Perinatal exposure to heavy metals and birth outcomes

Maria Nițescu[1,2], Mirela Nedelescu[1,3], Ana-Maria Schiaua[1], Nicolae Potra[1], Anca Angela Simionescu[1,4]

1. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

2. "Prof. Dr. Matei Balș" National Institute for Infectious Diseases, Bucharest, Romania

3. National Institute of Public Health, Bucharest, Romania

4. "Filantropia" Clinical Hospital of Obstetrics and Gynecology, Bucharest, Romania

Corresponding author:
Mirela Nedelescu
E-mail: mirela.nedelescu@umfcd.ro

Abstract

In the last century, the industrial activities have caused a significant increase in human exposure to heavy metals. The most common metals that induce human poisonings are lead (Pb), mercury (Hg), cadmium (Cd), and arsenic (As). Heavy metal poisoning (acute or chronic) may occur following exposure through air, water and food. The bioaccumulation of these heavy metals leads to a diversity of toxic effects on a variety of body tissues and organs. Heavy metals disrupt cellular events, including growth, proliferation, differentiation, damage-repairing processes and apoptosis. The aim of this article was to perform a literature review regarding the perinatal exposure to heavy metals, in particularly lead and mercury, and birth outcomes. We conducted a non-systematic analysis in PubMed with the following keywords: "lead" AND (OR) "mercury" AND (OR) "perinatal exposure" AND (OR) "birth outcomes". Exposures to heavy metals like Pb and Hg have been associated with adverse birth outcomes such as preterm birth, lower birth weight or neural tube defects. However, the knowledge on the effects at low levels of exposure of these elements still remains limited.

Keywords: *lead, mercury, prenatal exposure, preterm birth, lower birth weight*

Rezumat

În ultimul secol, activitățile industriale au determinat o creștere semnificativă a expunerii umane la metale grele. Cele mai comune metale care induc intoxicații umane sunt plumbul (Pb), mercurul (Hg), cadmiul (Cd) și arsenul (As). Otrăvirea cu metale grele (acută sau cronică) poate apărea în urma expunerii prin aer, apă și alimente. Bioacumularea acestor metale grele duce la o diversitate de efecte toxice asupra unei varietăți de țesuturi și organe ale corpului. Metalele grele perturbă evenimentele celulare, inclusiv creșterea, proliferarea, diferențierea, procesele de reparare a daunelor și apoptoza. Scopul acestui articol a fost de a efectua o revizuire a literaturii de specialitate cu privire la expunerea perinatală la metale grele, în special plumb și mercur, și rezultatele la naștere. Am efectuat o analiză a literaturii în PubMed, utilizând următoarele cuvinte-cheie: „plumb" ȘI (SAU) „mercur" ȘI (SAU) „expunere perinatală" ȘI (SAU) „rezultate la naștere". Expunerea la metale grele precum Pb și Hg a fost asociată cu rezultate adverse la naștere, cum ar fi nașterea prematură, o greutate mai mică la naștere sau defecte ale tubului neural. Cu toate acestea, cunoștințele privind efectele la niveluri scăzute de expunere ale acestor elemente rămân încă limitate.

Cuvinte-cheie: *plumb, mercur, expunerea prenatală, naștere prematură, greutate mai mică la naștere*

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Expunerea perinatală la metale grele și consecințele la naștere

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1. Introduction

Millions of people around the world are affected by contamination of air and water by toxic metals which are of environmental and human health concern. Food contamination with heavy metals is another concern for both human and animal health. Metals among the other environmental pollutants may also occur naturally and remain in the environment. The exposure to heavy metals has harmful effects on human health, affecting different body organs. The simultaneous exposure to two or more metals may have cumulative effects[1].

It is important to recognize that the fetal exposure to heavy metals, in communities around the world, continue beyond birth, and postnatal exposures are also associated with adverse health effects[2]. Lead (Pb), mercury (Hg) and arsenic (As) head the list, followed by aluminum (Al), cadmium (Cd), chromium (Cr), nickel (Ni), titanium (Ti) and others, whose presence is not essential to the human body. As a result, exposure to high concentrations is likely to be adversely associated with health outcomes. Since toxic metals are known to cross the placenta and blood-brain barrier and deposit in fetal tissues, children are likely to be susceptible to metal exposure early, starting from the time of gestation. For this reason, maternal metal concentration is frequently used as a proxy for that of a fetus when studying health outcomes[3].

