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HEAVY METAL TRANSFER FROM MOTHER TO FETUS DURING PREGNANCY: MOLECULAR MECHANISMS AND CLINICAL OUTCOMES (REVIEW)

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ABSTRACT
Environmental contamination with heavy metals poses a serious global health threat, with pregnant women being particularly vulnerable due to physiological changes that enhance metal absorption and distribution. This review synthesizes current knowledge on heavy metal intake pathways, molecular mechanisms of transplacental transfer, and subsequent fetal damage. Metals enter the maternal body through alimentary, inhalation, and endogenous routes, with lead mobilization from bone depots during the third trimester being especially dangerous. The placental barrier is not impermeable; metals exploit "ionic mimicry" to utilize transport systems for essential nutrients: lead uses calcium channels, cadmium employs DMT1 and ZIP transporters, methylmercury utilizes the L-amino acid system, and arsenic uses aquaporins. The transplacental transfer index is highest for methylmercury (0.9-1.2) and lead (0.7-0.9). Once in fetal circulation, metals trigger oxidative stress, driving mitochondrial dysfunction, inflammation via proinflammatory cytokines and NLRP3 inflammasome activation, steroidogenesis disruption through StAR and CYP11 suppression, and competitive displacement of essential micronutrients. Clinically, these disturbances increase risks of preterm birth (OR = 1.4 for lead), low birth weight (OR = 1.10 for cadmium), and long-term neurodevelopmental impairments, with no safe exposure threshold. The review addresses heavy metal contamination in several Russian regions, including Siberia and the Urals. Prevention requires multi-tiered strategies: exposure reduction, nutritional correction with calcium, iron, zinc, and selenium, and early detection through screening. Understanding these molecular mechanisms provides a foundation for effective preventive measures against anthropogenic environmental contamination.

KEYWORDS: heavy metals, pregnancy, placenta, transplacental transfer, ionic mimicry, oxidative stress

INTRODUCTION

Environmental contamination with heavy metals represents one of the most pressing global challenges of modern times. Lead, cadmium, mercury, arsenic, and other toxic elements with high density and bioaccumulation potential enter ecosystems primarily through anthropogenic activities – industrial emissions, mining, fertilizer use, and fossil fuel combustion [1]. Unlike many organic pollutants, heavy metals are not subject to biodegradation, which accounts for their prolonged persistence in soil, water, and food chains [2].

The territory of the Russian Federation exhibits considerable regional variation in contamination levels, attributable to the uneven distribution of industrial facilities and mining operations. In the Siberian Federal District, soils of the Novosibirsk region have revealed elevated chromium, nickel, and manganese content; in zones of anthropogenic impact, these metals acquire more mobile forms, increasing their ability to enter food chains [3]. Long-term studies in the Omsk region (2019-2024) demonstrated that copper, zinc, cadmium, lead, nickel, mercury, and arsenic levels in forest-steppe soils generally comply with hygienic standards; however, the integrated pollution index indicates the need for continuous monitoring [4]. Significant contamination of water bodies has been documented in the Ob River basin, where 311 cases of extremely high freshwater pollution with heavy metals from industrial sources were recorded during July and August 2024 alone [5]. In the Lake Gusinoe basin (Republic of Buryatia), manganese and copper concentrations exceeded regulatory limits during winter, spring, and autumn periods [6]. On the Kola Peninsula, within the impact zone of the copper-nickel smelter in Monchegorsk, a technogenic barren land has been forming since the 1950s with extreme contamination levels: maximum copper and nickel concentrations in soils reach 29.87 and 30.12 g/kg, respectively [7]. A comprehensive 2023 review of paleolimnological studies identifies three territory types by heavy metal pollution level (industrial, urbanized, and background) with the greatest exceedances above background recorded in lakes subjected to direct technogenic impact, particularly in northwestern regions, the Urals, and Siberia [8].

