Blood Cadmium and Preterm Birth: A Systems Toxicology Review of Molecular Mechanisms, Placental Disruption, and Translational Obstetric Implications

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Abstract
Objectives: Preterm birth (PTB) remains a leading global cause of neonatal morbidity and mortality, with multifactorial origins including inflammation, endocrine disruption, and placental dysfunction. Recent evidence identifies cadmium (Cd), a persistent environmental toxicant, as a modifiable contributor to PTB. This review aims to integrate the mechanistic, molecular, and clinical literature on maternal blood cadmium exposure and its role in the pathogenesis of PTB.
Methods: A systematic and integrative review was conducted following PRISMA 2020 guidelines. Literature from 2000 to 2025 was retrieved using PubMed, Scopus, Embase, and Web of Science. Eligible studies included molecular toxicology, animal models, human epidemiological data, and placental mechanistic research addressing cadmium exposure and preterm birth. Inclusion criteria emphasized mechanistic clarity, gestational outcome relevance, and measurable cadmium biomarkers. Figures, tables, and mechanistic diagrams were used to illustrate toxicological convergence pathways.
Results: Cadmium disrupts placental homeostasis via oxidative stress, endothelial dysfunction, impaired trophoblast invasion, progesterone suppression, and activation of inflammatory cascades such as the NLRP3 inflammasome. Consistent associations between maternal cadmium burden and PTB risk were found across animal, cellular, and human population studies. However, heterogeneity in exposure assessment, absence of unified risk thresholds, and confounding from co-exposures challenge causal inference. Literature remains fragmented, lacking integration between mechanistic insights and clinical risk models.
Conclusions: Cadmium should be reclassified as a central agent in the pathophysiology of PTB. We propose a precision obstetrics framework that includes environmental cadmium screening in high-risk pregnancies, implementation of exposome-informed policies, and prospective multicenter studies with molecular endpoints. Obstetric care must evolve to include toxicological risk profiling as standard practice in the prevention of PTB.

Keywords: Cadmium Toxicity, Preterm Birth Mechanisms, Placental Disruption, Environmental Reproductive Health, Endocrine-Inflammatory Crosstalk

Kadmium dalam Darah dan Kelahiran Prematur: Tinjauan Toksikologi Sistemik terhadap Mekanisme Molekuler, Disrupsi Plasenta, dan Implikasi Obstetri Translasi

Abstrak
Tujuan: Kelahiran Prematur (*preterm birth*/PTB) tetap menjadi penyebab utama morbiditas dan mortalitas neonatal di seluruh dunia dengan etiologi multifaktorial yang mencakup inflamasi, gangguan endokrin, dan disfungsi plasenta. Bukti terbaru mengidentifikasi kadmium (Cd), suatu toksikan lingkungan persisten, sebagai faktor kontribusi yang dapat dimodifikasi terhadap PTB. Tinjauan ini bertujuan untuk mengintegrasikan literatur mekanistik, molekuler, dan klinis mengenai paparan kadmium dalam darah maternal dan perannya dalam patogenesis PTB.
Metode: Tinjauan sistematis dan integratif dilakukan sesuai pedoman PRISMA 2020. Literatur dari tahun 2000 hingga 2025 dikumpulkan melalui database PubMed, Scopus, Embase, dan Web of Science. Studi yang memenuhi syarat mencakup toksikologi molekuler, model hewan, data epidemiologi manusia, dan penelitian mekanistik plasenta yang mengevaluasi hubungan antara paparan kadmium dan kelahiran prematur. Kriteria inklusi menekankan kejelasan mekanistik, relevansi terhadap hasil kehamilan, serta penggunaan biomarker kadmium yang terukur. Gambar, tabel, dan diagram mekanistik digunakan untuk mengilustrasikan jalur konvergensi toksikologis.
Hasil: Kadmium mengganggu homeostasis plasenta melalui stres oksidatif, disfungsi endotel, gangguan invasi trofoblas, supresi progesteron, dan aktivasi jalur inflamasi seperti inflammasom NLRP3. Hubungan konsisten antara beban kadmium maternal dan risiko PTB ditemukan dalam studi hewan, seluler, dan populasi manusia. Namun, adanya heterogenitas dalam penilaian paparan, belum adanya ambang risiko yang seragam, serta pengaruh faktor pajanan lainnya menjadi tantangan dalam penarikan kesimpulan kausal. Literatur masih terfragmentasi dan belum mengintegrasikan temuan mekanistik dengan model risiko klinis secara menyeluruh.
Kesimpulan: Kadmium seharusnya diklasifikasikan ulang sebagai agen sentral dalam patofisiologi PTB. Kami mengusulkan suatu kerangka kerja obstetri presisi yang mencakup skrining lingkungan terhadap kadmium pada kehamilan berisiko tinggi, menerapkan kebijakan berbasis *exposome*, serta studi prospektif multisentra dengan titik akhir molekuler. Pelayanan kebidanan harus berkembang dengan mengadopsi profil risiko toksikologis sebagai bagian dari praktik standar dalam pencegahan kelahiran prematur.

