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"Relación entre la exposición materna a elementos potencialmente tóxicos y el daño genético y capacidad de reparación del daño al ADN"

Tesis que presenta:

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Este trabajo se realizó en el Departamento de Toxicología del Centro de Investigación y de Estudios Avanzados del IPN bajo la tutoría de las Dras. María Betzabet Quintanilla Vega y María de la Luz Del Razo Jiménez con el apoyo de Conacyt a través de la beca de maestría con número de registro 1008326. Debido a la situación de la pandemia de marzo 2020 a agosto 2021 que no permitió actividades presenciales en el Cinvestav, esta tesis consiste en una revisión bibliográfica del tema de interés que se enviará a la revista *Journal of Trace Elements in Medicine and Biology* para su publicación.

RESUMEN

La liberación de contaminantes ambientales, entre ellos los metales ha aumentado en los últimos años debido al desarrollo tecnológico e industrial. La exposición a contaminantes ambientales en etapas tempranas de la vida puede determinar la susceptibilidad a desarrollar enfermedades crónicas en la edad adulta, debido a cambios genéticos o epigenéticos. El objetivo de esta revisión fue identificar la relación entre la exposición prenatal y posnatal temprana a metales potencialmente tóxicos (PTM, *Potentially Toxic Metals*, por sus siglas en ingles) y sus efectos adversos sobre el material genético en la descendencia.

Siguiendo la metodología Cochrane se realizó una revisión sistemática que incluyó cuatro bases de datos: PubMed, Scopus, Web of Science y Cochrane Library. Los artículos elegibles fueron estudios realizados en humanos y publicados en inglés entre el 01/01/2010 y el 30/04/2021 y cuyo resultado principal fuera los efectos adversos sobre el material genético en la descendencia relacionados con la exposición prenatal o posnatal temprana al menos a un PTM. Todos los artículos fueron revisados de manera independiente por tres miembros de nuestro equipo y fueron clasificados de acuerdo con el resultado principal evaluado.

Esta revisión incluyó 57 artículos, la mayoría de los cuales evaluaron la exposición prenatal, la exposición postnatal temprana fue reportada solo en uno de ellos. Los PTM más evaluados fueron As, Cd y Pb. Dos artículos reportaron interacciones sinérgicas y en seis artículos observaron interacciones antagónicas entre PTM y metales esenciales como el Cu, Mg, Se y Zn. Los principales efectos adversos al material genético de los recién nacidos asociados a la exposición prenatal fueron: alteraciones en la longitud del telómero, expresión de genes o proteínas, contenido de ADN mitocondrial, metabolómica, daño al ADN y modificaciones epigenéticas; muchos de estos efectos fueron específicos del sexo siendo más predominantes en las niñas.

Los hallazgos de esta revisión destacan que el problema de la exposición a PTM persiste afectando a las poblaciones más susceptibles, como los recién nacidos, y que algunos de estos efectos adversos dependen del sexo.

ABSTRACT

The release of environmental pollutants, including metals has increased in recent years, due to technological and industrial development. Pollutant exposures during the earliest stage of life may determine the disease chronic susceptibility in adulthood because of genetic or epigenetic changes. The objective of this review was to identify the relationship between prenatal and early postnatal exposures to potentially toxic metals (PTM) and their adverse effects on the genetic material of the offspring.

Following the Cochrane methodology, a systematic review was carried out that included four databases: PubMed, Scopus, Web of Science and Cochrane Library. Eligible articles were studies conducted in humans and published in English between 01/01/2010 to 04/30/2021 and whose main outcome was adverse effects on genetic material in offspring related to prenatal or early postnatal exposure at least to a PTM. All articles were independently reviewed by three members of our team and classified according to the main outcome evaluated.

This review included 57 articles, most of which evaluated prenatal exposure; early postnatal exposure was reported in only one of them. The most evaluated PTM were As, Cd, and Pb. Two articles reported synergistic interactions and six articles observed antagonistic interactions between PTM and essential metals such as Cu, Mg, Se, and Zn. The main adverse effects on the genetic material of newborns associated with prenatal exposure were: alterations in telomere length, gene or protein expression, mitochondrial DNA content, metabolomics, DNA damage, and epigenetic modifications; many of these effects were sex specific being more predominant in females.

The findings in this review highlight that the problem of PTM exposure persists affecting the most susceptible populations, such as the newborns, and that some of these adverse effects were sex-dependent.

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ABREVIATURAS

5mC	5-methylcytosine
ATSDR	Agency for Toxic Substances and Disease Registry
CBMN	Cytokinesis-block micronucleus cytome
FOAD	Fetal Origins of Adult Disease
IARC	International Agency for Research on Cancer
DNTM	DNA Methyltransferases
DMR	Differentially Methylated Regions
MMAT	Mixed Methods Appraisal Tool
mtDNA	Mitochondrial DNA
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTM	Potentially Toxic Metals
ROS	Reactive Oxygen Species
TL	Telomere Length
WHO	World Health Organization

1. INTRODUCCIÓN

La contaminación ambiental se ha convertido en un problema de salud pública debido a la liberación de sustancias nocivas al medio ambiente que afecta a los ecosistemas y a la salud de los humanos [1]. El desarrollo industrial y tecnológico ha llevado a la sobreexplotación de los recursos naturales, entre ellos los metales, removiéndolos de la corteza y liberándolos al medio ambiente [4]. Las actividades antropogénicas como la agricultura, la industria, la minería y el transporte son las principales causas de contaminación del aire, el suelo y el agua por metales [4].

Un metal es definido como cualquier elemento que se caracteriza por su ductilidad, brillo, tendencia a perder electrones, capacidad de conducir calor y electricidad [5]. Desde el punto de vista biológico, un metal se clasifica como esencial o no esencial; por su parte, los metales esenciales como el cromo trivalente (Cr^{3+}), cobre (Cu), hierro (Fe), manganeso (Mn), selenio (Se) y cinc (Zn) desempeñan funciones para el mantenimiento de la homeóstasis celular, además de formar parte de la estructura de diversas proteínas involucradas en procesos bioquímicos [6,7]. No obstante, estos deben estar en concentraciones óptimas, debido a que una deficiencia o un exceso desencadena una disfunción de los procesos biológicos [7,8].

Los metales y metaloides no esenciales como el arsénico (As), cadmio (Cd), mercurio (Hg), níquel (Ni), plomo (Pb) y vanadio (V) no desempeñan una función biológica, estos tienen la capacidad de mimetizar y reemplazar a los metales esenciales afectando los procesos biológicos [5,8]. Adicionalmente, estos tienen la particularidad de interactuar con algunas biomoléculas, entre ellas el ADN, ya sea de forma directa o indirecta por medio de la generación de especies reactivas de oxígeno (ROS, *Reactive Oxygen*

Species, por sus siglas en inglés), por lo tanto, tienen potencial genotóxico aún a concentraciones traza [9]. Por esta razón, son llamados metales potencialmente tóxicos (PTM, *Potentially Toxic Metals*, por sus siglas en inglés) [10]. Algunos PTM como el As, Cd, Cr^{6+} y Ni son reconocidos carcinógenos por la Agencia Internacional para la Investigación del Cáncer (IARC, *International Agency for Research on Cancer*, por sus siglas en inglés) [103].

La exposición a PTM en etapas tempranas de la vida se ha relacionado con el desarrollo de enfermedades crónicas durante la vida adulta, principalmente enfermedades cardiovasculares, respiratorias, del sistema inmune y alteraciones en el desarrollo y crecimiento [18,74,81-85]. El desarrollo embrionario y fetal son periodos altamente susceptibles a la exposición a compuestos tóxicos, como consecuencia de la alta proliferación y diferenciación celular que ocurre en estas etapas, así como por la inmadurez del feto para eliminar los compuestos tóxicos y reparar el daño [12,13]. Otro periodo relevante es el periodo postnatal temprano (comprendido desde el nacimiento hasta los 45 días de edad) ya que muchos órganos y sistemas aun no alcanzan la maduración [14,15].

La etiología de muchas de las enfermedades crónicas se desconoce, pero el concepto del Origen Fetal de la Enfermedad del Adulto (FOAD, *Fetal Origin of Adult Disease*, por sus siglas en inglés) puede aclarar dichas interrogantes [19]. De acuerdo con la hipótesis de Barker, un insulto físico, químico o alteraciones nutricionales serían capaces de producir una programación anormal de diversos sistemas relacionados entre sí, particularmente alteraciones del material genético que, bajo diversas condiciones

medioambientales, pueden hacer que los individuos sean más susceptibles a desarrollar algún tipo de enfermedad crónica [20-22].

Tomando en consideración estos puntos y empleando la metodología Cochrane, se decidió realizar una revisión sistemática, enfocada en la exposición prenatal y postnatal temprana a PTM y los efectos adversos causados al material genético en la descendencia. Esta revisión se enviará a publicar a la revista “Journal of Trace Elements in Medicine and Biology”, ISNN: 0946-672X, la cual tiene un factor de impacto de 3.849.

2. REVISION BIBLIOGRAFICA

Prenatal exposure to potentially toxic metals and their effects on the genetic material in the offspring: a systematic review

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Abstract

Background and Aim

In recent years, the release of environmental pollutants, including metals, has increased due to technological and industrial development. Pollutant exposures during the earliest stage of life may determine the disease chronic susceptibility in adulthood because of genetic or epigenetic changes. The objective of this review was to identify the relationship between prenatal and early postnatal exposures to potentially toxic metals (PTM) and their adverse effects on the genetic material of the offspring.

