Prenatal Metal Exposure and Child Health

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1 Introduction

Metals are fundamental elements of the Earth's crust; thus, human interaction with metals is a natural phenomenon. Some of these elements are essential for normal human development and body functions such as sodium, potassium, calcium, magnesium, and zinc, while others are not required and do not come in contact that often. Although another group of metals are not required by the human body, when exposed, they cause detrimental effects on the development and produce both short-term and long-term effects after birth. The effects of exposure and its detrimental effects are influenced by the trimester (i.e., the first trimester having organogenesis being highly vulnerable) and dose and duration of the metal exposure (i.e., high-dose acute exposure and low-dose chronic exposure both produce poor effects).

As metals are components of the Earth's crust, they are widely expressed in nature though some have rare interaction with human subjects, while others interact quite frequently. Essential metals are required to be part of daily diet (Fig. 1). Nonessential or toxic metals interact with human subjects by ingestions (i.e., eating vegetables, meat, fish, and lentils having high concentration of the toxic metals), drinking (water contamination), inhalation (air pollutant metals), and topical exposure (absorption through skin). A number of metals and metalloids including lead, cadmium, mercury, and arsenic have been labeled as carcinogenic even at low dose. Ten chemicals, which include arsenic, cadmium, lead, and mercury, have been labeled as a major public health concern by the World Health Organization (WHO) due to their detrimental effects on child health [1]. The first 1000 days of

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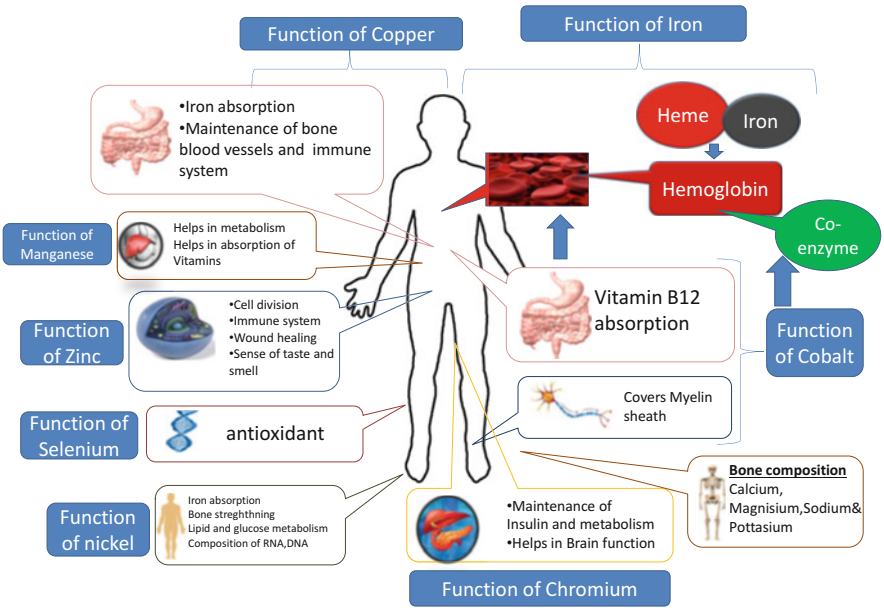

Fig. 1 Schematic diagram of the physiological functions of metals on the human body

a human's life starting from the day of conception till the second birthday are the most critical period as all the development and differentiation occur during this time [2]. The first trimester remains highly vulnerable due to organogenesis; thus, exposure during the first trimester results in most teratological effects and afterward functional disorders and deformities.

Epigenetic mechanisms are particularly involved in normal development and thus get affected in response to toxic metals [3]. The effects start as early as conception and continue throughout the prenatal period and can also occur at the postnatal period. After birth the most vulnerable system is reported to be the immune system as it continues to grow [3]. It is also an interesting finding that the direct effects on the growing fetus are obvious, but the epigenetic changes that occur in parents can be transferred to the offspring and produce transgenerational effects. These results involve environmental toxin exposure. The other most vulnerable system that remains at high risk during the developmental phase is the nervous system. However, the brain of the growing fetus has a double protection including the placental barrier from the mother, which prevents the entry of environmental toxins into the fetal environment and the blood brain barrier of the fetus, which then protects the growing brain from toxins that cross the placenta, but there still remain a number of factors that cross these barriers and produce their effects which might remain there before it becomes apparent years later [3].