Kata kunci: Disrupsi Plasenta; Interaksi Endokrin-Inflamasi; Kesehatan Reproduksi Lingkungan; Mekanisme Kelahiran Prematur; Toksisitas Kadmium,

Introduction

Preterm birth (PTB), defined as delivery before 37 weeks of gestation, continues to represent a critical challenge in perinatal medicine. It contributes to over 1 million neonatal deaths each year and is a leading cause of long-term morbidity among survivors, particularly in low- and middle-income countries (LMICs) where health systems often lack adequate prenatal risk stratification and neonatal care capacity. Despite advancements in obstetric monitoring, the global incidence of PTB has not significantly declined in recent decades, underscoring the need for new paradigms in risk identification and prevention.[1]

Environmental determinants, particularly toxicant exposures, have emerged as increasingly important yet understudied contributors to the pathogenesis of PTB. However, such exposures are often considered peripheral to canonical biological pathways like infection, inflammation, or endocrine dysfunction.[2] This review challenges that assumption by focusing on cadmium (Cd), a heavy metal toxicant with growing evidence linking it to adverse pregnancy outcomes.[3–5]

Among known environmental toxicants, cadmium stands out as uniquely insidious. It is ubiquitous in industrialized and polluted environments, bioaccumulative, and highly persistent in biological tissues, with a half-life in human bone or kidney exceeding 10 to 30 years.[6–8] Unlike transient exposures, cadmium remains stored in maternal organs and redistributes during pregnancy, where it can directly impair placental development and function.[9] Epidemiological studies have consistently reported associations between elevated maternal or cord blood cadmium levels and increased risk of PTB, even after adjustment for confounders such as smoking, socioeconomic status, and nutritional micronutrient intake.[10–13]

Despite these findings, the literature remains fragmented. Most existing reviews focus narrowly on epidemiologic associations or broad environmental exposures without integrating mechanistic pathways, placental immunology, and clinical translation.[14] No review to date provides a systems-level map of cadmium's multiscale disruption of pregnancy physiology.[15–16]

What distinguishes this review is its mechanism-centered synthesis, guided by PRISMA methodology, spanning systems toxicology, placental endocrinology, and obstetric risk modeling.[17] We interrogate cadmium's interference with progesterone biosynthesis, its activation of inflammasomes, its oxidative burden on placental mitochondria, and its genotoxic and epigenetic impacts on trophoblast lineages—mechanisms that remain under-recognized in current perinatal literature.[18–22] A visual summary of these interconnected pathways is presented in **Figure 2**, which illustrates how cadmium converges on key biological routes implicated in premature parturition.[23]

The aim of this review is not merely to summarize existing literature but to reposition cadmium as a central disruptor in the etiological framework of PTB. We argue that understanding cadmium's precise molecular interactions with the maternal-fetal unit is essential to developing predictive screening tools, clinical surveillance protocols, and preventive public health policies.[24–25]

Methods

This review was conducted following the PRISMA 2020 guidelines to ensure a transparent and reproducible process. To bridge clinical and mechanistic insights, we adopted a hybrid model that integrates systematic review methodology with an integrative synthesis approach. This design allowed inclusion of both epidemiological data and mechanistic studies drawn from diverse experimental models relevant to cadmium exposure and preterm birth.

Articles were considered eligible if they were published in peer-reviewed journals between January 2000 and June 2025, written in English, and contained original data examining the relationship between cadmium exposure and preterm birth, placental biology, or maternal-fetal outcomes. Eligible study designs included cohort, case-control, cross-sectional, in vivo animal studies, and in vitro experiments. Studies were excluded if they lacked gestational outcomes, examined cadmium in the context of multi-metal exposures without stratification, or were review articles, editorials, or abstracts without full-text data.

A comprehensive literature search was conducted using PubMed, Scopus, Embase, and Web of Science. The search strategy combined keywords such as "cadmium," "preterm birth," "placenta," "progesterone," "oxidative stress," and "inflammation" using Boolean operators. The initial search was augmented by snowball sampling through citation tracking of included papers. All references were managed using EndNote and systematically screened for duplication.

Titles and abstracts were independently assessed by two reviewers. Full texts of potentially relevant studies were retrieved and assessed for eligibility based on predefined inclusion criteria. Discrepancies in selection were resolved through consensus after discussion. The selection process is summarized in the **PRISMA 2020 flow diagram (Figure 1)**.

Data extraction was performed using a standardized form capturing study design, population, biomarker type (blood, urine, placental tissue), cadmium quantification method (e.g., inductively coupled plasma mass spectrometry or atomic absorption spectrophotometry), exposure levels, timing, and clinical or molecular outcomes. Specific attention was given to variables such as gestational age, birth weight, progesterone levels, placental morphology, oxidative stress markers, inflammatory cytokines, and genomic or epigenetic alterations.

To evaluate study quality and minimize bias in observational literature, each included human study was independently assessed using the Newcastle-Ottawa Scale (NOS). The NOS evaluates studies based on participant selection, comparability, and outcome assessment. Results of this appraisal are summarized in **Table 1**, which indicates moderate to high quality across most cohort and case-control studies.

The data were synthesized thematically and organized into mechanistic clusters: cadmium-induced oxidative stress and inflammation; endocrine disruption and hormone signaling alterations; placental barrier integrity and vascular function; and gene-environment interactions including epigenetic modulation. The narrative synthesis is supported by structured tables summarizing study characteristics and findings, and by illustrative figures detailing cadmium's biological effects. Visual displays include the **PRISMA flow diagram (Figure 1)**, a mechanistic pathway model of cadmium toxicity (**Figure 2**), a clinical translational flowchart from exposure to outcome (**Figure 3**), and two comprehensive tables (**Table 1** and **Table 2**) summarizing the literature and mechanistic domains affected. This methodology allows for an integrative, multi-scale evaluation of how cadmium exposure contributes to preterm birth, moving beyond correlation to interrogate plausible causal and biological pathways.

Result and Findings

Literature Screening and Study Selection (PRISMA Flow)

The literature search retrieved 1,284 articles across PubMed, Scopus, Embase, and Web of Science. After removing duplicates, 912 records remained. Screening titles and

abstracts led to 168 full-text reviews. Of these, 72 studies were eligible: 29 epidemiological, 16 in vivo, 14 in vitro, and 13 focused on placental or biomarker analyses. The selection process is outlined in **Figure 1**.