Methodology

A systematic review was carried out following the Cochrane methodology in four databases: PubMed, Scopus, Web of Science, and Cochrane Library. Eligible papers were those performed in human beings and published in English between 2010/01/01 and 2021/04/30, whose main outcome was the offspring's adverse effects on genetic material related to prenatal or early postnatal exposures to at least one PTM. All the papers were reviewed separately by three members of our team and were classified according to the main evaluated outcome.

Results

A total of 57 papers were included for this review. Seven adverse effects related to genetic material in newborns due to PTM prenatal exposure were identified, including alterations in telomere length, gene or protein expression, mitochondrial DNA, metabolomics, DNA damage, and epigenetic modifications, many of these effects were sex-specific. Only one study was identified that evaluated the adverse effect in the postnatal period. Interestingly, two articles were identified where they evaluated synergistic interactions

and six articles evaluated antagonistic interactions between PTM and essential metals, such as Cu, Mg, Se, and Zn. Finally, the most evaluated PTM were As, Cd, and Pb.

Conclusion

The findings in this review highlight that the problem of PTM exposure persists affecting the most susceptible populations, such as the newborns, and that some of these adverse effects were sex-dependent.

Keywords

Metals, genetic material, maternal exposure, fetal origin of adult disease, newborn, DNA damage.

Abbreviations

5mC, 5-methylcytosine; CBMN, cytokinesis-block micronucleus cytome; FOAD, fetal origins of adult disease; IARC, International Agency for Research on Cancer; DNTM, DNA methyltransferases; DMR: differentially methylated regions; MMAT, Mixed Methods Appraisal Tools; mtDNA, mitochondrial DNA; PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses; PTM, potentially toxic metals; ROS, reactive oxygen species; TL, telomere length; WHO, World Health Organization.

1. Introduction

Environmental pollution of air, water, and soil has become a global problem due to the long-term impact on ecosystems and human health [1]. Air pollution is one of the most important environmental risks to health. Ninety percent of the world's population lives in places where air quality exceeds the guidelines of the World Health Organization (WHO). During 2012, one of each ten deaths was associated with air pollution and three million deaths were attributed to poor outdoor air quality [2]. In addition, the WHO estimates that one of each nine people uses drinking water from untreated and unsafe sources, representing 829 thousand deaths per year due to the use of contaminated water [3].

In recent decades, the industrial and technological development has led to the overexploitation of natural resources, including metals, which have been released into the environment [4]. Anthropogenic activities, including mining, industries, transport, animal husbandry, agriculture, and some household activities are the main cause of contamination of air, water, and soil [4]. A metal is any element characterized by its ductility, luster, tendency to lose electrons, and able to conduct heat and electricity [5]. Some metals are key elements for various biological functions; while others can alter cellular homeostasis and be toxic even at trace concentrations [5].

From a biological point of view, metals are classified as essential and non-essential. Essential metals, such as trivalent chromium (Cr^{3+}), copper (Cu), iron (Fe), manganese (Mn), selenium (Se), and zinc (Zn) play functions for the maintenance of cellular homeostasis, and they are part of the structure of proteins involved in glucose and lipid metabolism, antioxidant system, oxygen transport, DNA replication, among others [6,7]. However, they should be in optimal concentrations in the body, because their deficiency

or excess cause dysfunction in biological processes with a behavior described in a U-shaped dose-response curve [7,8]. On the other hand, non-essential metals, and metalloids, such as arsenic (As), cadmium (Cd), mercury (Hg), nickel (Ni), lead (Pb), and vanadium (V) do not play a biological function, they can replace and/or mimic essential metals disrupting cellular processes [5,8].

Metals and metalloids, such as As, Cd, Cr^{6+}, and Hg can directly react with DNA or indirectly through the generation of reactive oxygen species (ROS), therefore they have genotoxic potential even at trace concentrations [9] and are called potentially toxic metals (PTM) [10]. They are at the top of the priority list of the Agency for Toxic Substances and Disease Registry (ATSDR) [11].

Embryonic and fetal development are two susceptible periods to toxic exposure, characterized by high proliferation, cell differentiation, and tissue growth. In addition, the detoxification systems are not completely mature, so the fetus is not capable to mitigate the damage [12,13]. Another relevant period is the postnatal period (from birth to 42 days of age), because many organs and systems, such as the immune system, do not yet reach maturation [14,15].

Prenatal and early postnatal exposure to PTM, such as, As, Cd, Hg, and Pb have been associated with neurological, cardiovascular, and endocrine disruption in advanced stages of life [16–18]. This support the concept of the fetal origin of adult disease (FOAD) [19], which states that exposures to adverse physical, chemical, or nutritional factors during fetal life determine the chronical disease risk during adult life that was originated under the Barker hypothesis [20,21]. This is based on the premise of "development of plasticity" where a singular phenotype, which is influenced by an adverse intrauterine

environment, produces a different phenotype (susceptible individual). This concept considers that there is a specific developmental period where the organism is plastic and susceptible to this adverse environment [22]. Therefore, it is important to review the literature about the effects on the offspring genetic material due to prenatal exposure to PTM. The aim of this review was to identify the studies on prenatal or early postnatal exposures to PTM and describe their effects on the offspring's genetic material.

2. Methodology

A systematic review was carried out following the Cochrane methodology. The eligible research articles were those studies performed in humans published in English. The main outcome had to be adverse effects on offspring's genetic material and report the concentration of at least one metal/metalloid (in the article or as complementary material), quantified in the pregnant woman (without age restriction) and/or in the newborn/infant (up to 42 days of age, postnatal period) related to prenatal and postnatal exposure to PTM. Studies in which the pregnant woman had a pregnancy-related pathology were excluded. Considering that the greatest analytical development for the quantification of multi-elements and the evaluation of interactions between metals have occurred during the last decade, we restricted our search to those articles published from 2010/01/01 to 2021/04/30 in the following databases: PubMed, Scopus, Cochrane Library, and Web of Science. Our search strategy included controlled language with Medical Subject Headings (MeSH) descriptors: *Metals, heavy metals, maternal exposure, maternal-fetal exchange, infant, newborn, oxidative stress, DNA*, and *genomic instability*. No restrictions or filters were applied regarding the type of documents to make our search more sensitive to identify potential studies by searching citation.

The critical review process for each article was carried out independently by three researchers. Subsequently, the following information was collected from each article: title, authors, journal, reference, year of publication, country, abstract, database, type of document, type of study, objective(s) of the study, results, conclusion, metal(s)/including metalloids, the analytic technique for metal quantification, concentration, variable (main outcome adverse), technique for variable determination, biological matrix, sample size (n), and mother's age.

The quality assessment of the articles included in this review was carried out using the Mixed Methods Appraisal Tool (MMAT), which allows evaluating the methodological quality of five categories of studies: qualitative research, randomized controlled trials, non-randomized studies, quantitative descriptive studies and mixed methods studies [23]. In this systematic review, the five criteria for quantitative non-randomized studies were used. For the interpretation of the quality of the studies, the average percentage of each study was calculated according to the criteria and were assigned as MMAT score: high (>75%), moderate (50-75%), or low (<50%). The variables of interest to answer our research question were those negative or positive effects depending on the synergistic or antagonistic effect between PTM and essential metals in the genetic material of the offspring.

3. Results

3.1. Search in the literature

With the search strategy, 718 articles were identified in the consulted databases where 87 duplicate records were removed. Subsequently, the selection criteria were applied in the title and abstract, resulting in 70 articles potentially eligible for full text review. An

additional citation search of potentially eligible articles identified 15 potential eligible articles for full text review. The summary of results is presented according to The Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) statement [24] (Figure 1).

Finally, 57 research articles were included. Only one study evaluated metal concentrations in the early postnatal period [25]. The most frequent biological matrices for metal quantification were maternal urine, umbilical cord blood, and maternal blood, in this order. The most common evaluated PTM were As, Cd, and Pb. Regarding the interactions between metals, two articles reported synergistic interactions and six articles observed antagonistic interactions. The essential metals, such a Cu, Mg, Se, and Zn showed a protective effect against PTM. The main evaluated outcomes were telomere length (TL, n=7), epigenetic modifications (n=31), protein expression (n=1), DNA damage (n=4), mitochondrial DNA (mtDNA, n=6), metabolomics (n=1), and gene expression (n=7).

According to the evaluation of the quality of the included articles, 46 articles showed high quality (>75%) and 11 articles showed moderate quality (50-75%). None of the items included showed low quality (<50%). The MMAT score is included in each table presented in this review.