In many regions of the world, exposure to toxic metals such as lead, mercury, cadmium, chromium, and arsenic has raised public health concern not only during pregnancy but also afterward with increased burden of morbidity and mortality due

to functional and morphological defects. A hospital-based case control study from Pearl River Delta was conducted to evaluate the effects of metals. Lead, chromium, cadmium, copper, mercury, and selenium were measured from maternal blood and correlated with congenital heart defects. The results suggested that the cases had a significantly higher concentration of lead and cadmium but a significantly lower concentration of copper, mercury, and selenium. However it is difficult to assess if copper, mercury, and selenium deficiency is involved in the development of congenital heart defects or they provide antagonistic effects on the toxicity of lead and cadmium [4]. Another population-based study from Sweden linked high concentration of aluminum, cadmium, lithium, lead, and mercury with autoimmune juvenile arthritis in early life [5]. Thus, metal exposure in the prenatal period appears to be significant for child health. This chapter discusses evidence on the exposure to metals and their effects on early life (i.e., the first 1000 days).

2 Metals Crossing the Placenta

The placenta is a natural shield to protect the developing human embryo from toxic elements, e.g., drugs and metals, and allows essential nutrients to reach the fetal environment. However, the placental barrier has limitation to allow some toxic compounds, including heavy metals and metalloids such as mercury, lead, and arsenic, which not only produce toxic effects during prenatal life but also have shown long-term effects after birth. The toxic substances get entry into maternal circulation by inhalation or ingestion (i.e., food and drinking water) or by absorption from skin exposure. The essential metals including iron, copper, zinc, selenium, sodium, potassium, calcium, magnesium, cobalt, and chromium needed for normal development in trace amount are collectively called as trace elements.

There are a number of studies on animals and human subjects that attempted to explore the transport of metals from maternal blood to the fetuses. These studies analyzed maternal blood for concentration and compared it with cord blood. The placental barrier allows these metals through active transport, facilitated transport, and passive diffusion. In order to understand the mechanism of transport of metals from the mother to the fetus, a study was conducted, where trace metals were measured in maternal serum, umbilical cord serum, and colostrums. The results were suggestive of active transport mechanism for manganese, calcium, rubidium, and zinc. The study showed that cesium, lithium and strontium get transported by concentration gradient, while arsenic and copper use blocking action [6].

3 Essential Metals Required for Normal Development

Metals including iron, zinc, and copper are required for normal human development and a small quantity is essential as part of dietary requirement for the maintenance of normal physiological functions (Fig. 1). There was a study on the concentration of metals including aluminum, arsenic, calcium, chromium, copper, iron, lead, magnesium, nickel, potassium, rubidium, selenium, silver strontium, and zinc from the amniotic fluid, which compared it with the fetal growth seen on the fifth and ninth month ultrasounds. The results of the study suggested that calcium has a positive association with biparietal diameter. Head circumference showed a positive association with nickel and copper, while femur length showed a positive association with selenium. Arsenic is shown to have a negative impact on fetal weight [7].

4 Teratogenic Effects of Toxic Metals

4.1 Lithium (Li)

Lithium is a soft silvery alkali metal, widely used in the industry in manufacturing batteries, heat-resistant glass, ceramic, and lithium-grease lubricants. It is utilized by the human body in trace amount. It is found in vegetables, grains, and drinking water where humans can be exposed. In addition, it is used in medication as a mood stabilizer and in bipolar disorders. Lithium crosses the placental barrier radially and the concentration fluctuates during pregnancy, where it decreases during the first trimester, starts to increase in the second trimester, and considerably increases during the third trimester [8]. It also shows a slight increase in the postpartum period. The literature suggests a significant difference in cardiovascular anomalies and abortions in the lithium-exposed group during pregnancy; however, there was a nonsignificant pattern of other genetic and cytogenetic anomalies in the offspring [9]. A systematic review was conducted including 72 studies on lithium and antipsychotic exposure during gestational period [10]. Out of them, seven preclinical studies and three clinical studies looked at the effects of lithium. The preclinical studies were conducted on rats, mice, and zebrafish. The studies showed slow brain responses in preclinical experiments; however, there was limited research on human subjects, which did not show any significant effects. Nevertheless, based on limited data, dose adjustment on lithium is recommended for women if they conceive. Another detailed review was conducted exclusively on lithium, and the cardiovascular anomalies were reported to be associated with lithium exposure; the Ebstein anomaly (tricuspid valve defect) has been reported by a number of studies, while some studies negated the association [9, 11, 12].There is literature showing a low 1-min APGAR score, high rate of jaundice, and longer hospital stay during the neonatal period [13]. Small case reports have also shown evidence of slow brain responses like hypotonia, lethargy, etc., though there is inadequate robust data confirming this finding.