Pregnant women constitute a population of exceptional vulnerability to this threat. Heavy metal intake occurs through contaminated drinking water, food products, and ambient air [9]. During gestation, metal toxicokinetics undergo substantial alterations: enhanced gastrointestinal absorption, mobilization of bone-stored reserves (particularly relevant for lead), and hemodynamic redistribution create conditions for increased xenobiotic delivery to the fetus [10]. The placenta, functioning as both barrier and transport organ between maternal and fetal circulations, does not represent an insurmountable obstacle for heavy metals. Research unequivocally demonstrates the capacity of lead, cadmium, mercury, and arsenic to cross the placental barrier and be detected in umbilical cord blood and fetal tissues [11]. The transport mechanisms are diverse, ranging from "ionic mimicry", where metals disguise themselves as essential micronutrients (calcium, zinc, iron), to active transport through specialized carrier proteins [12].

The magnitude of this problem is corroborated by epidemiological findings. A meta-analysis of 24 studies encompassing over 52,000 individuals revealed a statistically significant association between lead exposure and risk of preterm birth (OR = 1.4) and small for gestational age (OR = 1.66), as well as between cadmium exposure and low birth weight (OR = 1.10) [13]. At the molecular level, the damaging action of heavy metals is mediated through oxidative stress – generation of reactive oxygen species leading to lipid peroxidation of cell membranes, protein damage, and genetic material destabilization [14]. Additional mechanisms include endocrine disruption, apoptosis, and competitive displacement of essential micronutrients from enzyme active sites, creating a deficiency of nutrients critical for fetal development [15].

The aim of this review is to systematize current scientific knowledge regarding pathways of heavy metal intake into the pregnant woman's body, molecular mechanisms of their transport across the placental barrier, and subsequent damaging effects on the developing fetus, with emphasis on the role of oxidative stress as a universal pathogenetic link.

1. Sources and Routes of Heavy Metal Intake into the Pregnant Woman's Body

Understanding exposure pathways is fundamental for risk assessment and development of preventive measures. For pregnant women, who constitute a highly vulnerable group, the sources of xenobiotic intake acquire particular significance due to the physiological changes accompanying gestation [16]. A generalized scheme of heavy metal entry into the pregnant woman's body and their transplacental transfer is presented in Figure 1.