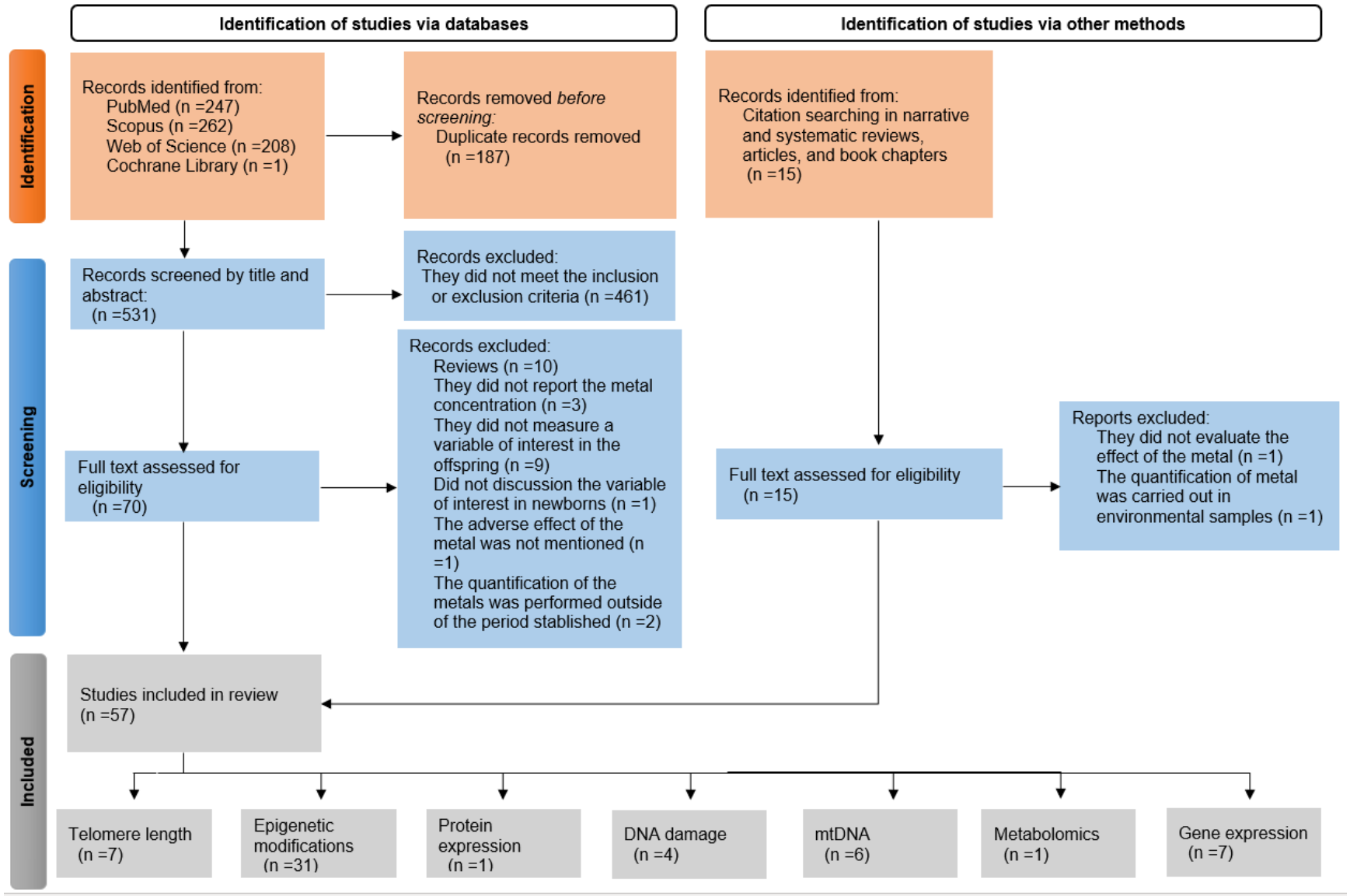

Figure 1. PRISMA flow chart of the systematic review

3.2. Telomere length (TL)

Telomeres are repetitive non-coding TTAGGG sequences located at the ends of eukaryotic chromosomes that form a protective layer to maintain genomic integrity during cell division [26]. Telomeres can be damaged by oxidative stress [27] causing a shortening of their structure [26]. It has been described that those chromosomes with telomere shortening are recognized by proteins in response to DNA damage, which leads the cell to enter a process of senescence, triggering genetic and morphological changes, ending in the loss of tissue functions [26,27]. Additionally, telomere shortening has been reported to be associated with an increased risk of developing cancer [28]. Seven articles reported the adverse effects on TL by prenatal exposure to PTM including As, barium (Ba), Cd, Pb, and thallium (Tl) in populations of Argentina, China, United States, and Myanmar and an antagonistic interaction was identified by Se. Results are presented in Table 1. Wu et al. [29] reported that only Tl concentration quantified in urine collected at delivery showed a significant inverse association with the TL shortening in umbilical cord blood. Cowell et al. [30] reported a significant inverse association between TL shortening in umbilical cord blood with Ba, Cd, and Pb only in mothers whose antioxidant intake was low, indicating that antioxidant intake could mitigate these effects by metals; As and Ni exposures were not significantly associated with this TL shortening.

In the Myanmar birth cohort, that included 409 mother-children pairs highly exposed to As (urinary median, IQR: 73.9, 45.6-126.4 μg/g Cr), a significant inverse association between maternal urinary As and Cd concentrations at the beginning of pregnancy and the shortening of TL in the umbilical cord blood was reported. No association was observed regarding Pb exposure [31]. These authors also found that Se had a protective

effect against the effects of Cd and Pb in multiple models adjusted for these two metals, but it does not exert a protective effect against As [32].

Cd quantified in maternal urine collected during delivery and placenta showed significant negative associations with TL in the placenta [33] and in the umbilical cord blood [34]. In the study of Zhang et al. [34] reported that this adverse effect was more pronounced in females. Also, Lin et al. [33] did not find a significant negative association between Pb and TL, in agreement with the study of Wai et al. [31]. Finally, in a population of Argentina, nine metals/metalloids were quantified in the umbilical cord blood and a significant association was observed only between Pb and TL shortening, this adverse effect was specific in males [35].

3.3. DNA damage

Four articles reported DNA damage by prenatal exposure to PTM, such as As, Cd, Cr, Hg, Ni, and Pb in populations of China, Saudi Arabia, and Vietnam. One antagonistic interaction was identified by Se. Results are presented in Table 2. Different markers of DNA damage were used in these studies, such as the comet assay that detects single and double strand breakage [36], the 8-OHdG and 8-oxoG, which are oxidation products used as biomarkers of DNA oxidative damage [37], and the cytokinesis-block micronucleus cytome (CBMN) assay that detects chromosomal aberrations [38].

Significant positive associations between As concentrations quantified in maternal urine at 8 and 30 weeks of gestation and 8-oxoG evaluated in the placenta in a Bangladesh population were reported, having the greatest negative impact with the concentrations evaluated at 30 weeks of gestation [39]. Additionally, Navasumrit et al. [40] reported a positive association between As quantified in cord blood and different parameters of the

comet assay (tail length, %DNA tail, and Olive tail moment-OTM) and micronucleus formation (especially binucleated cells) measured in the umbilical cord blood in a concentration-effect way in a population of Vietnam chronically exposed to this metalloid. Ni et al. [41] reported a positive correlation between Cd, Cr, and Ni quantified in the cord blood with 8-OHdG levels in newborns evaluated in the umbilical cord blood in a Chinese population; the authors did not find a significant correlation with Pb either. Al-Saleh et al. [42] identified a positive association between Hg quantified in the placenta and the OTM (comet assay); in the multiple models, the concentration of Se showed a protective effect against Hg effects.

3.4. Mitochondrial DNA (mtDNA)

In recent years, there has been an interest in evaluating the content of mtDNA as a biomarker of oxidative damage, since changes in its content may be indicative of mitochondrial dysfunction, which promotes the development of chronic diseases, such as diabetes [44] and cancer [43]. Six articles were identified that reported adverse effects on the content of mtDNA by prenatal exposure to PTM, such as aluminum (Al), As, Mn, Hg, Pb, and Tl in populations of Belgium, China, Mexico, and Seychelles (Table 3). The mitochondria has its own DNA, which is called mitochondrial DNA (mtDNA) due to the lack of protection and having less efficient mechanisms in DNA repair is susceptible to ROS damage leading to mutations or alterations in the content [43].

Hg and Tl were negatively associated with mtDNA content in populations from Seychelles [45], China [46], and Belgium [47]. Some studies reported significant associations according to the trimester of pregnancy. Mn was positively associated with mtDNA content in the third trimester but not in the second one [48], Al was associated with mtDNA

content in the second and third trimesters but not in the first one [49] and Pb was associated with mtDNA content in the second, third trimester and delivery [50]. Interestingly, the relationship of mtDNA content with Tl was sex-specific in females and not in males [46].

3.5. Protein and gene expression

A study referring to the expression of proteins by prenatal exposure to PTM was included (Table 5). Bailey et al. [51] found an association between the levels of As quantified in maternal urine and the expression of 111 proteins in newborns in a subset of 50 cord serum samples selected from a prospective pregnancy cohort where 200 pregnant women were recruited in Mexico; the proteins are involved in immune and inflammatory response, proliferation, and cell development.