Given the association of lithium exposure with slow brain development in animal models had not addressed the genetic predisposition to neurodevelopmental growth, the mother having bipolar disorder or depression and the child having slow mental growth and reflexes could be a genetic link rather than an influence of lithium. Table 1 summarizes the recent studies on lithium exposure and its effects on human development and early life. Nonetheless it has been advised to have a careful fetal monitoring during pregnancy when there is lithium exposure (Fig. 2).

4.2 Aluminum (Al)

It is one of the most commonly occurring metals in the Earth's crust and human beings get exposed to the metal quite often. It is widely used in the transportation industry, aerospace technology, and the construction industry. It has been reported to be noncarcinogenic and less likely to be accumulated in the body in normal physiological mechanisms for its excretion in urine and feces. Aluminum toxicity commonly occurs due to high intake in the form of medication (i.e., patients on parenteral nutrition) or decreased excretion (as it is excreted by kidneys, i.e., patients with compromised renal function) [14]. Premature neonates are also among the high-risk population. Aluminum used to be considered a nontoxic inert element until recently when animal data showed its toxic effects on genetic make-up and metabolic bone disease due to the inhibition of bone mineralization, by competing with calcium [14]. It is also reported to compete with Vitamin D. A detailed review on effects of aluminum in animals including mice and rats showed that prenatal exposure causes low but considerable effect on growth and is associated with delayed bone ossification and even malformations [15]. A recent study on humans was conducted to assess mitochondrial DNA copy number (mtDNAcn) in fetus in association with maternal urinary aluminum. A summary of the studies is given in Table 1. There is literature suggesting the neurotoxicity of aluminum in rats and mice. However oral aluminum intake has not been linked with any detrimental effects.

4.3 Technetium (Tc)

Technetium is a silvery grey transition metal, most commonly occurring as technetium 99 (99Tc). It is widely used in nuclear imaging as a radioactive tracer due to its penetration to many organs and clear metabolism. It is also used in the industry but human exposure mainly occurs while imaging. The study was conducted to assess the safe dose for workers in the radiology department dealing with CT using 99Tc [16]. The study suggested to limit the radiation exposure to 1.3 mSv corresponding to six adult studies on 99Tc CT scans. In a study on intrauterine death of the fetus, Tc99 was evaluated to be deposited in the brain, liver, and kidneys [17]. Older studies have also suggested the excretion of Tc99 in milk [18]. The technetium binds

Table 1 Summary of the studies on the prenatal exposure of toxic metals

S No	Author	Study type	Exposure type	Key findings		
Lithium						
01	Kindgren E et al. (2019) [5]	Registry-based prospective cohort study	Lithium was assessed in cord blood and correlated with juvenile idiopathic arthritis	High lithium concentration was significantly associated with development of autoimmune juvenile idiopathic arthritis		
02	Fosberg L et al. (2018) [47]	Retrospective cohort	1. Maternal mood disorder only 2. Lithium exposure 3. No MMD no lithium	No significant association was found between lithium and children's intelligent quotient		
03	Diav-Citrin O et al. (2014) [9]	Prospective comparative study	1. Lithium exposure group 2. Nonexposed	Outcome measure	Exposed	Nonexposed
				Miscarriages	9.3%	2.0%
				Cardiovascular anomalies	4.1%	0.6%
				Non-cardiovascular anomalies	13.7%	6.0%
04	Harari F et al. (2012) [48]	Prospective population-based cohort study	Blood and urine concentration of lithium was measured and compared with fetal size on ultrasound during the 2nd and 3rd trimesters	Increased serum lithium concentration was associated with shorter size of the fetus		
Aluminum						
01	Kindgren E et al. (2019) [5]	Registry-based prospective cohort study	Aluminum was assessed in cord blood and correlated with juvenile idiopathic arthritis	High aluminum concentration was significantly associated with development of autoimmune juvenile idiopathic arthritis		
02	Bingqing Liu et al. (2019) [49]	Prospective cohort study	Urinary aluminum was measured in all three trimesters and fetal cord blood was assessed for mtDNAcn	Rise in urinary aluminum in the second and third trimesters was associated with increased mtDNAcn		
03	Liu Z et al. (2018) [50]	Multicenter hospital-based case control study	Aluminum was measured in umbilical cord serum	High aluminum level was associated with cardiac anomalies		
Technetium						