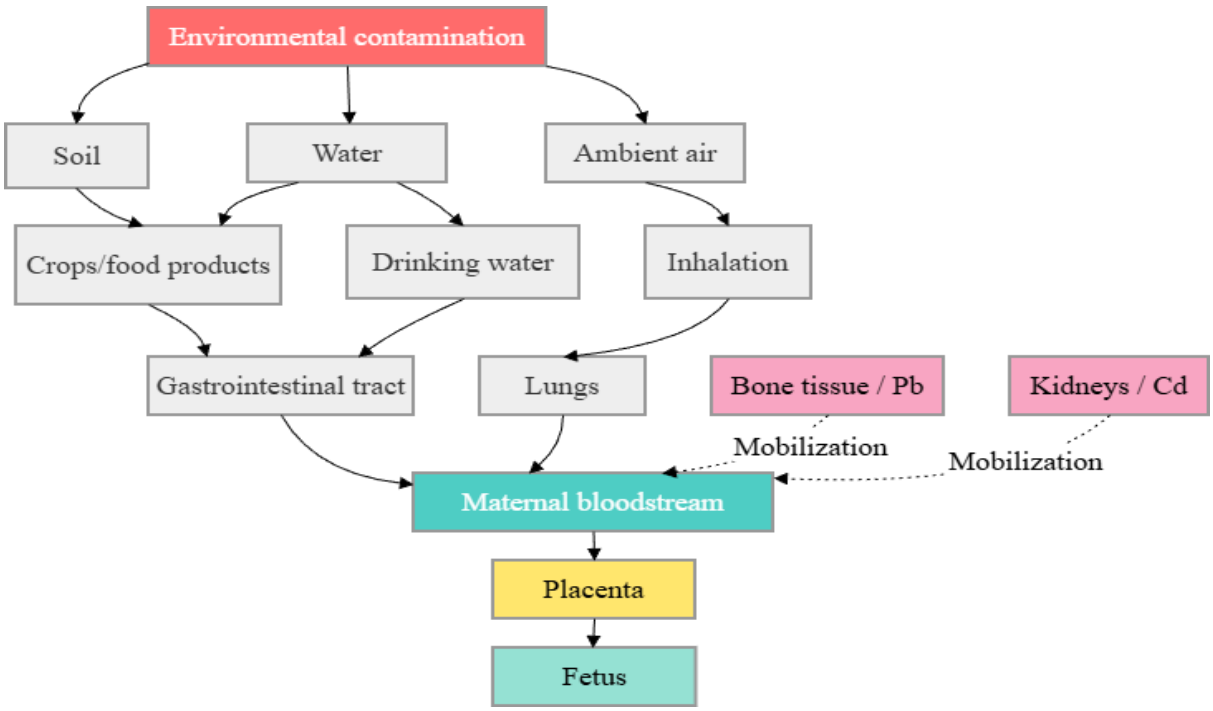

Figure 1. Major routes of heavy metal intake into the pregnant woman's body and their transplacental transfer to the fetus. Solid lines indicate exogenous exposure pathways; dashed lines indicate mobilization from endogenous depots.

Alimentary Route. The alimentary route, through contaminated food products and drinking water, constitutes the primary pathway of heavy metal entry into the human body, including pregnant women [17, 18]. In the context of modern industrial production, agricultural crops accumulate heavy metals from soil and water, with different plant species exhibiting species-specific accumulation capacities [19]. Drinking water represents a critical exposure source, particularly in regions with suboptimal water supply infrastructure or absence of centralized water systems. In the Russian Federation, numerous cases of exceeding maximum permissible concentrations of heavy metals in surface water bodies used for drinking water supply have been documented [5, 6]. Groundwater sources

in mining regions, where natural geochemical anomalies are compounded by technogenic impacts, pose particular danger [20]. Drinking water quality control is conducted in accordance with SanPiN 1.2.3685-21; however, monitoring studies indicate persistent risks [21].

Inhalation Route. Inhalation of ambient air polluted by industrial emissions and vehicle exhaust constitutes the second most significant route of heavy metal intake [22]. For lead, this pathway acquires particular importance in urban ecosystems with intensive traffic, where leaded gasoline was previously used [23]. Fine aerosol particles containing heavy metals can penetrate deep into the respiratory tract, reaching alveolar structures and being rapidly absorbed into the systemic circulation [24]. During pregnancy, inhalation exposure is exacerbated by increased minute ventilation (by 20-30% by the end of gestation), which predictably leads to higher dose loads on both maternal and fetal organisms [25].

Mobilization of Endogenous Depots. A unique feature of lead and cadmium toxicokinetics during pregnancy is the mobilization of these metals from endogenous depots – bone tissue and kidneys, respectively [26]. Lead, which exhibits pronounced affinity for bone tissue, is deposited in the hydroxyapatite crystal lattice, substituting for calcium ions [27]. During pregnancy, under the influence of hormonal changes (elevated parathyroid hormone, decreased estradiol), physiological bone resorption occurs to provide mineral substrates for the developing fetal skeleton [28]. Together with calcium, lead accumulated in bones over years is released into the systemic circulation, creating additional endogenous load on both the pregnant woman and the fetus [29, 30]. This mechanism explains why even when external lead intake ceases, its blood concentration during pregnancy may increase [31]. Cadmium, unlike lead, is deposited primarily in the kidneys and liver, bound to metallothioneins; during pregnancy, under hormonal influences and altered renal blood flow, cadmium redistribution occurs, also facilitating its entry into placental circulation [32].