Regarding gene expression, seven articles reported adverse effects on the expression of some genes by prenatal exposure to PTM, such as Al, As, and Cd in populations of Belgium, China, and United States. Two records were identified that reported antagonistic effects of magnesium (Mg) and Se (Table 4). Wang et al. [52] reported that Al concentrations quantified in umbilical cord blood increased the expression (mRNA) of *IL-1β* and decreased the expression of *IL-6* and *TNF-α* in the placenta. These effects of inflammation and oxidative damage were antagonized by Mg. Everson et al. [53] reported a sex-specific effect of Cd quantified in the placenta with the expression of nine genes that are related to growth and cognitive development in early life. These genes were: carboxypeptidase A4(*CPA4)*, growth factor receptor bound protein 10 (*GRB10)*, and integrin linked kinase (*ILK*) that were expressed only in females. The remaining six genes were not specific of sex, including distal-less homeobox 5 (*DLX5)*, H19 imprinted

maternally expressed transcript (*H19)*, necdin (*NDN)*, IGF2 antisense RNA (*IGF2-AS)*, insulin like growth factor 2 (*IGF2)*, and thrombospondin type 1 domain containing 7A (*THSD7*).

Deyssenroth et al. [54] performed a multi-elemental determination in a birth cohort of 195 mother-infant pairs enrolled in the Rhode Island Child Health Study of the United States and found that As and Cd quantified in maternal toenail modulated the expression of genes associated with the secretion of metabolic hormones in the placenta. As was associated with poly(A) specific ribonuclease subunit PAN3 (*PAN3),* polycomb repressive complex 2 subunit (*SUZ12)*, and zinc finger (*ZNF)* genes and Cd was associated with aryl hydrocarbon receptor nuclear translocator (*ARNT2)* and inhibin subunit beta A (*INHBA)*. It was identified that As quantified in maternal urine was positively correlated with the expression of *IL-1β* in the placenta in a birth cohort where pregnant women ages 18 to 45 were recruited to participate in The New Hampshire Birth Cohort of the United States, being specific in females [55]. Additionally, Remy et al. [56] reported changes in the expression of two genes, acetyl-CoA carboxylase Alpha (*ACACA),* related to fatty acid metabolism and fms related receptor tyrosine kinase 1 (*sFLT1)*, related to the development of embryonic vasculature due to As concentrations quantified in umbilical cord blood. Additionally, these authors reported that *sFLT1* expression was related to low birthweight in a birth cohort were newborn-mother couples were recruited from Flanders, Belgium.

Finally, Cd was associated with alterations in the expression patterns of various steroidogenic genes and the TNF pathway in a sub sample of the Rhode Island Child Health Study of the United States. In addition, when multiple analyses were performed,

these effects were antagonized by Se [57]. Xu et al. [58] reported that Cd quantified in maternal toenail had a significant correlation with the expression of the kiss-1 metastasis suppressor (*KISS1)* gene, related to cytoskeletal reorganization in the placenta. In addition, the authors reported that the expression of *KISS1* was positively correlated with low birthweight.

3.6. Metabolomics

Metabolomics comprises the study of hundreds of metabolites in a biological sample providing valuable information regarding a toxic insult [59]. In this section, only one record was reported adverse effects on metabolites in newborns due to PTM exposure (Table 5). Laine et al. [60] quantified As in the umbilical cord in a subset of 50 samples selected from a pregnancy cohort from Mexico and identified 17 altered metabolites in newborns by prenatal exposure to As. These were involved in biochemical pathways, such as amino acid and vitamin metabolism, and citric acid cycle.

3.7. Epigenetic modifications

Epigenetics is the study of heritable changes in the function of genes that cannot be attributed to alterations in the DNA sequence [21,62]. These epigenetic changes include DNA methylation, histone acetylation, and microRNA, which are the most frequent [21]. Thirty-one records were identified that reported effects at the level of epigenetic modifications due to prenatal and postnatal exposure to PTM as As, Cd, Cr, Co, Hg, Mn, Mo, and Pb in populations of Bangladesh, China, United States, Korea, Mexico, Norway, Taiwan, and Thailand. Results are presented in Table 6. One record reported an adverse effect in the postnatal period [25]. Additionally, four records were identified that reported interactions between PTM and essential metals, two were synergistic by As, Hg, Pb, and

Zn. Two antagonistic by Cu, Se, and Zn. Interestingly, one registry reported an effect at the transgenerational level [61].

3.7.1. Global DNA methylation

Twenty-three articles were identified that evaluated global methylation in newborns in relation to exposure to metals and metalloids (Table 6). Some effects were specific to sex, such as those of Hg quantified in maternal blood collected at gestational week 18, which showed a negative association with 5-methylcytosine (5mC) levels in the umbilical cord blood of the females [63]. Pb quantified early in pregnancy (12-20 gestational weeks) was associated with 11 differentially methylated regions (DMR) in the umbilical cord blood of males [64]. However, Wu et al. [65] reported a more pronounced effect in the hypomethylation in umbilical cord blood of females by Pb quantified in maternal blood collected at gestational week 28. As quantified in maternal urine collected at gestational week 8 showed a decrease DNA methylation in the umbilical cord in males [66]. Finally, Cd quantified in maternal urine was associated with a global hypermethylation in the umbilical cord blood of males and a hypomethylation in females [67,68] .

Weyde et al. [63] reported a protective effect of Se with respect to DNA methylation caused by Hg. Cardenas et al. [69] reported that the co-exposure of As and Hg was associated with a hypermethylation of DNA. In addition, some essential metals were also associated with global DNA methylation, such as Co and Cu that showed non-linear associations [63], Cu was associated with nine DMRs [70], and Mn with five different methylated loci [71].

Table 1. Studies related to an adverse effect on telomere length in newborns prenatally exposed to potentially toxic metals.

Year, country [Reference]	Analytical technique	Biological matrix, n	Collection period	Metal(s)	Median Concentration (P25-P75)	Main findings	MMAT Score
2021, China [29]	ICP-MS	Maternal urine, 410	1st trimester 2nd trimester 3rd trimester Delivery	Tl	0.34 (0.26-0.47) µg/L[a] 0.36 (0.27-0.49) µg/L[a] 0.33 (0.24-0.47) µg/L[a] 0.29 (0.22-0.39) µg/L[a]	Association between Tl concentrations (collected at delivery) with shortening of TL in leukocytes of newborns	High
2020, United States [30]	ICP-MS	Maternal urine, 100	15-40 GW	As Ba Cd Ni Pb	11.45 (16.44) ng/mL[b] 2.39 (3.19) ng/mL[b] 0.16 (0.21) ng/mL[b] 1.46 (1.31) ng/mL[b] 0.45 (0.44) ng/mL[b]	Inverse association between Ba, Cd, and Pb concentrations with TL in newborns. In mothers with high antioxidant intake, a mitigated effect was observed	High
2020, Myanmar [32]	ICP-MS	Maternal urine, 408	1-3 months of pregnancy	As Cd Se Pb	74 (45.6-126.4) µg/g Cr 0.8 (0.5-1.4) µg/g Cr 22.6 (17.7-29.5) µg/g Cr 1.7 (1.0-3.2) µg/g Cr	Inverse associations between As and Cd concentrations with TL in newborns. When adjusted for Se concentrations, a protective effect was observed for Cd and Pb not for As	High
2019, China [34]	ICP-MS	Maternal urine, 410	Delivery	Cd	0.68 (0.47-0.96) µg/g Cr	Cd concentrations associated with shortening of TL, a more pronounced effect in females	High
2019, Argentina [35]	ICP-MS	Cord blood, 169	Delivery	As B Cd Cs Li Pb Se Sb	2.3 (0.47-14) µg/L 193 (69-698) µg/L <0.02 (<0.02-0.12) µg/L 153 (7.2-690) µg/L 48 (9.5-156) µg/L 14 (6.3-60) µg/L 49 (34-105) µg/L 2.5 (0.84-18) µg/L	Only Pb was significantly associated with telomere shortening in umbilical cord blood, particularly in males	Moderate

				Zn	1.8 (1.2-4.8) μg/L		
2018, Myanmar [31]	ICP-MS	Maternal urine, 409	1-3 months of pregnancy	As	73.9 (45.6-126.4) μg/g Cr	As and Cd concentrations were significantly associated with newborn TL shortening	High
				Cd	0.9 (0.5-1.4) μg/g Cr		
				Pb	1.8 (1.0-3.2) μg/g Cr		
2013, China [33]	GFAAS	Placenta, control: 97	Delivery	Cd	0.0239 (0.0167-0.1432) μg/g	Cd concentrations negatively associated with TL. Pb did not show statistically significant effects	Moderate
				Pb	1.3525 (0.6823-4.1111) μg/g		
		Exposed: 227		Cd	0.0929 (0.0640-0.1432) μg/g		
				Pb	1.2491 (0.6681-2.5901) μg/g		

Notes: GW: Gestational week; MMAT: Mixed Methods Appraisal Tool; Cr: creatinine; GFAAS: Graphite Furnace Atomic Absorption Spectrometry; ICP-MS: Inductively Coupled Plasma Mass Spectrometry; SG: specific gravity. [a] SG-corrected; [b] Geometric mean (p25-p75)

3.7.2. Gene-specific DNA methylation

We also identified some research groups focused on evaluating DNA methylation patterns in specific genes (Table 6). Yang et al. [72] reported that wnt family member 3A (*WNT3A)* hypermethylation was associated with Pb concentrations in the umbilical cord blood, this gene is related to the activation of transcription factors. Montes-Castro et al. [73] reported some interactions between PTM and essential metals quantified in maternal urine collected at the time of birth: As, Hg, and Pb increased the methylation of *Nrf2*, Se showed an antagonistic effect against these metals. Furthermore, Zn showed a protective effect of *Nrf2* hypermethylation caused by Hg, while As was associated with *PARP1* hypermethylation, but Cu, Se, and Zn antagonized this effect. Hg was associated with hypermethylation of *PARP1*, an effect that was antagonized by Se. Molybdenum (Mo) was associated with a hypermethylation of *PARP1* and Cu antagonized this effect. Finally, these authors reported that Mn was associated with a hypermethylation of *OGG1,* and Cu antagonized this effect. All these genes are involved in DNA repair enzymes.