01	Schaefer C et al. (2009) [20]	Prospective cohort study	Fetal outcome of the pregnant women had 99Tc scans with those who were not exposed	There was no significant pattern of birth defects or additional abnormality was found in the exposed group
Cadmium				
01	Kindgren E et al. (2019) [5]	Registry-based prospective cohort study	Cadmium was assessed in cord blood and correlated with juvenile idiopathic arthritis	High cadmium concentration was significantly associated with development of autoimmune juvenile idiopathic arthritis
02	Wang Y et al. (2015) [51]	Prospective cohort study	Maternal blood was collected at the time of delivery and cord blood was collected for assessment of brain-derived neurotrophic factor (BDNF) and Gesell Developmental Schedules (GDS)	Maternal blood cadmium level showed negative association with fetal GDS scores and BDNF
03	Xu X et al. (2015) [52]	Prospective cohort study	KISS1 gene was analyzed in the cord blood	Low birth weight was associated with cadmium exposure and overexpressed KISS 1 gene
04	Yanqiu Ou et al. (2017) [4]	Hospital-based case control study	Cadmium level was measured in maternal blood and correlated with congenital heart defects	Significantly higher level of cadmium was found in cases as compared to controls
Vanadium				
01	Jie Hu et al. (2018) [53]	Prospective cohort study	Urine samples for vanadium concentration and fetal ultrasound at 16, 24 and 31 weeks	High concentration of vanadium during the first trimester, early second trimester, and late third trimester was associated with restricted fetal growth
02	Jie Hu et al. (2017) [54]	Population-based cohort study (healthy baby cohort)	Urinary vanadium and creatinine levels were measured	High risk of preterm and early term delivery, low birth weight, and smaller babies for gestational age were associated with vanadium exposure
03	Minmin Jiang et al. (2016) [55]	Nested case-control study	Urinary vanadium measured at delivery (i.e., 39 weeks)	A pattern was observed with high maternal urinary vanadium concentration with low birth weight

(continued)

Table 1 (continued)

S No	Author	Study type	Exposure type	Key findings
Lead				
01	Pi X et al. (2018) [56]	Case control study	Concentration of lead in placental tissue was measured and correlated with orofacial clefts	High concentration was associated with high risk of orofacial cleft
02	Yanqiu Ou et al. (2017) [4]	Hospital-based case control study	Lead level was measured in maternal blood and correlated with congenital heart defects	Significantly higher level of lead was found in cases as compared to controls
03	Silver MK et al. (2016) [57]	Prospective cohort study	Prenatal maternal blood lead during pregnancy and from cord blood were correlated with visual and auditory maturation	Exposure to lead during late pregnancy appears to be associated with delayed visual and auditory maturation
04	Shah-Kulkarni S et al. (2016) [58]	Prospective cohort study	Prenatal maternal blood lead level was measured and children's neurodevelopment was assessed at 6, 12, 24, and 36 months	Lead exposure in particular at late pregnancy produce detrimental effects on cognitive function
05	Liu Z et al. (2015) [50]	Case control study	Maternal hair lead measurement in cases and controls was compared with congenital heart defects	The high level of maternal lead was associated with subtypes of congenital heart defects
06	Hong YC et al. (2014) [59]	Prospective cohort study	Maternal blood levels were measured and correlated with child growth at 6, 12, and 24 months	Lead exposure in late pregnancy was associated with reduced infantile growth at 2 years
07	Mohsin Vigeh et al. (2014) [60]	Prospective cohort study	Blood lead level measured during pregnancy (each trimester), cord blood and early childhood development in pre-school children	Maternal lead level in the first trimester was inversely proportional to developmental scores
Thorium				
01	Wei Y (2019) [61]	Case control study	Scalp hair concentration at periconceptional (3 months before to 3 months after pregnancy) period	High thorium concentration showed strong association with high risk of orofacial clefts
Molybdenum				
01	Vazquez-Salas RA et al. (2014) [62]	Prospective cohort study	Apparently healthy women with normal pregnancy were chosen. Urinary molybdenum was assessed during pregnancy and correlated with neurodevelopmental and mental development indices up to 30 months of age	High urinary molybdenum was significantly negatively associated with infant neurodevelopment