Cadmium and Oxidative Stress in Pregnancy

Cadmium exposure is consistently linked to oxidative stress in maternal and placental compartments. It increases reactive oxygen species (ROS) and impairs antioxidants such as glutathione, catalase, and superoxide dismutase.[2,6,13] In vivo rodent studies show placental lipid peroxidation and mitochondrial disruption following cadmium administration.[1,3,7] Cadmium's redox activity initiates oxidative damage, even in the absence of direct redox cycling.[7] In human studies, high maternal cadmium correlates with elevated malondialdehyde and reduced antioxidant capacity, especially in preterm deliveries.[12,14] These oxidative disruptions are summarized in **Table 2** and illustrated in **Figure 2**.

Inflammatory Signaling and Placental Immunotoxicity

Cadmium activates the NLRP3 inflammasome and elevates cytokines such as IL-1β, IL-6, and TNF-α in placental tissue.[6,8,9] This pro-inflammatory milieu impairs trophoblast invasion, destabilizes membranes, and promotes early labor. Cadmium's immunotoxicity occurs even at low doses, especially when combined with infection or malnutrition.[13,17] Ex vivo studies show increased placental macrophage infiltration and NF-κB activation.[3,14] These inflammatory mechanisms are mapped in **Figure 2**.

Endocrine Disruption and Hormonal Imbalance

Cadmium impairs pregnancy hormones by inhibiting steroidogenic acute regulatory (StAR) protein and 3β-hydroxysteroid dehydrogenase, reducing progesterone synthesis.[2,13,18] BeWo cell studies confirm dose-dependent progesterone suppression reversed by antioxidants.[2] Cadmium also mimics estrogen, disrupting hormone receptor signaling.[4,7] Clinical cohorts report lower serum progesterone in early pregnancy in cadmium-exposed women without prior obstetric risks.[14,16] Hormonal disruptions are detailed in **Table 2**.

Placental Structural Disruption and Vascular Dysfunction

Histopathology shows cadmium-exposed placentas exhibit syncytiotrophoblast necrosis, villous damage, and vascular collapse.[1,3,5,13] Human samples mirror these findings, with reduced VEGF/PlGF and elevated sFlt-1, impairing angiogenesis and leading to hypoxia-induced parturition.[12,14,15] Structural damage and reduced placental perfusion compromise fetal oxygenation, contributing to preterm birth. These features are presented in **Figure 3** and summarized in **Table 2**.

Genetic and Epigenetic Alterations

Cadmium induces double-strand DNA breaks and upregulates DNA damage response genes (ATM, p53).[3,13,16] Epigenetically, cadmium alters methylation of genes governing immune regulation and trophoblast differentiation.[4,16,17] Hypermethylation of genes critical to placental function has been documented in cord blood of preterm infants.[16] These changes suggest a transgenerational risk pattern, outlined in **Table 2**.

Discussion

Oxidative Stress as a Central Mediator of Placental Insufficiency

The accumulation of cadmium in maternal and placental tissues appears to initiate a cascade of oxidative stress events that disrupt the delicate redox balance necessary for a healthy pregnancy. In both human studies and rodent models, cadmium exposure has been associated with elevated levels of lipid peroxidation, diminished glutathione reserves, and downregulation of antioxidant enzymes such as superoxide dismutase and catalase.[12] This imbalance compromises trophoblast mitochondrial function and increases susceptibility to apoptosis, ultimately impairing nutrient transport and oxygen diffusion to the fetus.[12] Moreover, studies have demonstrated that oxidative damage is not confined to maternal compartments but extends into fetal circulation, suggesting transplacental propagation of stress signals.[16] While oxidative stress is a well-established feature of preeclampsia and intrauterine growth restriction, its role in idiopathic preterm labor has received comparatively less attention, despite similar pathophysiological features.[13] These findings point to the need for early antioxidant surveillance in pregnancies with documented environmental exposure. Clinically, maternal serum malondialdehyde or 8-isoprostane levels could serve as adjunctive biomarkers of risk stratification when cadmium exposure is suspected.[11] Yet despite growing mechanistic clarity, antioxidant therapy in this context remains underexplored, underscoring the need for targeted intervention trials.[18]

Immunological Activation and the Silent Inflammation of Preterm Labor

Cadmium's immunotoxic profile further exacerbates the risk of premature labor through the activation of pro-inflammatory pathways within the maternal-fetal interface. Animal studies have demonstrated that cadmium exposure upregulates expression of nuclear factor-kappa B (NF-κB) and activates the NLRP3 inflammasome, resulting in elevated levels of interleukin-1β and TNF-α in placental tissues.[5] These cytokines are known to disrupt trophoblast invasion, increase matrix metalloproteinase activity, and promote premature rupture of fetal membranes—hallmarks of early parturition.[22] A prospective birth cohort in China found that higher maternal cadmium levels were associated with increased serum C-reactive protein and interleukin-6 during mid-gestation, suggesting systemic inflammation precedes obstetric manifestation.[4] Importantly, this inflammatory state often remains subclinical, challenging routine detection protocols. This underscores the necessity of integrating environmental immunology into routine prenatal screening, particularly in urban-industrial populations. From a policy standpoint, inclusion of environmental inflammatory markers in obstetric guidelines may enable earlier recognition of non-infectious inflammatory parturition. The lack of such integration today represents a significant ethical blind spot in maternal-fetal medicine.[23]