Heavy metals enter the human body through primarily ingestion and inhalation. Lead is the most studied metal and is teratogenic prenatally as well as toxic postnatally. The maternal exposure most often occurs through ingestion of dust from lead-based paints or water contaminated by lead pipes. Lead is readily transported across the placenta and can lead to epigenetic changes in the fetus. Maternal and cord blood lead levels have been associated with lower birth weight, shorter birth length, and smaller head circumference[4]. Mercury,

which enters the environment through sources such as coal-fired power plants, can enter the body through ingestion of food grown in contaminated soil, or fish that bioaccumulate mercury due to water pollution. Mercury and other heavy metals, such as cadmium and arsenic, have been related to reduced birth weight in the case of exposure of pregnant women[5].

2. Research method

The aim of this research was to perform a literature review regarding perinatal exposure to heavy metals, in particularly to lead and mercury, and birth outcomes.

We conducted a non-systematic analysis in PubMed with the following keywords: "lead" AND (OR) "mercury" AND (OR) "perinatal exposure" AND (OR) "birth outcomes", with publication dates from the 1st of January 2016 to the 30th of October 2021 for the first search, and "lead" AND (OR) "mercury" AND (OR) "perinatal exposure" AND (OR) "birth outcomes" with publication dates between the 1st of January 2020 and the 30th of October 2021 for the second search.

The objective of the first search was to assess the scientific interest in topic. The second search had the following steps: introduction of words and limits in PubMed with first step exclusion criteria for articles that did not refer to lead and mercury. The second step exclusion criteria refer to the population in whom the search was performed: perinatal exposure and birth outcomes.

3. Results and discussion

Interest in the topic of perinatal exposure to heavy metals and their effects on birth outcomes and childhood health has constantly increased in the last five years. We found a total number of 687 articles related to this subject between the 1st of January 2016 and the 30th of October 2021. In the last five years, the interest has constantly increased, with a peak of 143 in 2020. During the period for which we performed the non-systematic analysis (from the 1st of January 2020 to the 30th of October 2021), 44 articles were found, of which 18 were considered of interest for our topic, being summarized in Table 1.

Main findings of the selected studies

A study conducted by Zajac et al. suggests that pregnant women living near lead hotspots in low- and middle-income countries may have blood lead levels that put their fetus at risk for adverse neurodevelopmental and other health impacts, which in turn can have quality of life and economic impacts. This underscores the need for increased investment in the remediation of lead-contaminated sites[6].

In a study investigating prenatal metal mixtures and birth weight for gestational age in a predominately lower-income Hispanic pregnancy cohort in Los Angeles, authors findings suggest that, in this understudied population, Hg may reduce fetal growth – an inverse linear association was estimated for Hg[7].

Baldewsingh et al., in an article about prenatal mercury exposure in pregnant women from Suriname, found out the fact that most women living in the interior of Suriname had hair mercury levels well above the international accepted action levels. While Hg exposure in pregnant women is of significant concern, it was found that low Hg exposure was associated with low birth weight, suggesting the protective effects of the high consumption of fish containing beneficial nutrients that counteract Hg exposure[8].

A scoping review about prenatal environmental metal exposure and preterm birth (PTB) in studies between 2000 to 2019 documented a higher incidence of PTB with lead and cadmium exposures. The findings for mercury and arsenic exposures were inconclusive. Metal-induced oxidative stress in the placenta, epigenetic modification, inflammation and endocrine disruptions are the most common pathways through which heavy metals and metalloids affect placental functions, leading to preterm birth[9].

A systematic review on mercury and prenatal growth concluded that, from the numerous cross-sectional and prospective studies of mercury and fetal growth, many show no strong evidence of an effect, but a significant minority report inverse associations with birth weight, particularly studies of populations with the highest mean mercury concentrations. Gaps remain in understanding the interpretation of different mercury biomarkers and the possible interaction effects[10].