Transformation of Chemical Forms in the Maternal Organism. An important aspect of toxicokinetics is the transformation of chemical forms of heavy metals in the pregnant woman's body. Inorganic arsenic forms ingested with water and food are metabolized in the liver to monomethylarsonic and dimethylarsinic acids; metabolic activity may change during pregnancy under hormonal influence [33, 34]. Mercury enters the body in three principal forms: elemental (vapor), inorganic salts, and methylmercury, with the latter being the most toxic and most efficiently crossing the placental barrier [35]. Methylmercury, formed in aquatic ecosystems through microbial methylation, accumulates in food chains, reaching maximum concentrations in predatory fish species, making fish consumption by pregnant women a focus of particular attention in epidemiological surveillance systems [36, 37].

Thus, the sources of heavy metal intake into the pregnant woman's body are multicomponent, encompassing both exogenous (water, food, air) and endogenous (mobilization from depots) routes. The complex nature of exposure, schematically represented in Figure 1, necessitates an integrated approach to risk assessment and the development of preventive strategies.

2. Placental Barrier: Structure and Function

The placenta is a unique temporary organ that provides metabolic and physiological connection between the maternal and fetal organisms. Simultaneously functioning as a barrier, transporter, and endocrine organ, the placenta is a key link in the "mother-fetus" system, determining the nature and intensity of xenobiotic impact on the developing organism [38, 39]. The schematic structure of the placental barrier and the main mechanisms of heavy metal transport are shown in Figure 2.

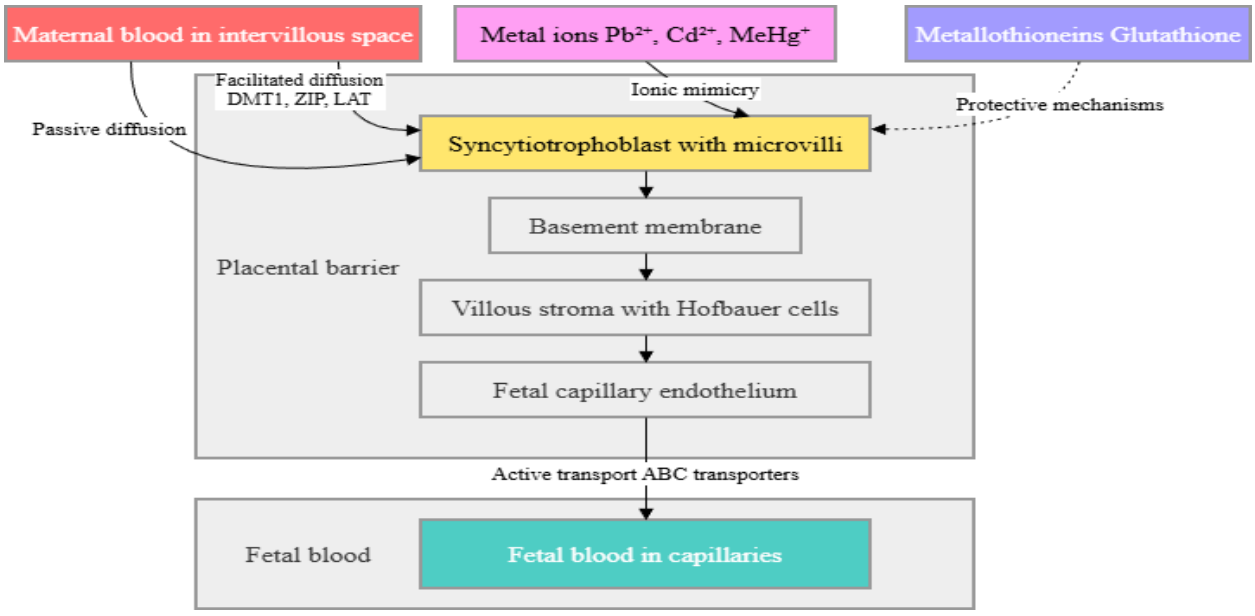

Figure 2. Structure of the placental barrier and mechanisms of heavy metal transport.

The placental barrier is composed of the syncytiotrophoblast with microvilli, cytotrophoblast, basement membrane, villous stroma, and fetal capillary endothelium [40]. Barrier thickness decreases from 35-50 μm in the first trimester to 2-5 μm by the third trimester, facilitating the passage of toxicants [41]. Transport occurs via passive diffusion (characteristic of methylmercury), facilitated diffusion through carrier proteins, and active transport via ATP-dependent pumps [42].