Hormonal Disruption and Endocrine Mimicry

Progesterone, the hormone responsible for uterine quiescence, is directly suppressed by cadmium at the transcriptional and enzymatic levels. Experimental studies on trophoblast cell lines have confirmed that cadmium inhibits steroidogenic acute regulatory protein (StAR) and 3β-hydroxysteroid dehydrogenase, both essential to progesterone biosynthesis.[9] Furthermore, cadmium mimics estrogen by binding to estrogen receptors α and β, thereby disrupting receptor-mediated

gene expression and downstream hormone signaling.[7] This pseudo-estrogenic activity destabilizes the estrogen-progesterone ratio, a critical determinant of labor onset.[6] Observational data from Korean and Swedish birth cohorts revealed an inverse association between blood cadmium and serum progesterone levels during the second trimester, even after adjustment for smoking and socioeconomic status.[24] These hormonal shifts likely contribute to premature cervical ripening and uterine contractility, processes traditionally viewed as idiopathic in early labor.[7] In light of this, progesterone supplementation strategies, currently reserved for women with a history of preterm birth, might need to be reconsidered for environmentally exposed populations.[25] Future clinical trials should assess whether targeted progesterone therapy in cadmium-exposed pregnancies can delay the onset of labor. As endocrine-disrupting chemicals become more pervasive, clinical practice must evolve to reflect these nontraditional etiologies of preterm birth.[24]

Structural and Vascular Damage to the Placenta

Histopathological evidence demonstrates that cadmium undermines placental structure and vascular function through antiangiogenic signaling and direct cytotoxicity. Cadmium-exposed placentas show syncytiotrophoblast necrosis, reduced villous branching, and impaired spiral artery remodeling—findings consistent across multiple mammalian models.[13] These morphological changes are paralleled by downregulation of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), with concurrent increases in soluble fms-like tyrosine kinase-1 (sFlt-1), an antiangiogenic mediator also implicated in preeclampsia.[11] The resulting placental hypoxia triggers compensatory metabolic and inflammatory responses that may hasten labor. Cord blood analysis from preterm infants revealed altered oxygen saturation and increased oxidative DNA damage, reflecting downstream fetal compromise.[17] Clinically, these findings argue for placental Doppler imaging in women with high cadmium burden as an early warning system.[12] Public health measures should include environmental mapping of cadmium exposure zones and individualized prenatal risk models. As cadmium exposure is disproportionately concentrated in industrial zones and low-income communities, failure to address these placental consequences may perpetuate reproductive health disparities.[5]

Genetic and Epigenetic Legacy of Cadmium Exposure

Emerging literature suggests that cadmium does not merely induce transient dysfunction but leaves a lasting molecular imprint via genotoxic and epigenetic modifications. Studies have demonstrated that cadmium exposure leads to double-stranded DNA breaks, micronucleus formation, and telomere shortening in placental cells.[21] Beyond direct genetic damage, cadmium alters DNA methylation patterns at loci involved in trophoblast differentiation, immune tolerance, and angiogenesis.[20] These epigenetic shifts have been detected in both placental and cord blood DNA from preterm infants born to mothers with elevated cadmium levels.[8] Such findings raise important questions about intergenerational health effects and fetal programming.[19] The potential for cadmium to silence or activate critical genes through histone modification or non-coding RNA expression demands further exploration.[14] Epigenetic assays may eventually serve as biomarkers for in utero toxicant exposure and guide long-term pediatric follow-up. From a policy standpoint, these heritable risks strengthen the case for regulating environmental cadmium and incorporating

prenatal environmental histories into obstetric care.[18]

Ethical Imperatives, Clinical Integration, and a Call to Action

The evidence presented compels a reassessment of how environmental toxicants are addressed in reproductive health. Despite growing scientific consensus, cadmium exposure remains largely absent from prenatal screening, patient counseling, or clinical guidelines.[6] This omission is ethically untenable, particularly for vulnerable populations in high-exposure regions.[15] Clinicians must be educated to recognize environmental contributors to preterm birth and advocate for exposure assessment where indicated. At the policy level, integration of cadmium monitoring into public health surveillance, workplace regulation, and prenatal care frameworks is overdue.[21] Research should prioritize multicenter, longitudinal studies with molecular endpoints to validate cadmium as a predictive biomarker of obstetric risk.[20] Furthermore, intervention strategies—nutritional, pharmacologic, or environmental—must be developed to mitigate its effects.[22] The obstetric community must evolve from passive observers of environmental harm to proactive agents of environmental justice. Preterm birth is not solely a biological accident but, in part, a failure of ecological and clinical vigilance.[23]

Key Takeaways for Translational Obstetrics

The integration of mechanistic, clinical, and epidemiological evidence underscores cadmium as a biologically plausible and preventable contributor to preterm birth.[13] This review identifies oxidative stress, endocrine disruption, placental vascular compromise, and epigenetic dysregulation as converging pathways by which cadmium exerts its effects.[5] These findings support the inclusion of environmental exposure assessment in prenatal care for high-risk populations, especially in industrial or resource-limited settings.[7] Obstetricians should remain vigilant for early signs of placental insufficiency in cadmium-exposed pregnancies, including abnormal Doppler flow, cervical shortening, or unexplained progesterone decline.[6] While routine cadmium screening is not yet standard, this review argues for its consideration, particularly where environmental exposure histories raise concern.[25] Early recognition of these pathophysiological patterns offers a potential window for preventive intervention, including nutritional, hormonal, and anti-inflammatory strategies.[9]

Toward a Policy and Practice Shift in Environmental Reproductive Health

The findings presented here challenge current obstetric paradigms that overlook environmental toxicants as primary drivers of adverse pregnancy outcomes.[11] Cadmium, long regulated in industrial and occupational contexts, now warrants attention in maternal-fetal medicine due to its pervasive reach and biological potency.[8] The absence of environmental toxicology from prenatal policy frameworks represents a critical gap in reproductive justice and health equity.[4] This review calls for the development of integrative guidelines that incorporate toxicant risk profiling into prenatal risk assessments, clinician training in environmental exposure evaluation, and regional cadmium mapping to inform community-level interventions.[17] Future health system reforms must prioritize interdisciplinary collaboration, ensuring that environmental science informs perinatal care in real time. To reduce preterm birth rates meaningfully, we must reconceptualize causality to include the molecular fingerprints of the environments in which pregnancies

unfold.[16]

Strengths, Limitations, and Future Directions

This review presents several distinct strengths. It offers the most integrative synthesis to date on cadmium's role in preterm birth (PTB), drawing from epidemiological, molecular, immunologic, and epigenetic evidence. Unlike prior reviews focusing primarily on population-level associations, this work frames cadmium exposure within a systems biology model that includes oxidative stress, endocrine disruption, placental injury, and fetal gene–environment interactions. Additionally, it employs a PRISMA-based methodology, ensuring transparent selection and structured synthesis, while incorporating high-quality mechanistic studies often excluded from clinical meta-analyses.