Hg quantified in maternal blood collected in the second trimester was associated with a hypomethylation of paraoxonase 1 (*PON1*), an enzyme that hydrolyzes the toxic metabolites of organophosphate pesticides, a specific effect observed in males [74].

High concentrations of As, Cd, Mn, and Pb quantified in maternal urine collected at 28-38 weeks of gestation were associated with a hypermethylation of nuclear receptor subfamily 3 group C member 1 (*NR3C1,* related to inflammatory response, cellular proliferation, and differentiation) in the umbilical cord blood and low concentrations of Zn were associated with a hypermethylation of this gene. A stratified analysis revealed the interaction between Pb, Mn, and Zn with a hypermethylation of *NR3C1* in females [75].

Phookphan et al. [76] reported a negative correlation of As quantified in the umbilical cord blood with the methylation of prostaglandin-endoperoxide synthase 2(*COX2),* early growth response 1 *(EGR1)*, and suppressor of cytokine signaling 3 (*SOCS3),* these genes are related to the inflammatory response.

Everson et al. [77] identified that Cd quantified in maternal toenail was associated with a hypomethylation of protocadherin alpha subfamily C, 1 (*PCDHAC1)* in the placenta, this gene is related to the maintenance of specific neuronal connections in the brain. Vidal et al. [78] reported that Cd quantified in maternal blood collected at the beginning of pregnancy was associated with a hypomethylation of paternally expressed 3 (*PEG3*), and a gene related to apoptosis and with lower methylation of PLAG1 like zinc finger 1 (*PLAGL1*) whose mothers had low Zn and Fe concentrations. However, the hypermethylation of *PEG3* in females was antagonized when mothers had high Zn concentrations.

Table 2. Studies about adverse effects on DNA damage in newborns due to prenatal exposure to potentially toxic metals.

Year, country [Reference]	Analytical technique	Biological matrix, n	Collection period	Metal(s)	Median concentration (P25-P75)	Main findings	MMAT Score
2019, Vietnam [40]	ICP-MS and HPLC	Maternal toenail, 205	25 GW	As	Low, 0.29 (0.10-0.49) µg/g Medium, 0.71 (0.50-0.99) µg/g High, 1.55 (1.00-6.07) µg/g	As concentrations in cord blood were positive correlated with DNA damage: comet assay (tail length, OTM and %DNA in tail) and micronucleus frequency (binucleated cells)	High
		Maternal urine	25 GW		Low, 46.68 (1.57-162.39) µg/g Cr Medium, 61.88 (13.39-166.66) µg/g Cr High, 75.59 (16.57-339.59) µg/g Cr		
		Cord blood	Delivery		Low, 1.50 (0.17-4.60) µg/L Medium, 1.78 (0.85-6.22) µg/L High, 2.05 (0.89-9.72) µg/L		
2014, Saudi Arabia [42]	HG-AAS	Cord blood, 250	Delivery	Hg	3.46 ± 2.507 µg/L[a]	Positive correlation between placental Hg and OTM (comet assay). When the analysis was carried out with ratio Se/Hg, Se showed a protective effect.	High
				Se	67.618 ± 12.897 µg/L[a]		
		Placenta		Hg	0092 ± 0.0124 µg/g wet wt[a]		
				Se	0.175 ± 0.021 µg/g wet wt[a]		
2014, China [41]	GFAAS	Cord blood, control: 75	Delivery	Cd	2.50 (0.25-9.82) ng/mL	Positive correlation between oxidative DNA damage marker (8-OHdG) with the concentrations of Cd, Cr, and Ni. Pb did not show a significant correlation.	Moderate
				Cr	27.52 (8.70-339.50) ng/mL		
				Ni	8.63 (3.68-544.20) ng/mL		

				Pb	110.45 (28.09-379.30) ng/mL		
		Exposed: 126		Cd	2.50 (0.25-9.82) ng/mL		
				Cr	26.42 (11.80-1169) ng/mL		
				Ni	9.09 (4.67-152.40) ng/mL		
				Pb	57.31 (11.68-285.40) ng/mL		
2011, Bangladesh [39]	HG-AAS	Maternal urine, 130	8 GW 30 GW	As	136 ± 167 µg/L[a,b] 143 ± 164 µg/L[a,b]	Positive correlation between oxidative DNA damage marker (8-oxoG) and As concentrations.	High

Notes: GW: Gestational week; MMAT: Mixed Methods Appraisal Tool; GFAAS: Graphite Furnace Atomic Absorption Spectrometry; HG-AAS: Hydride Generation Atomic Absorption Spectroscopy; HPLC: High Performance Liquid Chromatography; ICP-MS: Inductively Coupled Plasma Mass Spectrometry; OTM: Olive tail moment; SG: Specific gravity. [a] Mean ± Standard deviation; [b] SG-adjusted

Table 3. Studies of mitochondrial DNA (mtDNA) alterations in newborns prenatally exposed to potentially toxic metals.

Year, country [Reference]	Analytical technique	Biological matrix, n	Collection period	Metal(s)	Median concentration (P25-P75)	Main findings	MMAT Score
2019, Seychelles [45]	AFS	Maternal hair, 1055	Delivery	Hg	2.93 (0.010-31.66) ng/mL	Negative association between Hg concentrations in cord blood and mtDNA copy number in newborns	High
		Maternal blood	28 GW		15.97 (1.87-84.15) ng/mL		
		Cord blood	Delivery		30.25 (1.91-181.27) ng/mL		
2019, Mexico [50]	ICP-MS	Maternal urine, 410	2nd trimester	Pb	3.79 ± 2.63 µg/dL[a]	Pb quantified in the 2nd and 3rd trimesters of pregnancy and in the umbilical cord blood was positively associated with increased mtDNA content in newborns	High
			3rd trimester		3.90 ± 2.84 µg/dL[a]		
			Delivery		4.16 ± 2.85 µg/dL[a]		
		Cord blood	Delivery		3.50 ± 2.59 µg/dL[a]		
2019, China [49]	ICP-MS	Maternal urine, 746	1st trimester	Al	31.0 (13.6-59.7) µg/g Cr[b]	Second and third trimester concentrations of Al were positively related to the content of mtDNA in the newborn	High
			2nd trimester		40.9 (17.7-94.6) µg/g Cr[b]		
			3rd trimester		58.4 (21.0-130.6) µg/g Cr[b]		
2019, China [46]	ICP-MS	Maternal urine, 746	1st trimester	Tl	0.34 (0.26-0.47) µg/L[b, c]	Tl concentrations were negatively associated with the number of copies of mtDNA in the newborn, being the concentrations in the first trimester the ones that showed the most negative association. These associations were stronger in females	High
			2nd trimester		0.36 (0.27-0.49) µg/L[b, c]		
			3rd trimester		0.34 (0.24-0.47) µg/L[b, c]		
2019, Mexico [48]	ICP-MS/MS	Maternal blood, 485	2nd trimester	Mn	1.46 ± 0.49 µg/dL[a]	Maternal blood Mn in the 3rd trimester and in cord blood was positively associated with copies number of mtDNA in the newborn	Moderate
			3rd trimester		1.88 ± 0.63 µg/dL[a]		
			Delivery		2.47 ± 0.95 µg/dL[a]		
		Cord blood	Delivery		4.86 ± 2.33 µg/dL[a]		
			Delivery	As	1.19 ± 1.84 µg/L[a]		High

2017, Belgium [47]	HR-ICP-MS	Cord blood, 233	Cd Cu Mn Pb Tl	0.02 ± 0.01 µg/L[a] 564 ± 97.0 µg/L[a] 31.5 ± 11.1 µg/L[a] 7.09 ± 3.40 µg/L[a] 19.4 ± 5.77 ng/L[a]	As concentrations were positively associated with the content of mtDNA in the placenta. Additionally, Tl was negatively associated.

Notes: GW: Gestational week; MMAT: Mixed Methods Appraisal Tool; AFS: Atomic Fluorescence Spectrometry; Cr: creatinine; HR-ICP-MS: High Resolution Inductively Coupled Plasma Mass Spectrometry; ICP-MS: Inductively Coupled Plasma Mass Spectrometry; ICP-MS/MS: Inductively Coupled Plasma-tandem Mass Spectrometry; SG: specific gravity. [a] Mean ± Standard deviation; [b] Geometric mean (P25-P75) [c] SG-adjusted

Table 4. Studies related to gene expression effects in newborns due to prenatal exposure to potentially toxic metals.