The key mechanism enabling heavy metal entry to the fetus is "ionic mimicry" – the substitution of essential micronutrients in transport systems [43]. Lead utilizes calcium channels and calcium-binding proteins [44]. Cadmium competes with zinc and iron, employing the DMT1 transporter and ZIP transporters [45]. Methylmercury is transported through the L-system of neutral amino acids (LAT1/LAT2), accounting for its accumulation in fetal neural tissue [46]. Arsenic employs aquaporins AQP7 and AQP9 [47].

The placenta possesses protective mechanisms, though their capacity is limited. Metallothioneins bind metal ions, preventing their diffusion to the fetus, but under chronic exposure, their synthetic capacity becomes exhausted [48]. Glutathione participates in metal excretion; however, its activation leads to depletion of the antioxidant pool and diminished placental protection [49]. Heavy metals accumulate in placental tissues, forming a depot that serves as a source of prolonged fetal exposure [50]. The transplacental transfer index is highest for methylmercury (0.9-1.2) and lead (0.7-0.9) and lowest for cadmium (0.1-0.3) [51].

Thus, the placental barrier does not constitute an absolute obstacle for heavy metals. The ability of toxicants to exploit transport systems of essential micronutrients through ionic mimicry accounts for their efficient delivery to the fetus, providing a rationale for developing nutritional correction strategies.

3. Molecular Mechanisms of Fetal Damage: Oxidative Stress and Inflammation

Penetration of heavy metals across the placental barrier triggers a cascade of pathological processes at the cellular and molecular levels. Central among these mechanisms are oxidative stress, inflammatory response, and mitochondrial damage [53, 54]. A scheme of key molecular processes induced by heavy metals in fetal and placental cells is presented in Figure 3.

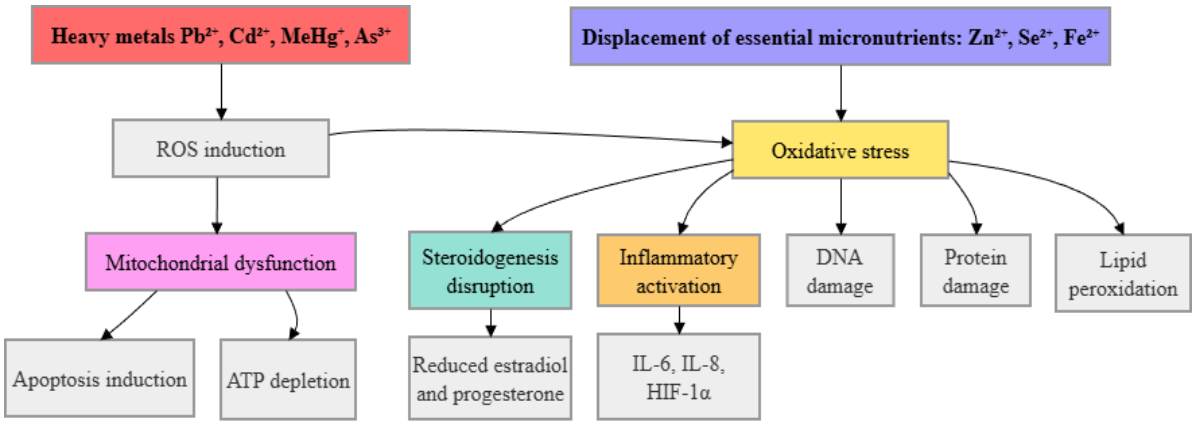

Figure 3. Molecular mechanisms of fetal damage induced by heavy metals.