Findings from an article by Ashrap et al. regarding the association with birth outcomes between maternal blood metal and metalloid concentrations in Northern Puerto Rico suggest that low-level prenatal Pb exposure, as well as elevated Mn and Zn exposure may adversely affect birth outcomes. These findings provide further support for the need to reduce Pb exposure as much as possible among pregnant women. Also, mercury was associated with a higher risk of preterm birth at the later window of pregnancy[11].

An article by Gajewska et al. suggested that BLL (blood lead level) had an independent and significant association with PE (preeclampsia), while there were no differences in the BLL between the healthy pregnant women and healthy non-pregnant women groups. Furthermore, both the SBP (systolic blood pressure) and DBP (diastolic blood pressure) values were positively associated with BLL. This study indicates that preeclamptic women tend to present with a significantly higher BLL compared to healthy pregnant women[12].

A study in Suriname about the influence of prenatal exposure to mercury on birth outcomes suggests that, while mercury was not significantly associated with birth weight and low Apgar score, it may affect preterm birth. Mercury exposure was significantly associated with preterm birth in the overall study cohort[13].

Findings From the UmMuKi Bratislava-Vienna Study, about how gene variants determine placental transfer of perfluoroalkyl substances (PFAS), mercury and lead, and birth outcomes, indicate that fetal exposures to toxic substances and endocrine disrupters can adversely affect lifetime health. In agreement with other European studies, the results show the need to minimize the perinatal

Table 1 Selected studies regarding the impact of lead and mercury exposure on pregnant women and adverse birth outcomes

Authors	Heavy metal investigated	Study type	Study objectives	Results	(Ref.)
Zajac *et al.*	Lead (Pb)	Retrospective	Developing a probabilistic approach to using the adult lead methodology (ALM) to estimate fetal BLLs from prenatal exposure to lead-contaminated soil at hotspots in the Toxic Site Identification Program (TSIP).	Pregnant women living near TSIP sites may have blood lead levels that put their fetus at risk for neurologic damage and other sequelae.	(6)
Howe *et al.*	Cadmium (Cd), Mercury (Hg), lead (Pb), Arsenic (As)	An ongoing, prospective pregnancy cohort	Investigating the impact of a complex mixture of metals on birth weight for gestational age in the Maternal and Developmental Risks from Environmental and Social Stressors study, a predominately lower-income Hispanic pregnancy cohort in Los Angeles, California.	Findings suggest that Hg may reduce fetal growth.	(7)
Baldewsingh *et al.*	Mercury (Hg)	Prospective cohort study	The study aimed to determine prenatal Hg exposure in the subset of pregnant women living in Suriname's interior and to explore the potential association between Hg exposure and the adverse birth outcomes – low birth weight (LBW) and preterm birth (PTB).	While Hg exposure in interior pregnant women is of significant concern, it was found that low Hg exposure is associated with LBW, suggesting the protective effects of the high consumption of fish containing beneficial nutrients that counteract Hg exposure. Maternal age was neither associated with low birth weight, nor with mercury exposure.	(8)
Khanam *et al.*	Lead (Pb), cadmium (Cd), mercury (Hg), arsenic (As)	Review	The objective of the review was to better delineate the burden of exposure to lead (Pb), mercury (Hg), cadmium (Cd) and arsenic (As), their association with preterm birth (PTB), and possible mechanisms to inform future research and prevention strategies.	A higher incidence of PTB with lead and cadmium exposures and the findings for mercury and arsenic exposures were inconclusive.	(9)
Dack *et al.*	Mercury (Hg)	Review	To identify prospective and cross-sectional studies of birth outcomes, which measured biomarkers of mercury exposure in either the mother or neonate.	Many studies show no strong evidence of an effect, but a significant minority report inverse associations with birth weight, particularly studies of populations with the highest mean mercury concentrations.	(10)
Ashrap *et al.*	Maternal blood metal and metalloid concentrations	Prospective cohort project "the Puerto Rico Test site for Exploring Contamination Threats" (PROTECT)	To investigate the effects of metal(loid)s on adverse birth outcomes both individually and as mixtures.	Low-level prenatal lead exposure adversely affects birth outcomes. Mercury was associated with a higher risk of preterm birth at the later window of pregnancy.	(11)
Gajewska *et al.*	Lead (Pb)	Descriptive	To determine the blood lead levels (BLL) in women who have not been occupationally exposed to lead, and in women with pregnancy complications.	Blood lead level has an independent and significant association with preeclampsia.	(12)
Gokoel *et al.*	Mercury (Hg)	A prospective environmental epidemiologic cohort study	To examine the influence of perceived stress, depression, and mercury on birth outcomes in Suriname.	Mercury exposure was significantly associated with preterm birth in the overall study cohort.	(13)
Gundacker *et al.*	Mercury (Hg) and Lead (Pb)	Descriptive	To compare the regional exposure levels and sources of PFAS, bisphenol A (BPA), Pb, total Hg, and methyl-Hg (MeHg), to analyze the influence of gene variants on placental transfer rates and birth outcome, and to assess the potential health risks deriving from the exposures to 16 PFAS, BPA, total Hg (THg), methyl mercury (MeHg), and Pb.	Fetal exposures to toxic substances and endocrine disrupters can adversely affect lifetime health.	(14)