Year, country [Reference]	Analytical technique	Biological matrix, n	Collection period	Metal(s)	Median concentration (P25-P75)	Main findings	MMAT Score
2020, China [52]	ICP-MS	Maternal blood, 2441	1st trimester	Al	69.25 (58.85-82.58) mg/L	Al concentrations in cord blood were associated positively with the mRNA expression of IL-1β and negatively with IL-6 and TNF-α. Regarding Mg concentrations, it was positively associated with IL-6 and TNF-α	High
				Mg	20.41 mg/L		
			2nd trimester	Al	56.99 (47.85-69.02) mg/L		
				Mg	19.47 mg/L		
		Cord blood	Delivery	Al	46.48 (28.27-66.59) mg/L		
				Mg	17.60 mg/L		
2019, United States [53]	ICP-MS	Placenta, NHBCS: 326	Delivery	Cd	Male, 3.27 (2.14-4.62) ng/g	Association of Cd concentration in the placenta with the expression of nine genes, some of them sex-specific. In the case of females (*CPA4, GRB10*, and *ILK*), while the remaining 6 were not sex specific (*DLX5, H19, NDN, IGF2-AS, IGF2 and THSD7*)	High
					Female, 3.00 (2.07-4.74) ng/g		
		RICHS: 211			Male, 3.97 (2.79-5.43) ng/g		
					Female, 4.38 (2.94-5.27) ng/g		
2018, United States [54]	ICP-MS	Maternal toenail, 195	2.8 month postpartum	Al	19.0 ± 40.5 μg/g dry weight[a]	As and Cd were associated with modulation of the expression of genes involved in the secretion of metabolic hormones and gene expression. As (*PAN3, SUZ12, ZNF*) and Cd (*ARNT2* and *INHBA*)	High
				As	0.059 ± 0.045 μg/g dry weight[a]		
				Cd	0.02 ± 0.02 μg/g dry weight[a]		
				Cr	0.386 ± 0.492 μg/g dry weight[a]		
				Cu	23.14 ± 60.16 μg/g dry weight[a]		
				Fe	18.2 ± 19.5 μg/g dry weight[a]		
				Mn	0.265 ± 0.742 μg/g dry weight[a]		
				Mo	0.02 ± 0.03 μg/g dry weight[a]		
				Ni	20.1 ± 61.3 μg/g dry weight[a]		

				Pb	0.315 ± 0.541 µg/g dry weight[a]		
				Sb	0.038 ± 0.064 µg/g dry weight[a]		
				Se	0.979 ± 0.241 µg/g dry weight[a]		
				Sn	0.286 ± 0.374 µg/g dry weight[a]		
				U	0.007 ± 0.020 µg/g dry weight[a]		
				V	0.029 ± 0.055 µg/g dry weight[a]		
				Zn	102.3 ± 17.75 µg/g dry weight[a]		
2017, United States [57]	ICP-MS	Maternal toenail, 143	2.8 month postpartum	Cd Se	0.0083 ± 0.013 µg/g[a] 0.97 ± 0.20 µg/g[a]	Cd altered the expression patterns of steroidogenic genes and TNF; however, these effects were antagonized by Se	High
2015, China [58]	GFAAS	Placenta, control: 59 Exposed: 192	Delivery	Cd	20.87 (16.19-27.77) ng/g 96.56 (70.95-141.72) ng/g	Significant (weak) positive correlation between Cd and *KISS1* mRNA expression	High
2014, United States [55]	ICP-MS	Maternal urine, 116	24-28 GW	As	7.8 ± 26.8 µg/L[a]	As concentrations in maternal urine were positively associated with IL-1β expression in the placenta	High
2014, Belgium [56]	ICP-MS	Maternal blood, 183 Cord blood	Delivery	As	0.7 (0.3-1.3) µg/L 0.5 (0.2-1.2) µg/L	Two genes showed changes in expression (*ACACA* and *sFLT1*) due to As concentrations	High

Notes: GW: Gestational week; MMAT: Mixed Methods Appraisal Tool; GFAAS: Graphite Furnace Atomic Absorption Spectrometry; ICP-MS: Inductively Coupled Plasma Mass Spectrometry; NHBCS: New Hampshire Birth Cohort Study; RICHS: Rhode Island Child Health Study. [a] Mean ± Standard deviation

Table 5. Studies of effects on protein expression and metabolomics in newborns due to prenatal exposure to potentially toxic metals.

Year, country [Reference]	Analytical technique	Biological matrix, n	Collection period	Metal(s)	Median concentration (P25-P75)	Main findings	MMAT Score
Protein expression							
2014, Mexico [51]	HG-AAS	Maternal urine, 50	Delivery	As	30.7 (6.2-319.7) µg/L[a]	111 proteins were identified that have a significant association with As	High
Metabolomics							
2017, Mexico [60]	HG-AAS and HG-CT-ICP-MS	Maternal urine, 50 Cord blood	Delivery	As	30.7 (6.2-319.7) µg/L[a] 0.322 (0.048-2.98) µg/L	As concentrations were associated significantly with 17 metabolites involved in biochemical pathways, vitamin metabolism, amino acid metabolism, citric acid cycle	High

Notes: MMAT: Mixed Methods Appraisal Tool; HG-AAS: Hydride Generation Atomic Absorption Spectroscopy; HG-CT-ICP-MS: Hydride Generation-Cryotrapping and Inductively Coupled Plasma Mass Spectrometry; SG: Specific gravity. [a] SG-corrected

3.7.3. miRNA

miRNAs are small molecules that are composed of non-coding RNA, their function is the regulation of gene expression through mRNA degradation, and some of them play functions in intercellular signaling since they are circulating in different fluids (saliva, urine, and blood). Therefore, in recent years, they have been used as biomarkers of exposure since they are indicative of processes of inflammation and angiogenesis, among others [79]. Only one study was identified about PTM exposure and miRNA. Rager et al. [80] reported an increased expression of 12 miRNAs that were associated with the concentration of As quantified in maternal urine collected at the time of delivery. In addition, 334 transcripts were identified that had latent expression, which were associated with As in the mild childhood (110 had increased expression and 224 decreased their expression). These miRNAs were related to various genes involved in cancer and inflammatory response (Table 6).

4. Discussion

With the present systematic review of papers published from 2010/01/01 to 2021/04/30 from four databases, we identified seven adverse effects in the offspring's genetic material related to the prenatal and early postnatal PTM exposure. These include TL, DNA damage, mtDNA, protein and gene expression, metabolomics, and epigenetic modifications, such as global DNA methylation, gene-specific DNA methylation, and miRNAs. As, Cd, and Pb were the most reported PTM with these adverse effects. Some of these PTM showed a sex-specific adverse effect, such as Cd, Hg, Pb, and Tl.

During embryonic development, cellular differentiation processes take place, which are due to cascades of transcription factors that regulate the expression of genes [62], which

in turn is modulated by epigenetic plasticity that define the differentiation of cells. This epigenetic process is natural and essential for mammals. However, the presence of environment factors during the epigenetic reprogramming period may predispose the individual to adverse effects in adult life [62]. The adverse effects identified in this systematic review are good predictors of susceptibility to diseases in middle and adult life by PTM, such as cardiovascular, respiratory, in the immune system, neurodevelopment, development, and growth [18,74,81–85].

Several research groups were identified working on the evaluation of PTM effects on epigenetic mechanisms, such as global methylation and gene-specific methylation. According to global DNA methylation several PTM, including As, Cd, Hg, and Pb were associated with alterations in different populations [25,68,86,87], as well as some essential metals, such as Cu, Co, Cr^{3+}, and Mn [63,70,71,88]. The probable toxic mechanism of PTM on DNA methylation could be by inducing or inhibiting the transcription of the DNA methyltransferases (DNMT), which are the enzymes responsible for the methylation, or by interacting with proteins that modify the chromatin [94]. In addition, some of these associations between PTM and DNA methylation were sex-specific, such as those of Hg in females [63], and As in males [66,89]. This suggests that there is a sex-related susceptibility in newborns to the insult of some PTM, such as As, Cd, Hg, and Pb, probably because the sex-hormones mark the susceptibility between each gender, which has been hypothesized by other authors [90,91]. This is in agreement with other xenobiotics that have been linked to sex-specific effects on DNA methylation by prenatal exposure, such as polychlorinated biphenyls, perfluorooctane sulfonate, hexachlorobenzene, *p,p'*-dichlorodiphenyldichloroethylene [92], and bisphenol A [93].

Additionally, some studies observed interactions between PTM and essential metals, such as the synergism between As and Hg and global DNA hypermethylation [69] or the antagonism of Se on the DNA hypermethylation caused by Hg [63]. Some essential metals, such as Cu^{3+}, Mg, Se, and Zn actively participate in different metabolic processes and are part of the antioxidant defense system, guaranteeing a correct development during pregnancy [5]. This is relevant since we are exposed to mixtures of metals. A very important issue is that these epigenetic marks can be transmitted transgenerational. In this regard, one study found alteration in DNA methylation patterns among children whose mothers were prenatally exposed to high concentrations of Pb [61]. Regarding gene-specific methylation, we identified some papers reporting effects of some PTM, such as As, Cd, Hg, Mn, and Pb on genes related to cell-adhesion, DNA-repair, inflammation, metabolism, and embryonic development [68,72,75–78,86]. Similar to global DNA methylation, some interactions were observed between the cord blood concentrations of PTM and essential elements, such as Cu, Se, and Zn on the methylation of genes related to DNA repair [73].