In physiological pregnancy, reactive oxygen species (ROS) production predictably increases and plays an important signaling role in embryogenesis [55]. However, heavy metals disrupt this balance, inducing excessive ROS generation and depletion of antioxidant systems [56]. Induction of oxidative stress occurs through Fenton and Haber-Weiss reactions (catalysis of hydroxyl radical formation), disruption of mitochondrial electron transport, glutathione depletion, and inactivation of antioxidant enzymes, superoxide dismutase and glutathione peroxidase, in whose active sites essential micronutrients are displaced by toxic metals [57]. Experimental studies in rats confirmed that lead and cadmium exposure during pregnancy leads to decreased antioxidant activity and elevated lipid peroxidation [58].

Lipids constitute approximately 36% of placental tissue mass and play a critical role in maintaining cell membrane structure [59]. Lipid peroxidation disrupts membrane integrity; the PROTECT cohort study demonstrated that arsenic and mercury levels in pregnant women's blood are associated with plasma plasmalogen levels, reflecting a compensatory response [60]. In experiments on trophoblastic cell lines, lead and cadmium exposure caused decreased mitochondrial membrane potential and reduced mitochondrial DNA copy number [61].

Mitochondrial dysfunction has far-reaching consequences: ATP deficiency impairs cell division, membrane potential dissipation triggers apoptosis, and imbalance between mitochondrial fission and fusion exacerbates energy deficit [62]. Experimental studies in mice demonstrated that early-life lead exposure leads to structural defects in sarcomeres and mitochondria in offspring cardiomyocytes [63].

Oxidative stress is closely linked to inflammatory activation. The Ma'anshan cohort study showed that transplacental transfer efficiency of copper and mercury is negatively associated with children's intelligence, with up to 17.5% of this effect mediated by placental proinflammatory cytokines – interleukin-6, interleukin-8, and

HIF-1α [64]. Heavy metals promote NLRP3 inflammasome activation; under hypoxic conditions, lead and cadmium exposure enhances NLRP3 and procaspase-1 expression [65]. In preeclampsia, chronic metal exposure combined with placental microenvironment hypoxia may lead to a full-blown inflammatory response [66].

Beyond oxidative stress and inflammation, heavy metals disrupt hormonal regulation of pregnancy. In an experimental rat model, lead and cadmium exposure suppressed StAR and CYP11 gene expression, reducing estradiol and progesterone levels [67]. A clinical study involving 100 pregnant women demonstrated that placental tissue from preeclamptic patients had significantly higher cadmium and lower zinc levels than controls, with concomitant elevation of FOXO3a transcription factor, activated under oxidative stress conditions [68].

Competitive displacement of essential micronutrients (zinc, selenium, iron, and calcium) from enzyme active sites exacerbates the damaging effects of heavy metals [69]. Zinc displacement in Cu/Zn-superoxide dismutase and zinc-finger transcription factors weakens antioxidant defense and disrupts regulation of genes responsible for cell growth [70].

Thus, the cascade of molecular damage (oxidative stress, mitochondrial dysfunction, inflammation, and steroidogenesis disruption) translates into clinically significant outcomes. The intrauterine period is characterized by successive critical windows of nervous system development, and disturbances at any of these stages may have long-term consequences [71]. Molecular mechanisms of fetal damage from heavy metal exposure represent a complex multicomponent system in which oxidative stress is the central link, triggering inflammation, mitochondrial dysfunction, and hormonal imbalance. Understanding these mechanisms provides a foundation for developing nutritional support strategies aimed at restoring antioxidant status and replenishing essential micronutrient deficiencies.

4. Clinical Outcomes and Consequences for Child Health

The molecular disturbances developing in fetal tissues under heavy metal exposure (oxidative stress, mitochondrial dysfunction, inflammation, and hormonal imbalance) predictably translate into clinically significant outcomes, many of which have long-term consequences for child health [53, 54].

Adverse Pregnancy Outcomes. A systematic review and meta-analysis of 24 studies involving 52,390 participants quantitatively assessed the association between heavy metal exposure and adverse pregnancy outcomes [72]. Lead exposure was associated with increased risk of preterm birth (OR = 1.4) and small for gestational age (OR = 1.66). For cadmium, significant associations were identified with low birth weight (OR = 1.10) and small for gestational age (OR = 1.27) [72]. A systematic review of 92 studies confirmed robust evidence for lead-preterm birth associations and suggestive evidence for cadmium and chromium [73]. Meta-analysis of combined metal exposure demonstrated that risk of preterm birth and low birth weight increases monotonically with exposure level from the 25th to 75th percentile [74].