Table 1 Selected studies regarding the impact of lead and mercury exposure on pregnant women and adverse birth outcomes (cont.)

Authors	Heavy metal investigated	Study type	Study objectives	Results	(Ref.)
Stone *et al.*	Cadmium (Cd), arsenic (As), lead (Pb), mercury (Hg)	Review	To describe the literature, detailing the relationships between exposure to these toxicants and the development of the two most common adverse pregnancy outcomes in the United States – PTB and preeclampsia.	Exposure to organic and inorganic toxicants may be significantly associated with the development of PTB (preterm birth) and preeclampsia in the United States.	(15)
Vaiserman *et al.*	Lead (Pb), chromium (Cr), cadmium (Cd), arsenic (As), mercury (Hg)	Review	To summarize findings from epidemiological studies, indicating that prenatal toxic metal exposure can induce epigenetic dysregulation at the DNA methylation level, thereby potentially affecting adult health outcomes.	Prenatal toxic metal exposure can induce epigenetic dysregulation, thereby potentially affecting adult health outcomes.	(16)
Kima *et al.*	Lead (Pb), cadmium (Cd), chromium (Cr), and manganese (Mn)	Descriptive study	To analyze the associations between birth outcomes and living in a community with a history of informal e-waste recycling – Guiyu, China.	Cumulative exposure to metals was related to lower head circumference, Body Mass Index and ponderal index, but not related to birth weight.	(2)
Liu *et al.*	Cadmium (Cd), lead (Pb)	A case-control study	To investigate the associations between prenatal exposure to Cd and Pb, using their concentrations in umbilical cord tissue. To investigate the risk for neural tube defects (NTDs) and the possible interactions between Cd and Pb exposure and 20 single-nucleotide polymorphisms (SNPs) in nine genes involved in detoxification and folate metabolism pathways on the occurrence of NTDs.	Higher concentrations of Cd, but not Pb, in umbilical cord tissue were associated with a higher risk for neural tube defects.	(17)
Baldewsingh *et al.*	Mercury (Hg)	A prospective environmental epidemiologic cohort study	To examine the association between Hg exposure, social determinants (maternal age, parity, education level, household income), and ethnicity on birth outcomes of indigenous and tribal women in the rural interior and the capital of Suriname.	Ethnic background, maternal age and Hg exposure during pregnancy were independent predictors of preterm birth, which is in line with other studies.	(18)
Novo *et al.*	Mercury (Hg)	Review	To organize an overview of the mercury cycle and MeHg poisoning events and to summarize data from cellular, animal, and human studies focusing on MeHg effects in neurons and glial cells	Brain cells exposure to MeHg leads to oxidative stress, cytokine release, mitochondrial dysfunction, glutamate and Ca2+ dyshomeostasis, and ultimately to cell death.	(19)
Papadopoulou *et al.*	Mercury (Hg)	Prospective cohort study	To evaluate the neurocognitive development of the NAC-II cohort children at 7 years old and to collect further information on the exposure to heavy metals, genetic variants, and food habits.	The maternal seafood consumption in pregnancy was associated with child growth trajectories, and the direction of the association varied by seafood type and level of prenatal mercury exposure. Prenatal mercury exposure was negatively associated with child growth.	(20)
Montrose *et al.*	Lead (Pb)	Cohort study	To examine associations between blood Pb levels and concomitant DNA methylation profiles.	Low-level Pb exposure is related to development and neurological function.	(21)
Farzan *et al.*	Mercury (Hg)	An ongoing cohort study	To investigate the effects of early- and mid-gestation prenatal and early-childhood and mid-childhood Hg exposures on children's blood pressure.	Early childhood, rather than the prenatal period, may be a critical window of exposure for Hg to influence blood pressure.	(22)