Cesium				
01	Callan AC et al. (2016) [63]	Cross-sectional study	Maternal urinary samples were collected 2 weeks before delivery and fetal outcome details were recorded from medical record of the time of birth (i.e., Baby book)	Cesium was associated with low birth weight in female fetuses
Barium				
01	Pi X et al. (2019) [64]	Case control study	Barium concentration was measured from placental tissue and correlated with the orofacial cleft	There was significant association of barium concentration and orofacial clefts
02	Zhang N et al. (2018) [65]	Case control study	Barium concentration was measured from the mother's hair and fetal placenta and correlated with congenital heart defects	There was significant difference in the presence of septal defects, conotruncal defects, right and left ventricular outflow track obstruction, and abnormal pulmonary venous system
03	Callan AC et al. (2016) [63]	Cross-sectional study	Maternal urinary samples were collected 2 weeks before delivery and fetal outcome details were recorded from medical record of the time of birth (i.e., Baby book)	Barium was associated with increased birth length and proportional of optimal birth weight and reduction ponderal index in male fetuses
04		In vitro study	Colostrum phagocytes were evaluated for the effects of barium contamination	Increased apoptosis and superoxide release and decreased viability
05	Han BH (2011) [66]	Prospective cohort study	Fetal outcome was correlated with the inadvertent use of barium and ionizing radiation during pregnancy and controls were not exposed	No significant difference in the fetal outcome of cases and controls
06	Han BH et al. (2010) [67]	Prospective cohort study	Women exposed to barium and ionizing radiation	There was no significant teratogenic effect of barium
Mercury				
01	Kindgren E et al. (2019) [5]	Registry-based prospective cohort study	Mercury was assessed in cord blood and correlated with juvenile idiopathic arthritis	High mercury concentration was significantly associated with development of autoimmune juvenile idiopathic arthritis
02	Yanqiu Ou et al. (2017) [4]	Hospital-based case control study	Mercury level was measured in maternal blood and correlated with congenital heart defects	Significantly lower level of mercury was found in cases as compared to controls
03	Pi X et al. (2019) [64]	Case control study	Mercury concentration was measured from placental tissue and correlated with the orofacial cleft	There was borderline significant association of mercury concentration and orofacial clefts

(continued)

Table 1 (continued)

S No	Author	Study type	Exposure type	Key findings
04	Barbone F et al. (2019) [68]	Cohort study	Total mercury level was measured as sum of the hair, maternal blood, cord blood, and milk and correlated with neurodevelopment	The higher total mercury concentration was associated with lower neuronal development of the child at 18 months age
05	Kim Y et al. (2018) [69]	Cohort study	Mercury concentration in maternal and cord blood was measured and correlated with neurocognitive development of child	Mercury concentration was associated with neurocognitive development of child
Thallium				
01	Qi J et al. (2019) [70]	Prospective cohort study	Maternal blood samples were collected at the first and second trimesters and cord blood sample was collected at birth	Umbilical cord concentration of thallium was negatively association with weight of the fetus according to age
Arsenic				
01	Mullin AM et al. (2019) [71]	Prospective cohort study	Maternal arsenic level was measured in the second and third trimesters, at delivery, and from cord blood and correlated with fetal weight	High arsenic concentration at the third trimester was associated with low birth weight
02	Suhl J et al. (2018) [72]	Case control study	Interview-based information collected for arsenic exposure and correlated with orofacial clefts	Significant association was found between arsenic exposure and cleft palate in infants
03	Wang B et al. (2018) [73]	Cross-sectional study	Arsenic was measured from umbilical cord blood and correlated with neurodevelopment at the 3rd day of life	There was inverse relationship of arsenic concentration with neurodevelopment of newborn
04	Liao KW et al. (2018) [74]	Cohort study	Arsenic concentration was measured in maternal urine and correlated with fetal growth features	High arsenic concentration was associated with low birth weight and head and chest circumference
05	Huyck KL et al. (2007) [75]	Cohort study	Arsenic concentration was measured in maternal hair, toenail, and drinking water samples and correlated with birth weight	High arsenic concentration was associated with low birth weight