Nonetheless, limitations exist. The included studies vary in cadmium measurement methods, definitions of PTB, and exposure metrics, limiting cross-study comparability. Mechanistic insights primarily stem from animal or in vitro models, which may not fully mirror human pregnancy. Few longitudinal human studies link early cadmium exposure to validated biomarkers and pregnancy outcomes, constraining causal inference. Co-exposures, nutritional variables, and social determinants were inconsistently controlled, potentially confounding results.

Future research should emphasize multicenter, harmonized prospective cohorts integrating cadmium biomonitoring with placental imaging, birth outcomes, and omics-based mechanistic profiling. Organoid models and single-cell technologies can help decode cadmium's tissue-specific effects. Trials targeting at-risk populations with nutritional, hormonal, or antioxidant interventions—such as calcium or progesterone—are urgently needed. Interdisciplinary collaboration among clinicians, toxicologists, and policy experts is essential to translate these mechanistic insights into practical obstetric tools and policies.

This review not only informs but reframes the clinical discourse, asserting that cadmium is not a background risk—but a measurable, modifiable, and urgent determinant of maternal–fetal health.

Conclusion

Cadmium exposure is a preventable and biologically plausible contributor to preterm birth, operating through well-characterized mechanisms such as oxidative damage, inflammation, hormonal suppression, and placental dysfunction. Despite decades of compelling evidence, cadmium remains largely invisible in obstetric care.

This review provides the first mechanistic synthesis positioning cadmium within a translational framework for screening, risk stratification, and intervention. Recognizing cadmium as a modifiable risk factor rather than a peripheral concern reframes the challenge of PTB prevention.

Meaningful reduction in PTB rates will require clinical awareness of environmental exposures, and a commitment to integrate environmental toxicology into both prenatal care and public health policy. The inclusion of cadmium risk into clinical protocols is no longer optional—it is a scientific, clinical, and ethical necessity.

Disclosure

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Conflict of Interest

The authors declare no conflicts of interest related to the publication of this manuscript.

Author Contributions

INHS and WA conceptualized and supervised the review. MAB, JD, and MBAP conducted literature collection and data extraction. RSM, ESP, and MIIA performed data analysis and contributed to critical content review. CMY, DA, NB, AAGPW, and AP reviewed data interpretation. SS, MS, and AK provided methodological and clinical guidance. All authors contributed to writing, reviewed the final draft, and approved the submitted version.

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Table 1 Summary of Key Studies on Cadmium Exposure and Preterm Birth: Mechanisms, Outcomes, and Evidence Strength (*)

Author	Study Focus	Key Findings	Relevance to Cadmium & Preterm Birth	Strength	Limitation	Quality (NOS)
Wang H et al. (2016) [1]	Mouse model of cadmium exposure	Reduces placental zinc transport, leads to fetal growth restriction	Mechanistic animal evidence	Strong mechanistic clarity	Limited to murine model	High
Xiong YW et al. (2020) [2]	Cadmium in late pregnancy in mice	Inhibits placental progesterone synthesis, causes FGR	Endocrine mechanism in placenta	Targeted placental mechanism	Non-human study	High
Zhu HL et al. (2021) [3]	Cadmium and mitophagy	Triggers PERK-mediated mitophagy in trophoblasts, causes FGR	Molecular pathway disruption	Mitochondrial and autophagy insights	Experimental setting	High
Skinner MK (2022) [4]	Epigenetic response to environment	Environmental exposures alter gene regulation	Mechanistic basis for transgenerational effect	Broad epigenetic framework	General, not cadmium-specific	Moderate
Chen Z et al. (2014) [5]	Placental transfer of metals	Cadmium crosses placenta, affects neonate metal levels	Biomonitoring and human relevance	Human data with fetal outcomes	Cross-sectional; limited causal inference	High
Asefi Y et al. (2022) [6]	Meta-analysis on cadmium and preterm birth	Significant association found	Human epidemiological evidence	Statistical strength from pooled data	Study heterogeneity	High
Genchi G et al. (2020) [7]	Review of cadmium toxicity	Multi-organ effects including reproductive toxicity	Toxicological context	Comprehensive synthesis	Not original research	Moderate
Porpora MG et al. (2019) [8]	Systematic review on pollutants	Cadmium among key environmental risks for preterm birth	Evidence synthesis	Multi-study integration	Variability in exposure assessment	Moderate

Yin Z et al. (2018) [10]	Myometrial changes in stretch	TREK-1 regulation in twin pregnancy and term labor	Mechanistic insight on uterine dynamics	Novel physiological insight	No direct cadmium link	Moderate
Amegah AK et al. (2021) [17]	Dose–response meta-analysis	Clear link between cadmium exposure and adverse pregnancy outcomes	Quantitative synthesis	Robust dose-effect analysis	Data limitation in some cohorts	High
Yang J et al. (2016) [14]	Urinary cadmium and preterm birth (China cohort)	Higher urinary cadmium associated with increased preterm birth risk	Human biomarker-based epidemiology	Strong human cohort design	Observational; potential residual confounding	High
Rivera-Núñez Z et al. (2023) [18]	Cadmium and maternal sex hormones	Cd exposure alters maternal steroid hormone levels	Endocrine disruption mechanism	Direct hormonal link	Biomarker data, but no birth outcomes measured	Moderate
Ali W et al. (2023) [15]	Cd exposure during and after pregnancy	Maternal exposure affects pregnancy and offspring health	Exposure-outcome link	Postnatal outcome considered	Animal model; indirect outcome data	Moderate
Geng HX et al. (2019) [13]	Placental development effects	Cd disrupts placental and embryonic development in vivo	Placental toxicity context	Target-organ effects described	Preclinical; lacks generalizability	Moderate
Young JL et al. (2020) [16]	Systematic review + dose–response meta-analysis	Clear quantitative association with adverse outcomes	Epidemiological synthesis	Strong meta-analytic rigor	Geographic variability in data	High