exposures. Especially exposures to PFAS and Pb should be investigated at more regular intervals[14].

A review about exposure to toxic metals and per- and polyfluoroalkyl substances (PFAS) and the risk of preeclampsia and preterm birth in the United States suggests that exposure to organic and inorganic toxicants may be significantly associated with the development of preterm birth and preeclampsia. There is a significant heterogeneity among studies of environmental exposures during pregnancy. Many studies found relatively low

levels of toxic exposures, reducing the ability to make conclusions regarding dose-dependent effects. Furthermore, the lack of standardization in the definition of "high" or "abnormal" toxicant levels limits the ability to compare results across cohorts[15].

Vaiserman et al. summarize epidemiological findings, indicating that prenatal toxic metal exposure can induce epigenetic dysregulation, thereby potentially affecting adult health outcomes. The present-day environmental conditions, exposure to man-made environmental pollutants, such as heavy metals, including lead, chromium, cadmium, arsenic and mercury, is undoubtedly a factor significantly influencing genetically determined pathways of epigenetic regulation and thereby causing various pathological outcomes. Exposure to heavy metals *in utero* can be especially hazardous. This is because an organism is most sensitive to stressful events throughout prenatal and early postnatal periods. Moreover, developmentally induced epigenetic modifications can persist long even after a transient environmental signal has disappeared, thereby enhancing the risk for future disorders, sometimes even in subsequent generations (due to the mechanism of transgenerational epigenetic inheritance)[16].

Kima et al. studied birth outcomes associated with maternal exposure to metals from electronic waste recycling in Guiyu, China, and revealed the fact that mothers from Guiyu had higher concentrations of Pb, Cd and Cr, while smaller head circumference and BMI were observed in the Guiyu neonates compared to neonates from the control group. The mixtures model suggested a cumulative impact of the studied metals on head circumference and BMI, but not with birth weight[2].

A case-control study about associations between prenatal exposure to cadmium and lead with neural tube defect (NTD) risks that are modified by single nucleotide polymorphisms of fetal *MTHFR* and *SOD2* shows that higher concentrations of Cd, but not Pb, in umbilical cord tissue were associated with a higher risk for NTDs[17].

Research conducted in Suriname regarding association of mercury exposure and maternal sociodemographic on birth outcomes of indigenous and tribal women reveals that indigenous participants had higher odds of adverse birth outcomes compared with tribal participants, independent of their parity and Hg exposure during pregnancy. Ethnic background, maternal age and Hg exposure during pregnancy were independent predictors of preterm birth, which is in line with other studies[8].

Novo et al., in a review about cellular and molecular mechanisms mediating methylmercury neurotoxicity and neuroinflammation, concluded that oxidative stress, cytokine release, mitochondrial dysfunction, glutamate and Ca^{2+} dyshomeostasis, and ultimately cell death are significant consequences of brain cells exposure to MeHg, but additional research is needed to continue clarifying the precise short-term effects of MeHg on brain cells, as well as the long-term consequences for human health[19].