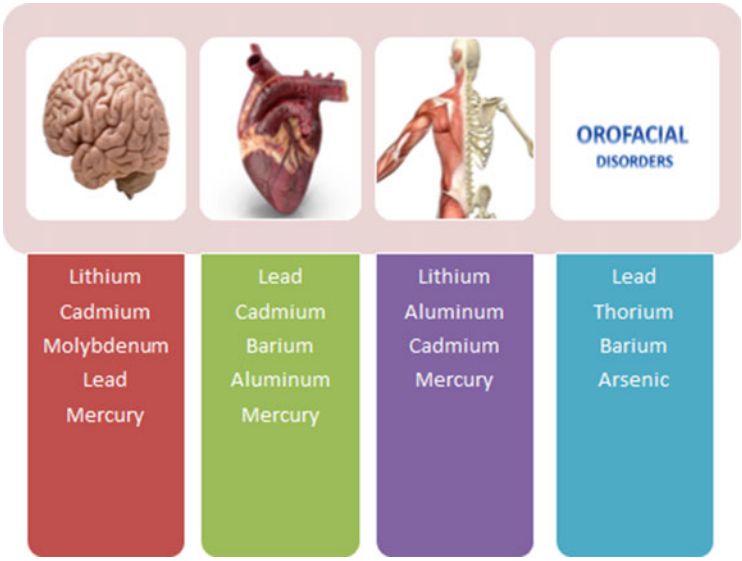

Fig. 2 Summary of the systemic toxic effects of prenatal metal exposures

to the placenta and a small amount crosses to reach the growing fetus, where it is suggested to be deposited mainly in the liver and to some extent in the brain tissue and kidneys [19]. Nonetheless it is reported to be safe [20] (Table 1).

4.4 Cadmium (Cd)

Cadmium is a silvery white metal, commonly used for manufacturing batteries, pigments, coating, and electroplating. It is also used in laboratories with helium to produce blue ultraviolet laser light. The common exposure to human occurs by inhalation. There is limited literature available that suggests its carcinogenic effects, as well as cardiotoxic (i.e., congenital heart defects) and bone effects (juvenile idiopathic arthritis). In younger children cadmium was associated with adiposity in girls [21]. Rat models have shown increased breast buds and enhanced mammary gland development as a result of cadmium exposure [22]. Preschool children have shown negative association with the mother's urinary cadmium concentration during pregnancy [23]. A summary of the studies is given in Table 1.

4.5 Vanadium

It is a silvery grey transition metal, used in the industry in making steel alloy and stab zig titanium and combining lithium, which are then used for different purposes. Vanadium is an essential trace element required in a small quantity (i.e., 10 μg/day) and consumed from olive oil, peanuts, etc. Vanadium concentration has been shown to be associated with premature rupture of a member in a Chinese cohort [24] and low birth weight [25]. The National Institute for Occupational Safety and Health considered high exposure to be toxic and made a limit over 35 mg/m^3 to be injurious to health. The fetal exposure of vanadium has been studied in rats showing its effects on the body systems, including nervous, cardiovascular, respiratory, and musculoskeletal systems. A summary of the studies on human subjects is presented in Table 1.