As, Cd, Cr, and Ni exposure were associated with genotoxic effects in populations from Bangladesh [39], China [41], Saudi Arabia [42], and Vietnam [40]. Some PTM, such as, As, Cd, Cr^{6+}, and Ni are well recognized as carcinogens by the International Agency for Research on Cancer (IARC) [103], due to their interaction with DNA repair enzymes, alterations in DNA repair genes or replication machinery. This could lead to poor repair or unrepaired damage, causing stable mutations and increasing the risk of developing diseases, such as cancer in childhood and adulthood [8,9,104,105].

Table 6. Studies about epigenetic modifications in newborns due to prenatal exposure to potentially toxic metals.

Year, country [Reference]	Analytical technique	Biological matrix, n	Collection period	Metal(s)	Median concentration (P25-P75)	Main findings	MMAT Score
DNA methylation							
2021, Norway [63]	ICP-SFMS	Maternal blood, 652	17-18 GW	As	2.23 ± 3.07 µg/mL[a]	*Hg negative associations with methylations levels (5mC), particularly in girls (global methylation) *Se positive associations with 5mC levels in women who did not smoke during pregnancy *Co and Cu non-linear associations with 5mC levels	High
				Cd	0.28 ± 0.26 µg/mL[a]		
				Cs	2.18 ± 0.71 µg/mL[a]		
				Co	0.21 ± 0.22 µg/mL[a]		
				Cu	1462 ± 245 µg/mL[a]		
				Hg	1.47 ± 1.04 µg/mL[a]		
				Mg	27.5 ± 3.12 mg/mL[a]		
				Mn	10.5 ± 7.81 µg/mL[a]		
				Mo	1.25 ± 4.95 µg/mL[a]		
				Se	94.7 ± 18.0 µg/mL[a]		
				Pb	9.07 ± 9.04 µg/mL [a]		
				Zn	4677 ± 826 µg/mL[a]		
2021, China [72]	ICP-MS	Cord blood, case: 59	Delivery	Pb	49.88 ng/g	Pb was associated with hypermethylation of *WNT3A* in cases versus controls	Moderate
		Control: 118			25.59 ng/g		
2021, Korea [64]	GFAAS	Maternal blood, 384	12-20 GW	Pb	13.043 (3.90-90.95) µg/L[b]	In males, 11 sites were different methylated positions associated with Pb levels during early pregnancy (global methylation)	High
			28-42 GW		12.471 (1.20-62.19) µg/L[b]		
		Cord blood	Delivery		9.131 (3.00-26.12) µg/L[b]		
2020, United States [70]	ICP-MS	Placenta, NHBCS: 306	Delivery	Cu	847.1 (602-2428.5) ng/g	*9 regions differentially methylated associated with Cu (global methylation) *One differentially methylated region negatively associates with gene expression of *ZNF197*	High
		RICHS: 141			880.1 (623.1-2643.5) ng/g		

2020, United States [25]	HR-ICP-MS	Neonatal blood, 96	24 hours of birth	Pb	0.78 ± 0.85 µg/dL[a]	Associations between DNA methylation and Pb at 33 CpG sites, most of them present hypomethylation as the concentration of Pb increases (global methylation)	High
2019, China [88]	GFAAS	Cord blood, control: 103 Exposed: 101	Delivery	Cd Cr Mn Pb Cd Cr Mn Pb	0.29 ± 0.51 µg/L[a] 6.23 ± 5.92 µg/L[a] 51.21 ± 16.43 µg/L[a] 3.07 ± 0.84 µg/dL[a] 0.22 µg/L ± 0.21[a] 5.90 ± 3.30 µg/L[a] 54.01 ± 21.88 µg/L[a] 7.34 ± 2.69 µg/dL[a]	*125 CpG sites were differential methylation in the exposed group with higher metals concentrations (global methylation) *79 CpG sites were hypomethylated and 46 were hypermethylated	Moderate
2019, Mexico [73]	ICP-MS	Maternal urine, 181	Delivery	As Cu Hg Mn Mo Pb Se Zn	22.94 (14.76-36.32) µg/g Cr[b] 32.25 µg/g Cr (21.18-47.67)[b] 16.44 (9.54-28.56) µg/g Cr[b] 4.10 (3.00-6.63) µg/g Cr[b] 36.37 (25.63-51.10) µg/g Cr[b] 2.97 µg/g Cr (2.04-5.84)[b] 37.35 (33.44-69.49) µg/g Cr[b] 579.75 (360.43-875.29) µg/g Cr[b]	*Hypermethylation of LINE-1 related with As and Hg at lower Zn *Hypermethylation of LINE-1 associated with Mn at lower Cu *As, Hg, and Pb increase methylation of *Nrf2*, Se antagonizes this effect *Hg increase methylation of *Nrf2*, Zn antagonizes this effect *As was associated with hypermethylation of *PARP1*, Cu, Se, and Zn antagonizes this effect *Hg was associated with hypermethylation of *PARP1*, Se antagonizes this effect *Mo was associated with hypermethylation of *PARP1*, Cu antagonizes this effect *Mn was associated with hypermethylation of *OGG1*, Cu antagonizes this effect	High

2018, United States [95]	ICP-MS	Placenta, NHBCS: 343 RICHS: 141	Delivery	Cd	3.13 (2.61) ng/g 4.37 (2.71) ng/g	Cd was associated with 17 CpG sites were differentially methylated (global methylation)	High
2018, United States [96]	ICP-MS	Maternal blood, high exposed: 10 Low exposed: 10	12 GW	Cd	0.165 (0.090-0.338) µg/dL 0.012 (0.004-0.023) µg/dL	Cd was associated with 641 different methylated regions (global methylation)	Moderate
2017, United States [65]	ICP-MS	Maternal blood, 268	28 GW	Pb	1.22 ± 0.63 µg/dL[a]	Low concentrations of Pb were associated with altered methylation patterns and were more pronounced in girls than boys (global methylation)	High
2017, United States [74]	Direct Hg analyzer	Maternal blood, 321	2nd trimester	Hg	3.8 ± 3.1 ng/g[a]	Hg was associated with hypomethylation of the *PON1* gene, this effect was sex-specific (males)	Moderate
2017, United States [86]	Direct Hg analyzer	Maternal blood, 481	2nd trimester	Hg	3.23 (3.29) µg/g	*Hg concentrations quantified in the second trimester of pregnancy associated with a lower % 5hmC and with a higher rate of change% 5mC to% 5hmC (global methylation) *Apparently, this effect is stronger in females but without statistical significance in the stratified analysis	High
2017, United States [75]	NAA	Infant toenail, 222	2.8 months after birth	As Cd Hg Mn Pb Zn	0.06 ± 0.11 µg/g[a] 0.08 ± 0.13 µg/g[a] 0.07 ± 0.10 µg/g[a] 0.98 ± 2.8 µg/g[a] 0.94 ± 2.1 µg/g[a] 299.6 ± 798.5 µg/g[a]	*High concentrations of As, Cd, Pb, Mn, and Hg were associated with *NR3C1* hypermethylation *Low concentrations of Zn were associated with hypermethylation of *NR3C1* *Stratified analysis by sex revealed interaction between Pb, Mn and Zn	High

						associated with females and *NR3C1* hypermethylation	
2017, Taiwan [87]	HPLC-ICP-MS	Maternal urine, 64	28-38 GW	As	23.19 µg/g Cr (21.2)	*579 CpG sites associated with exposure to As (Global methylation) *60% positively associated with hypermethylation	Moderate
2017,Thailand [76]	ICP-MS	Cord blood, control: 16 Exposed: 55	Delivery	As	1.97 ± 0.64 µg/g[a] 5.79 ± 0.5 µg/g[a]	Negative correlation (hypomethylation) of the three genes evaluated with As concentrations (*COX2, EGR1*, and *SOCS3*)	Moderate
2016, United States [77]	ICP-MS	Maternal toenail, 94	2.8 months postpartum	Cd	0.01 ± 0.02 µg/g	Cd was associated with hypomethylation in the promotor region of PCDHAC1	High
2015, United States [69]	ICP-MS and HPLC	Maternal urine, 138 Maternal toenail	24-28 GW 2 weeks postpartum	As Hg	0.07 (0.001-1.44) µg/g 3.19 (0.34-17.9) µg/L	Hg as well as the co-exposure of Hg and As were associated with hypermethylation of DNA (global methylation)	High
2015, United States [71]	NAA	Infant toenail, 61	1 week postpartum	Mn	0.131 to 5.666 µg/g[d]	*Mn was associated with 713loci (global methylation) *Five were significantly differentially methylated	High
2015, United States [68]	ICP-MS	Placenta, 24	Delivery	Cd	Female, 5.0 (<2.0-7.09) ng/g Male, 2.0 (<2.0-5.0) ng/g	*Cd was associated with hypomethylation in nearby areas of the *ARL9*, *SIAH3*, *HS3T4*, *CROT*, and *TP53T61* genes in females *In males, Cd was associated with hypomethylation of *MECOM* and *ARHGEF10* and hypermethylation with *SALL1*	High
2015, United States [78]	ICP-MS	Maternal blood, 319	12 GW	Cd	Male, 4.43 ± 6.66 ng/g[a] Female, 4.65 ± 5.53 ng/g[a]	*Cd was associated with lower methylation of different methylated regions of *PEG3* in females *Cd was associated with lower *PLAGL1* methylation in females with low Zn and Fe *Cd was associated with higher *PEG3* methylation in females with	High