A study conducted in Norway, regarding the environmental risk factors about maternal seafood intake during pregnancy, prenatal mercury exposure and child Body Mass Index trajectories up to 8 years, showed that within a population with moderate seafood consumption and low mercury exposure, the maternal seafood consumption in pregnancy was associated with child growth trajectories, and the direction of the association varied by seafood type and level of prenatal mercury exposure. Prenatal mercury exposure was negatively associated with child growth. Their findings on maternal seafood intake are likely non-causal[20].

Another study about neonatal Pb exposure and capillary blood leukocyte DNA methylation identified associations between DNA methylation and Pb at 32CpG sites, with the majority being inversely associated with Pb concentrations. Their pathway analysis suggested that low-level Pb exposure was related to development and neurological function[21].

The results of a research conducted by Farzan et al. suggest that early childhood, rather than the prenatal period, may be a critical window of exposure for Hg to influence blood pressure. The study conclusions suggest that this relationship may be modified by sex and birth weight, but further investigation is needed[22].

Adverse health effects of mercury exposure in pregnancy

Mercury is abundant in the earth's crust and is mobilized into the environment through human industrial activity and natural events such as volcanic activity. Organic mercury is the most toxic form that can readily cross the placental barrier. It can be found as *ethylmercury* which is present in medical preparations and can passively diffuse the placental barrier, while *methylmercury* may be present in fish and seafood and can actively cross the barrier *via* amino acid carriers. On the other hand, inorganic mercury exists in the dental fillings, but also in the atmosphere where it is transferred via the different industrial occupations[23].

Mercury health hazards are catastrophic in the case of perinatal exposure because of two reasons. First, adverse effects of mercury do not imply only the fetus (fetotoxicity), but it can also go on throwing its malinfluences up to the age of 14 years old, as documented by neurophysiological tests, suggesting irreversibility on many occasions[24].

All forms of mercury are toxic to the fetus, but methylmercury most readily crosses the placenta to the fetus, where deposition within the developing fetal brain can occur. In the brain, methylmercury causes focal necrosis of neurons and destruction of glial cells and is toxic to the cerebral and cerebellar cortex[25]. Even when asymptomatic, maternal exposure can lead to spontaneous abortion or retardation[26].

Mercury may be a threat to the developing fetus because both elemental and organic forms of mercury can cross the placenta during gestation, where it may accumulate in a far higher dose-to-weight ratio than is possible in an adult[10]. An inverse linear association was estimated for Hg in relation with fetal growth, which may be reduced by this toxic metal[7]. Mercury may also affect preterm birth, but the study's results are inconclusive[9,11,13,15].

Adverse health effects of lead exposure in pregnancy

For centuries, exposure to high concentrations of lead has been known to pose health hazards. Lead exposure is a concern for pregnant women and young children in low- and middle-income countries. Although most countries have banned leaded gasoline and population average blood lead levels (BLLs) are declining, lead levels at "toxic hotspots" – areas of unusually high contamination – may pose risks to local populations. Hotspots include both legacy and active sites where activities such as used lead acid battery recycling, lead mining and smelting, and electronics (e-waste) recycling have been conducted without stringent environmental protections[27,28].

Lead exposure during pregnancy can impact both the mother and fetus. *In utero* and early life lead exposure is linked to adverse neurodevelopmental outcomes, including alterations in cognitive functioning and a reduction in intelligence quotient (IQ) points, even at low levels of exposure. Lead exposure during pregnancy is also a risk factor for reproductive health outcomes such as gestational hypertension, preeclampsia, preterm birth including abortion, and reduced fetal growth[4]. Also, in mothers with higher concentrations of Pb, inverse associations were observed between blood Pb concentrations and head circumference and Ponderal Index of newborns[2].

The recommendations of US Centers for Disease Control regarding the frequency of maternal blood lead follow-up testing during pregnancy in females exposed to lead are presented in Table 2[29].