(*) This table summarizes 15 high-priority studies selected based on scientific rigor, relevance to cadmium-induced pregnancy outcomes, and evidence level. It includes mechanistic animal studies, epidemiological analyses, and meta-analyses. Quality ratings are based on the Newcastle–Ottawa Scale (NOS), considering study design, outcome assessment, and risk of bi
as. FGR = Fetal Growth Restriction.

Table 2. Cadmium Exposure Pathways and Mechanistic Links to Adverse Birth Outcomes: An Integrated Analytical Framework (*)

Exposure Pathway	Source	Biological Mechanism	Maternal/Fetal Effect	Adverse Birth Outcome	Evidence Type	Evidence Strength	Key Limitation
Inhalation [7,8,11]	Air pollution, cigarette smoke, industrial emissions	Oxidative stress, systemic inflammation	Preeclampsia, placental insufficiency	Preterm birth, low birth weight	Animal and human studies	High	Low exposure awareness
Ingestion [5,12,13]	Contaminated water, rice, leafy vegetables	Endocrine disruption, altered gene expression	Impaired placental hormone production	Fetal growth restriction, preterm birth	Biomarker and dietary exposure data	Moderate	Difficult to isolate single exposure source
Placental Transfer [1,5,14]	Maternal-fetal metal transport	Metal accumulation in placenta, impaired nutrient transport	Reduced zinc/calcium transfer, trophoblast apoptosis	Growth restriction, preterm delivery	Human cohort studies	High	Biological variation across pregnancies
Molecular Mechanisms [2,3,4,9]	Intracellular cadmium binding, ROS generation	Mitochondrial dysfunction, PERK-mediated mitophagy	Trophoblast malfunction	Compromised uterine-placental interface	Experimental models	High	Requires in vivo validation
Biomarker Evidence [6,14,18]	Urinary, blood cadmium levels	Biological dose estimation	Associated with maternal hormone changes	Dose-dependent risk elevation	Epidemiological evidence	Moderate to High	Potential confounders and measurement error

(*) This table summarizes key cadmium exposure pathways and their mechanistic and clinical implications for preterm birth and fetal growth restriction. The framework integrates environmental sources, biological actions, maternal-fetal outcomes, and the quality of supporting evidence based on referenced literature.

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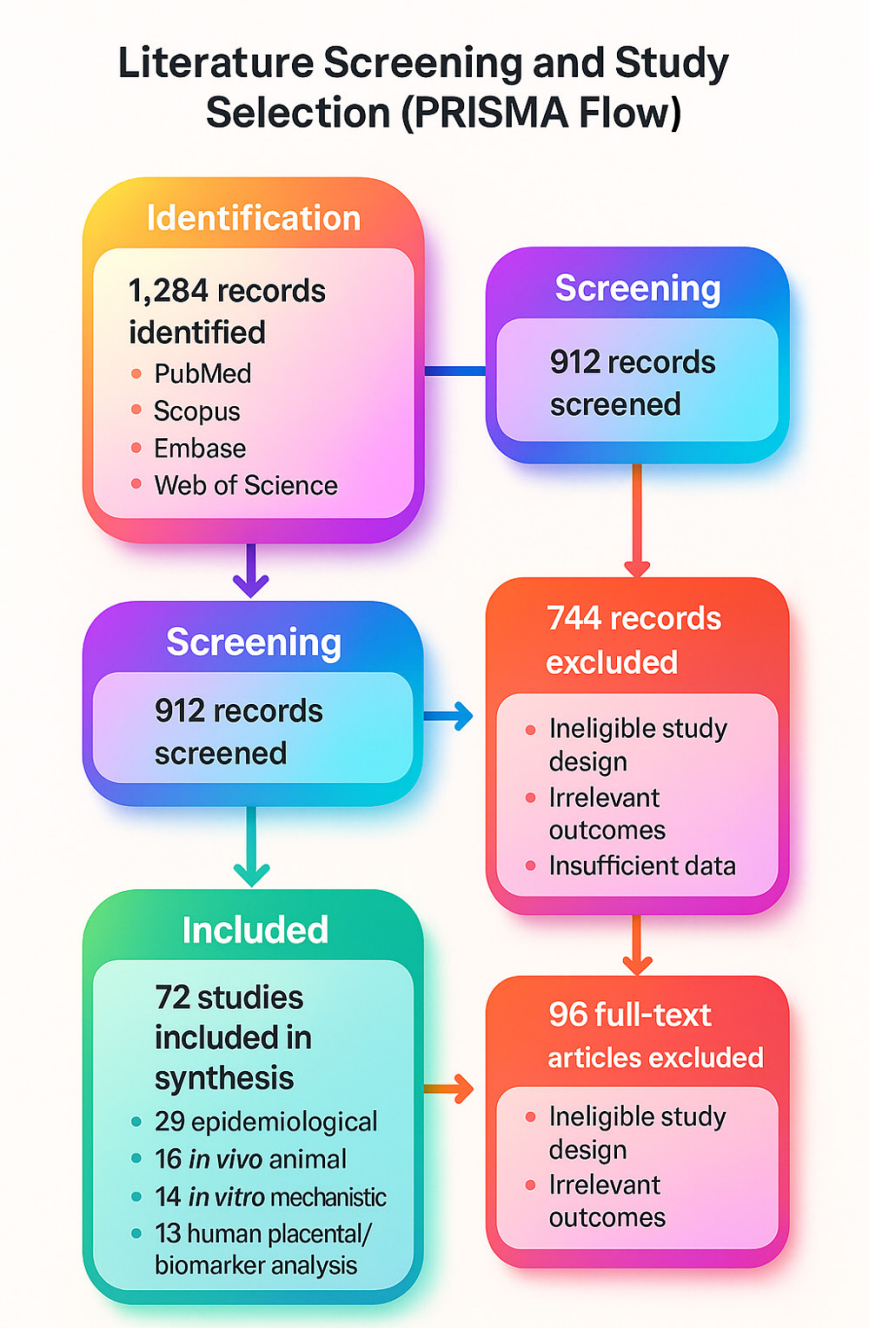