Neurodevelopmental Impairments. The intrauterine period is characterized by successive critical windows of nervous system formation - from neurulation to synaptogenesis and myelination [75]. A systematic review of 68 studies involving 215,195 children from 23 countries demonstrated that prenatal heavy metal exposure is associated with a broad spectrum of neurodevelopmental impairments [76]. Lead and mercury showed the most pronounced negative effects on cognitive and motor functions, while behavioral disturbances were primarily associated with lead and arsenic exposure [76].

A meta-analysis of 17 studies (6,907 participants) quantified the impact of prenatal exposure on children's intellectual development [77]. A 50% increase in cadmium levels was associated with a 0.44-point reduction in full-scale intelligence quotient in children aged 5-9 years, with high effect stability [77]. An integrated approach study (cohort of 941 mother-child pairs in Shanghai combined with zebrafish experiments) demonstrated that prenatal exposure to metal mixtures (Pb, Cd, Hg, As) significantly impairs motor and social functions in children; lead contributed most to motor deficits, while cadmium contributed most to social interaction impairments [78]. Analysis of 201 mother-child pairs demonstrated that prenatal exposure to toxic metal mixtures was negatively associated with verbal comprehension, processing speed, and verbal fluency in 4-year-old children [79].

Long-Term Consequences. Adverse pregnancy outcomes are not isolated events. Children born preterm or with low birth weight have elevated risk of developing chronic diseases in later life [80]. Placental inflammatory cytokines activated in response to metal exposure may mediate long-term effects: the Ma'anshan cohort study showed that up to 17.5% of the influence of transplacental metal transfer on cognitive development was mediated by placental inflammation [64]. Epidemiological data indicate that prenatal heavy metal exposure is associated with elevated risk of childhood obesity, endocrine disorders, and neurobehavioral disorders, including attention deficit hyperactivity disorder [74, 79]. These observations align with the DOHaD (Developmental Origins of Health and Disease) concept, according to which adverse factors during critical developmental periods program metabolic trajectories for subsequent life [81].

Thus, clinical outcomes of prenatal heavy metal exposure encompass a broad spectrum of disturbances - from immediate (preterm birth, low birth weight) to long-term (cognitive deficits, social behavioral impairments). Understanding the molecular mechanisms underlying these effects provides a scientific basis for developing preventive strategies.

DISCUSSION

The present review of current scientific evidence permits formulation of key conclusions regarding heavy metal transfer from mother to fetus and identification of promising preventive directions. Heavy metal entry into the pregnant woman's body occurs through multiple routes: alimentary (food and water), inhalation (ambient air), and mobilization from endogenous depots. The latter mechanism is particularly concerning, as lead mobilization from maternal bones during the third trimester coincides with peak fetal calcium demand for skeletal formation [29, 30, 32]. This phenomenon explains why even when external lead intake ceases, its blood concentration during pregnancy may increase, creating additional endogenous burden.

The placental barrier, despite its protective functions, does not constitute an insurmountable obstacle for heavy metals. The key molecular mechanism of transplacental transfer is "ionic mimicry," whereby toxic metals exploit transport systems of essential micronutrients: lead – calcium channels and calcium-binding proteins [44]; cadmium – the DMT1 transporter and ZIP transporters [45]; methylmercury – the L-system of neutral amino acids [46]; arsenic – aquaporins [47]. The transplacental transfer index, reflecting the ratio of metal concentration in cord blood to that in maternal blood, is highest for methylmercury (0.9-1.2) and lead (0.7-0.9) and lowest for cadmium (0.1-0.3) and inorganic mercury (0.2-0.4) [51, 52]. These quantitative differences have direct clinical significance: metals with high transfer indices pose the greatest threat to the fetus.