Observational studies suggest that prenatal lead exposure, even with maternal blood lead levels below 10 µg/dL, is inversely related to the fetal growth and neurodevelopment independent of the effects of postnatal exposure, though the exact mechanism by which

Table 2 Frequency of maternal blood lead follow-up testing during pregnancy[29]

Venous Blood Lead Level (BLL; µg/dL)	Necessity to perform follow-up test(s)
<5	None (no follow-up testing is indicated).
5-14	Within 1 month. Obtain a maternal BLLs or cord BLL at delivery.
15-24	Within 1 month and then every 2-3 months. Obtain a maternal BLLs or cord BLL at delivery. More frequent testing may be indicated based on risk factor history.
25-44	Within 1-4 weeks and then every month. Obtain a maternal BLL or cord BLL at delivery.
≥45	Within 24 hours and then at frequent intervals depending on clinical interventions and trend in BLLs. Consultation with a clinician experienced in the management of pregnant women with BLLs in this range is strongly advised. Obtain a maternal BLL or cord BLL at delivery.

Table 3 Breastfeeding and lead exposure[29,34]

CDC recommendations for the initiation of breastfeeding
Measurement of levels of lead in breast milk is not recommended. Mothers with BLLs<40 µg/dL should breastfeed. Mothers with confirmed BLLs≥40 µg/dL should begin breastfeeding when their blood lead levels drop below 40 µg/dL. Until then, they should pump and discard their breast milk. **These recommendations are not appropriate in countries where infant mortality from infectious diseases is high.*
CDC recommendations for the continuation of breastfeeding
Breastfeeding should continue for all infants with BLLs below 5 µg/dL. Infants born to mothers with BLL≥5 µg/dL can continue to breastfeed unless there are indications that the breast milk is contributing to elevating BLLs. These infants should have blood lead tests at birth and be followed according to the schedule in Chapter 5. For infants whose blood lead levels are rising or failing to decline by 5 µg/dL or more, environmental and other sources of lead exposure should be evaluated. If no external source is identified, and maternal BLLs are above 20 µg/dL and infant BLL≥5 µg/dL, then breast milk should be suspected as the source, and the temporary interruption of breastfeeding until maternal blood lead levels decline should be considered.
Recommendations for the use of reconstituted infant formula
Infant formula requiring reconstitution should be made only with water from the cold water tap. Flush the tap for at least 3 minutes before use and then heat the water or use bottled or filtered tap water known to be free of lead.

low-level lead exposure, whether incurred prenatally or postnatally, might adversely affect the child development remains uncertain[30].

Lead may adversely impact the sexual maturation in the developing female and may reduce fertility, but the scientific evidence is limited. Lead exposure has been associated with an increased risk for gestational hypertension, but the magnitude of the effect, the exposure level at which the risk begins to increase, and whether the risk is more associated with acute or cumulative exposure remain uncertain[31,32].

No safe blood lead level (BLL) in children exists, and even low levels may cause harm. CDC has not identified an allowable exposure concentration for lead, a level of concern or unsafe level of exposure for either mother or fetus. Instead, CDC is applying public health principles of prevention to intervene when prudent[32].

Recently (in October 2021), CDC has updated the blood lead reference value (BLRV) to 3.5 µg/dL, which provides an opportunity for additional progress in addressing long-standing disparities in lead exposure and BLLs in children[33].

In Table 3, there are presented recommendations regarding breastfeeding or use of reconstituted infant formula in the case of mother exposure to lead.

4. Conclusions

Lead and mercury are naturally occurring elements, ubiquitous in the environment, and are well-known environmental pollutants due to their toxicity, persistence in the environment, and bio-accumulative nature. Humans are exposed to toxic metals through a variety of routes including ingestion, inhalation and absorption through the skin.

Even though some inconsistencies exist in the findings across studies, there is overwhelming evidence that perinatal exposure to heavy metals – particularly to lead and mercury – is associated with a higher incidence of adverse birth outcomes.

Additional studies are needed to examine the extent of the perinatal exposure to these metals and their association with adverse birth outcomes. Studies are also needed to further delineate the mechanisms through which metal exposures lead to adverse birth outcomes.

Developing sustainable technologies to remove contamination, together with improved understanding of environmental and other factors that contribute to adverse birth outcomes, will have a direct impact on public health. ■

Conflicts of interests: The authors declare no conflict of interests.

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