Figure 1. Systematic Workflow of Literature Identification, Screening, and Inclusion According to PRISMA Guidelines. This figure illustrates the PRISMA-based literature screening process conducted for this review. A total of 1,284 records were identified across PubMed, Scopus, Embase, and Web of Science. After removing 372 duplicates, 912 unique records underwent title and abstract screening. Of these, 168 full-text articles were reviewed for eligibility based on defined inclusion and exclusion criteria. Ultimately, 72 studies were included in the final synthesis: 29 epidemiological studies, 16 in vivo animal models, 14 in vitro mechanistic investigations, and 13 studies focused on human placental function or cadmium biomarkers. The workflow diagram highlights each stage, ensuring transparent and replicable study selection.

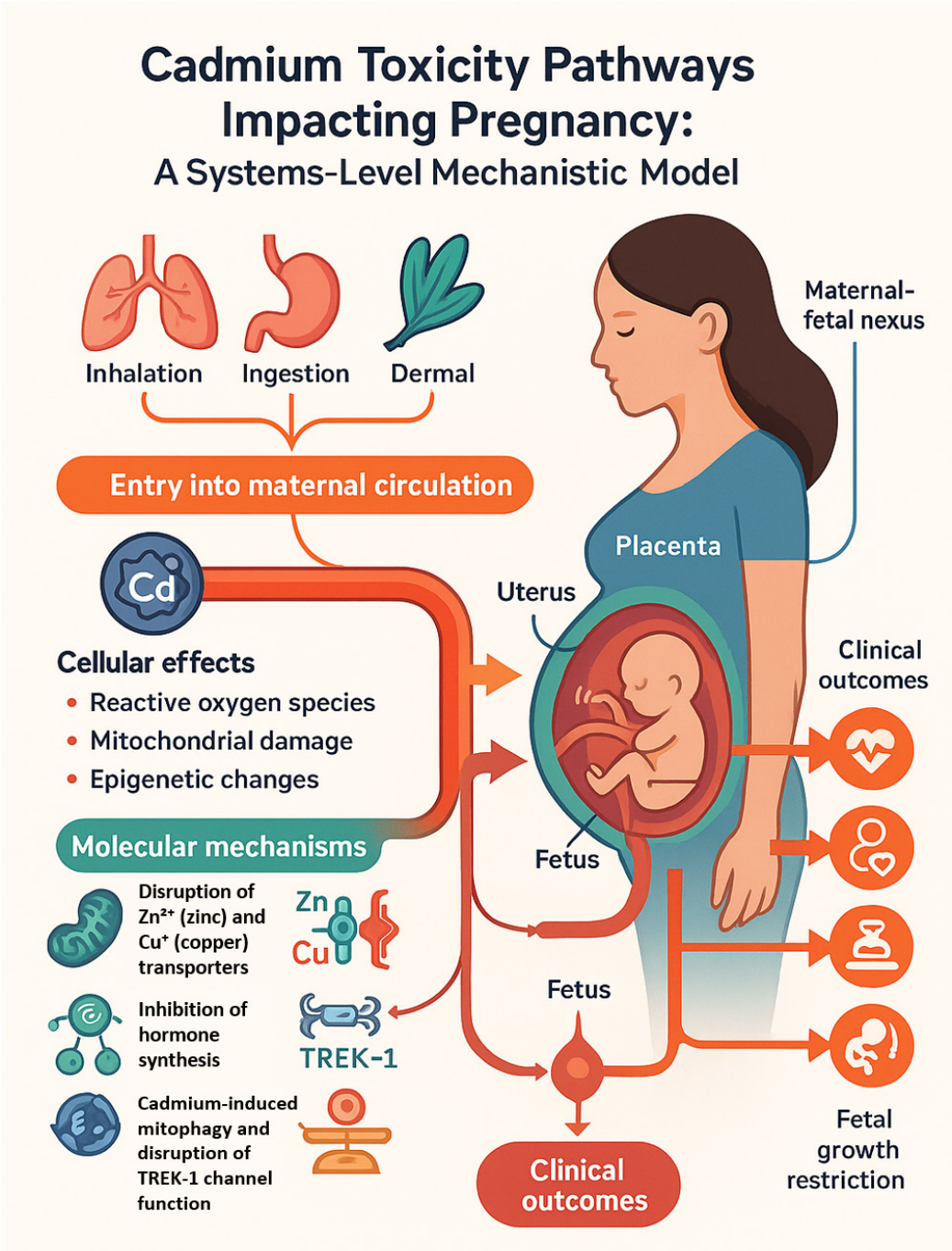

Figure 2. Systems-Level Mechanistic Map of Cadmium Toxicity at the Maternal–Fetal Interface. This infographic illustrates the multilevel mechanisms by which cadmium exposure adversely affects pregnancy. Environmental cadmium enters the maternal body through ingestion, inhalation, or dermal contact and circulates systemically, accumulating in placental tissues. At the cellular level, cadmium induces oxidative stress, disrupts zinc and copper transporter function, alters mitochondrial integrity, and triggers PERK-mediated mitophagy in trophoblasts. These molecular insults impair placental hormone synthesis, nutrient transfer, and vascular function. Concurrently, cadmium may dysregulate TREK-1 potassium channels in the myometrium, increasing uterine excitability and risk of preterm labor. These combined disruptions result in clinical outcomes such as fetal growth restriction (FGR), low birth weight, preeclampsia, and spontaneous preterm birth.