						high Zn *Cd was associated with higher *PEG3* methylation in females with low Fe	
2015, United States [61]	AAS	Maternal blood, 35 Neonatal blood	Delivery	Pb	Low, < 5 µg/dL[c] High, >5 µg/dL[c]	Transgenerational alteration of methylation patterns in the grandchildren of pregnant women with elevated Pb (global methylation)	High
2015, United States [97]	HR-ICP-MS	Infant toenail, 192	2.8 months after birth	Hg	Low, 0.05 to 0.031 µg/g[d] Medium, 0.032 to 0.076 µg/g[d] High, 0.077 to 0.425 µg/g[d]	Hg was associated with 339 loci that were differentially methylated (global methylation)	High
2015, United States [98]	ICP-MS and ICP-DRC-MS	Cord blood, 141 Cord blood (serum)	Delivery	Hg Cu Se	1.4 (1.0-2.0) µg/L 39.7 (28.2-53.4) µg/dL 70.0 (62.0-78.0) µg/dL	Hg was associated with 4 different methylated regions (global methylation)	High
2015, Mexico [99]	HG-AAS and HG-CT-ICP-MS	Maternal urine, 38	Delivery	As	32.57 (6.2-319.7) µg/L	*2919 genes were identified with As-associated differences in DNA methylation (global methylation) *34% were hypomethylated and 66% were hypermethylated	High
2014, Bangladesh [66]	HG-AAS	Maternal urine, 127	8 GW 30 GW	As	66 (20-457) µg/L[d] 89 (18-562) µg/L[d]	As was associated with changes in DNA methylation in cord blood, the relationship was more pronounced in males (hypomethylation in 55% sites) (global methylation)	High
2014, United States [100]	ICP-MS	Maternal blood, 34	Delivery	Cd	0.44 ± 0.31 µg/L[a]	Cd was associated with 61 different methylated genes (most of them hypermethylated) (global methylation)	Moderate
	ICP-MS	Maternal urine, 127	8 GW	As	68 (20-446) µg/L[d]	*Sex-specific effects were observed on DNA methylation by Cd (global	High

				Cd	0.77 (0.25-2.4) µg/L[d]	methylation)	
2013, Bangladesh [67]		Maternal blood	14 GW	Cd	1.3 (0.54-3.1) µg/kg	*Males presented hypermethylation in genes related to cell death *Females presented hypomethylation in genes related to organ development, bone morphology, and mineralization	
2013, United States [101]	ICP-MS	Maternal urine, 134	24-28 GW	As	4.1 (1.8-6.6) µg/L	*Hypermethylation was observed in CpG islands associated with elevated As concentration (global methylation)	High
2012, Bangladesh [102]	ICP-MS	Maternal urine, 113	< 28 GW	As	1.01 ± 2.6 µg/g Cr[a]	Positive association between methylation of LINE-1 and As	High
2012, Bangladesh [89]	GFAAS and ICP-MS	Maternal Urine, 101 Maternal blood Cord blood	Delivery	As	271 ± 489.5 µg/g Cr[a] 11.9 ± 8.6 µg/L[a] Male, 16.0 ± 9.9 µg/L[a] Female, 15.3 ± 6.9 µg/L[a]	Males to exposed to As were positively associated with DNA methylation (global methylation)	High
miRNA							
2014, Mexico [80]	HG-AAS	Maternal urine, 40	Delivery	As	25.2 (6.2-319.7) µg/L	*12 miRNAs increased its expression associated by As expression. *Let-7a, miR-126, miR-16, miR-17, miR-20a/miR20b, miR-26b, miR-103, miR-454, miR107, miR-96, miR-98	High

Notes: GW: Gestational week; MMAT: Mixed Methods Appraisal Tool; AAS: Atomic Absorption Spectroscopy; ICP-MS: Inductively Coupled Plasma Mass Spectrometry; ICP-SFMS: Inductively Coupled Plasma Sector Field Mass Spectrometry; GFAAS: Graphite Furnace Atomic Absorption Spectrometry; NHBCS: New Hampshire Birth Cohort Study; RICHS: Rhode Island Child Health Study; HR-ICP-MS: ; NAA: Neutron Activation Analysis ; HPLC-ICP-MS: High-performance liquid chromatography coupled to Inductively Coupled Plasma – Mass spectrometry ; ICP-DRC-MS: Dynamic Reaction Cell for Inductively Coupled Plasma Mass Spectrometry ; HG-CT-ICP-MS: Hydride Generation-Cryotrapping and Inductively Coupled Plasma Mass Spectrometry; SG: Specific gravity. [a] Mean ± Standard deviation, [b] Geometric mean (P25-P75), [c] Categorized, [d] Rank, [d] SG-corrected

To our knowledge, this is the first systematic review that discuss adverse effects on offspring's genetic material by prenatal exposure to PTM in newborns. The reported findings strongly suggest that newborns are susceptible to develop diseases in adult life, due to the exposure during their early development and that some of these effects are sex-specific.

5. Conclusions

We were able to identify seven adverse effects on the genetic material by prenatal exposure to PTM in different populations around the world, some of them exposed to high concentrations of PTM. It is important to mention that only one effect was identified that evaluated the adverse effect in the postnatal period. Thanks to the technological development of analytical techniques and statistical analysis, it was possible to identify some interactions between potentially toxic and essential metals, identifying the ability of some essential metals, such as Cu, Se, Mg, and Zn to antagonize the toxic effects and the importance of considering their quantification in prenatal care. The literature presented in this review makes us to understand that despite the efforts of various organizations and public health policies, the problem of PTM exposure persists affecting the most susceptible populations and that many of these adverse effects were sex-dependent. Therefore, the biomonitoring of PTM and essential metals in populations at risk should continue to implement better public health policies regarding infants.

Declaration of competing interest

The authors declare that they have no competing interests.

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3. DISCUSION y CONCLUSIONES

En la presente revisión sistemática se incluyeron 57 artículos, en los cuales evaluaron los efectos adversos sobre el material genético en la descendencia por la exposición prenatal y postnatal temprana en el periodo 01/01/2010 a 30/04/2021. Se identificaron siete efectos adversos: longitud del telómero, ADN mitocondrial, expresión de genes y proteínas, metabolómica y modificaciones epigenéticas, entre ellas la metilación global del ADN, metilación especifica de genes y microRNAs. Los PTM que más se relacionaron con estos efectos adversos fueron el As, Cd y Pb. Las matrices biológicas más utilizadas para la cuantificación de los PTM fueron la orina materna, sangre de cordón umbilical y sangre materna. Adicionalmente, identificamos que algunos de estos efectos fueron específicos del sexo por parte del Cd, Hg, Pb y Tl, donde se ha hipotetizado que dicha susceptibilidad se debe a la marca de las hormonas sexuales [90,91].

El desarrollo de las técnicas analíticas ha permitido la cuantificación multielemental, lo que permite, junto con los análisis estadísticos inferir si existe una interacción entre los PTM y metales esenciales. De esta manera, logramos identificar ocho artículos en los cuales reportaron dichas interacciones, dos de ellos reportaron interacción de tipo sinérgica entre el As, Hg, Pb y Zn y seis reportaron una interacción tipo antagónica por parte de los metales esenciales como el Cu, Mg, Se y Zn, debido a que estos participan de forma activa en diferentes procesos metabólicos y forman parte del sistema de defensa antioxidante [5] mitigando el daño oxidante por parte de los PTM.

Es importante remarcar que varias de las poblaciones donde se realizaron dichas evaluaciones están expuestos de forma crónica a algunos PTM, tales como Argentina, Bangladesh, China, México y Vietnam. De acuerdo con el FOAD [62], los recién nacidos serán susceptibles a desarrollar diferentes enfermedades crónicas y cáncer en la vida

media y adulta [18, 74, 81-85], debido a que algunos PTM identificados en esta revisión, como el As, Cd, Cr^{6+} y Ni son reconocidos carcinógenos para los seres humanos de acuerdo con la IARC [103].

Interesantemente, algunos biomarcadores novedosos como la longitud del telómero y el contenido de ADN mitocondrial pueden ser de gran interés, ya que pueden indicar la susceptibilidad a enfermedades crónicas en etapas más adelante en la vida [26]. Por otro lado, hay muy pocos estudios realizados en seres humanos determinando multielementos con el uso de estos biomarcadores en poblaciones vulnerables como los recién nacidos que estuvieron expuestos a PTM antes y durante el desarrollo embrionario y fetal.

Es de nuestro conocimiento que esta es la primera revisión sistemática que discute los efectos adversos sobre el material genético por exposición prenatal y postnatal temprana a PTM. Los resultados presentados aquí demuestran que, a pesar del esfuerzo de las políticas de salud pública, aún queda mucho por resolver, ya que el problema de contaminación por parte de los PTM persiste en las diferentes poblaciones alrededor del mundo, y sobre todo, afectando a los recién nacidos que constituyen una población muy vulnerable y que podrían traer repercusiones en su vida media y adulta. Adicionalmente, se requieren más estudios multielementales en esta población vulnerable para comprender mejor el comportamiento entre los PTM y metales esenciales.