At the molecular level, the damaging effects of heavy metals on the fetus are mediated through a cascade of interconnected pathological processes. Oxidative stress, characterized by ROS induction, glutathione depletion, and antioxidant enzyme inactivation, constitutes the central link of this cascade [56, 57]. Mitochondrial dysfunction manifests as decreased membrane potential, reduced mitochondrial DNA copy number, and apoptosis induction [61, 62]. Inflammatory response, mediated by proinflammatory cytokine activation (interleukin-6, interleukin-8, HIF-1α) and potential NLRP3 inflammasome activation, further exacerbates fetal tissue damage [64, 65]. Steroidogenesis disruption, evident as suppressed StAR and CYP11 expression and reduced estradiol and progesterone levels, creates additional risk for normal pregnancy maintenance [67]. Competitive displacement of essential micronutrients (zinc, selenium, iron, and calcium) from enzyme active sites closes the vicious circle, weakening antioxidant defense and disrupting cell growth regulation [69, 70]. Importantly, all these processes are interconnected and mutually potentiating, creating a systemic pathological effect.

Clinical consequences of prenatal heavy metal exposure encompass both immediate pregnancy outcomes and long-term disturbances. Meta-analyses convincingly demonstrate statistically significant associations of lead with preterm birth (OR = 1.4) and small for gestational age (OR = 1.66), and of cadmium with low birth weight (OR = 1.10) [72]. Long-term consequences manifest as reduced cognitive function, impaired motor skills, and social behavioral deficits, with no safe threshold: even low metal concentrations may cause irreversible changes during critical periods of nervous system development [76, 77, 78]. The DOHaD concept emphasizes that adverse prenatal factors program metabolic trajectories for subsequent life, increasing risk of obesity, endocrine disorders, and neurobehavioral disturbances [81].

Preventive strategies should be multi-tiered. Primary prevention aims to reduce exposure through environmental monitoring, public education, and implementation of water treatment systems [5, 21]. Secondary prevention is based on nutritional correction: enriching the pregnant woman's diet with calcium, iron, and zinc can significantly reduce absorption and transplacental transfer of lead and cadmium through competitive inhibition of transport systems [69, 70]. Selenium supplementation facilitates glutathione peroxidase activity restoration and reduction of oxidative stress [57]. Tertiary prevention includes screening for heavy metal levels in blood of at-risk pregnant women, placental function monitoring, and neuropsychological follow-up of children [75].

Despite considerable progress in understanding molecular mechanisms, several questions remain open. Further longitudinal studies employing omics technologies are required for quantitative assessment of individual metal contributions and their mixtures to adverse pregnancy outcomes [60, 78]. Investigation of transgenerational effects, whether heavy metal exposure during pregnancy affects grandchild health through epigenetic inheritance, represents an underexplored area requiring close attention [81]. Development of effective chelating agents safe for use during pregnancy remains a complex pharmacological challenge, as traditional chelators have limitations in gestational use [82]. Personalized prevention approaches accounting for genetic polymorphisms of transport proteins and metal metabolism enzymes may enhance nutritional correction efficacy [83].

CONCLUSIONS

Heavy metal transfer from mother to fetus is an established fact, confirmed by numerous studies at molecular, cellular, and clinical levels. "Ionic mimicry" enables lead, cadmium, mercury, and arsenic to exploit transport systems of essential micronutrients, thereby crossing the placental barrier. Once in the fetal organism, these metals trigger a cascade of pathological reactions (oxidative stress, inflammation, mitochondrial dysfunction, and steroidogenesis disruption) which translate into preterm birth, low birth weight, and long-term neurodevelopmental impairments.

Of particular concern is the high prevalence of heavy metal contamination in several regions of the Russian Federation, where pregnant women are subject to chronic exposure often exceeding permissible levels. Understanding the molecular mechanisms of toxicity opens avenues for effective prevention based on exposure reduction, nutritional correction of essential micronutrient deficiencies, and early detection of disturbances.

Integration of these approaches into perinatal health care systems is a necessary measure to minimize risks associated with anthropogenic environmental contamination.

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