methylation. Ecotoxicology and Environmental Safety. 2022 Aug 1;241:113816.

[74] Sindhu P, Magotra A, Sindhu V, Chaudhary P. Unravelling the impact of epigenetic mechanisms on offspring growth, production, reproduction and disease susceptibility. Zygote. 2024 Jun;32(3):190-206.

[75] Greco E, Talarico E, Guarasci F, Camoli M, Palermo AM, Zambelli A, Chiappetta A, Araniti F, Bruno L. Epigenetic Mechanisms of Plant Adaptation to Cadmium and Heavy Metal Stress. Epigenomes. 2025 Nov 2;9(4):43.