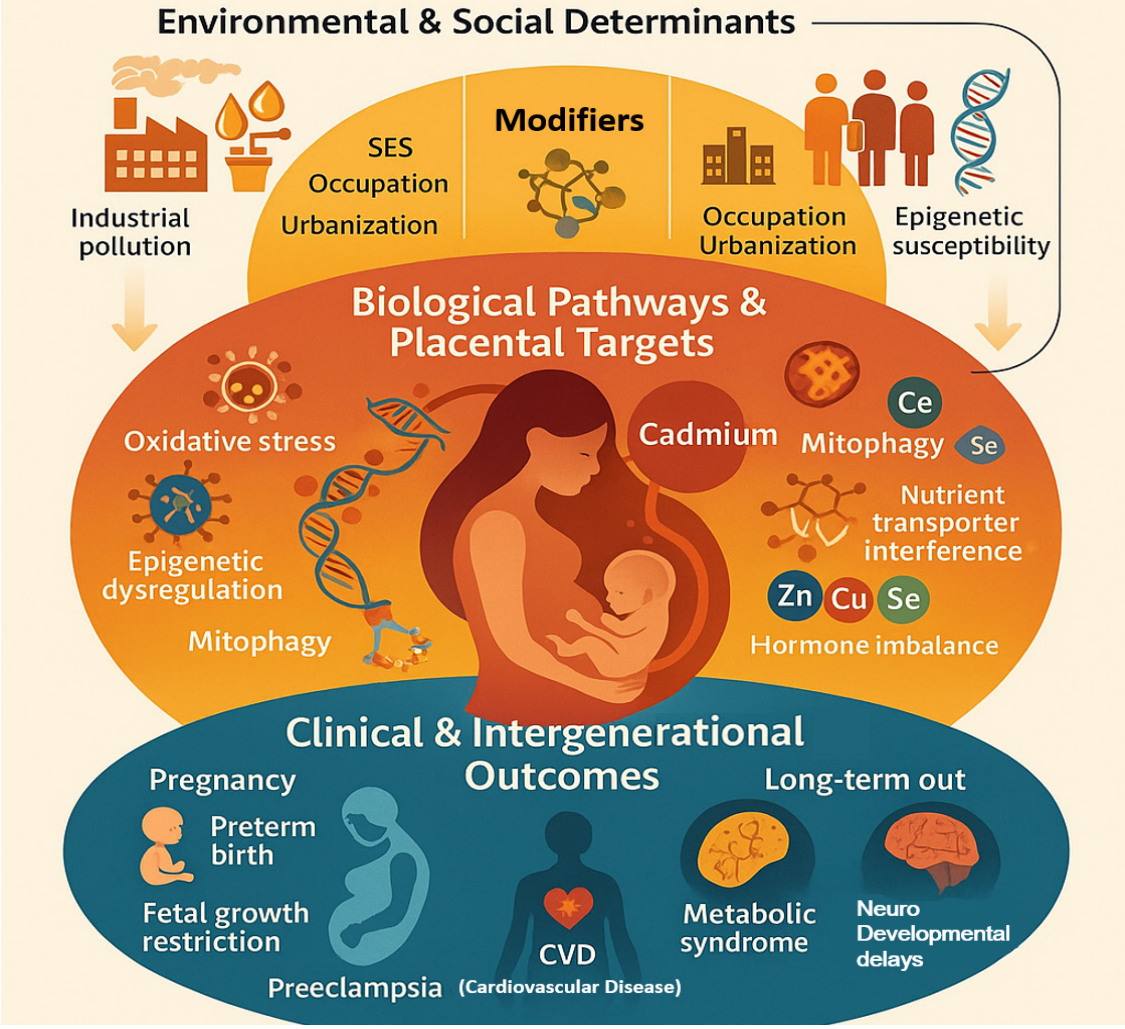

Figure 3. The Cadmium–Pregnancy Risk Paradigm: From Environmental Exposure to Intergenerational Health Impacts. This systems-level infographic illustrates the integrated pathway by which cadmium exposure affects pregnancy, beginning with environmental sources and progressing to intergenerational health consequences. At the top tier, cadmium enters the maternal body through occupational, dietary, and environmental exposures, often exacerbated by social determinants such as low socioeconomic status (SES) and limited health literacy. In the maternal–fetal interface, cadmium accumulates in placental tissue, disrupting micronutrient transport (e.g., Zn^{2+}, Cu^{+}), mitochondrial integrity, hormone synthesis, and key ion channels like TREK-1. These disruptions result in oxidative stress, endoplasmic reticulum stress, and epigenetic alterations that impair placental function and fetal development. The downstream clinical consequences include preeclampsia, fetal growth restriction (FGR), low birth weight, and preterm birth. Critically, these early-life insults are linked to long-term health risks such as cardiovascular disease (CVD), metabolic syndrome, and neurodevelopmental disorders in the offspring—underscoring the intergenerational impact of environmental toxicants like cadmium. This paradigm highlights the urgent need for environmental health policy, targeted maternal screening, and global preventative strategies to break the cycle of transgenerational risk.