4.6 Lead

It is a silvery grey post-transition metal. Lead is an essential trace element. Adults can only accumulate 1% of lead which then mainly gets stored in bones, while in children half of the lead is stored. However, when the developing fetus is exposed to a higher concentration (i.e., $\geq$5.0 μg/dl of maternal blood), it poses risk of mental and behavioral abnormalities. It readily crosses the placenta and gets accumulated in the developing fetus, given that the developing fetus has a less developed system for excretion. Studies have also shown the association of lead exposure with low birth weight and preterm labor [26, 27]; however, confounding factors were not appropriately addressed. Lead exposure is also linked with difficult temperament in toddlers (i.e., 24 months) [28]. Cognitive impairment and high blood pressure have been reported in exposed children [29, 30]. A summary of the studies is presented in Table 1.

4.7 Thorium

It is a silvery and tarnish black actinide metal found in large quantities in the Earth's crust. It is highly radioactive. The most common source of exposure is ingestion and the skeleton is the likely site for deposition. There is limited literature available studying the effects of thorium on human subjects. A small case control study linked high thorium concentration with orofacial cleft; however, further substantial evidence is still awaited (Table 1).

4.8 Molybdenum

It is a silvery transition metal considered to be an essential trace element in the human body. However limited literature is available to associate its high prenatal exposure with development issues in the nervous system. A summary is given in Table 1.

4.9 Cesium (Cs)

It is a silvery golden alkali metal, nearly liquid at room temperature. Cesium is most widely used in drilling of earth. The radioactive form cesium^{137} has uses in the industry including medical applications in radiotherapy for the treatment of cancer. The research activities conducted after the Chernobyl accident in April 1986, where there was a huge release of radioactive substances in the environment, including cesium^{137} showed that immediately after the accident, the contamination was high but with passage of time, it was reduced to a low dose. The women were exposed to cesium by eating vegetables and fruits and drinking contaminated water [31]. However the data from registries for the entry of the congenital defects and developmental anomalies did not appear to show any rise attributable to the accident [32]. The animal studies on rats showed that fetal and after birth continuous exposure to cesium disturbs cholesterol metabolism at the genetic level [33]. Fort M et al. studied the concentration level of a number of alkali metals and showed that cesium concentration was high in the first trimester as compared to the third trimester [34]. A small cross-sectional showed association of cesium exposure with low birth weight (Table 1).

4.10 Barium (Ba)

It is a silvery white alkaline earth metal. Barium sulfate in insoluble form is used as a contrast medium for imaging of the gastrointestinal tract. Barium in insoluble form does not cause any harmful effects but in soluble form at low dose acts as a muscle stimulant while at high concentration is neurotoxic. However, there is data available suggesting barium as a safe contrast medium during pregnancy though low-dose chronic barium exposure causes toxic effects. Table 1 summarizes the studies exploring the exposure of barium during pregnancy. Some studies have shown its exposure in pregnancy to be linked with orofacial defects and congenital cardiac anomalies.

4.11 Mercury (Hg)

It is silvery grey in color and the only liquid metal. It comes in contact in two forms: inorganic and organic. Inorganic mercury interacts via dental amalgam which is used for dental fillings while organic forms including methyl and ethyl forms interact via sea food and medical preparations, respectively. The toxicity from mercury occurs by inhalation and ingestion in any form. A summary of the recent studies is presented in Table 1 suggesting its association with cognitive and neurodevelopment. It has been linked with genetic methylation resulting in cognitive effects. Mercury exposure has been reported to be linked with low birth weight and growth restrictions. However, the evidence is not that strong but it is recommended that pregnant women should avoid mercury exposure.

4.12 Thallium (Tl)

It is a grey post-transition metal. Its isoform thalium^{201} is used for cardiography to evaluate the risk of coronary artery disease. It is labeled as an extremely toxic element and has been linked with carcinogenesis. There is evidence available suggesting low birth weight when exposed during pregnancy (Table 1). In animal models there is suggestion of achondroplasia but there is a lack of substantial evidence in human subjects.

4.13 Titanium

It is a silver transition metal, which is used with other metals, including iron, which is then used in aerospace technology. It is also used in making medical implants (orthopedic and dental) and sports stuff and the mobile industry. It is also used in making paints, papers, toothpastes, and plastics. Given its noncorrosive property, it is used to store nuclear material for a long time. Titanium oxide nanoparticles were evaluated for toxicity in human fetal lung fibroblasts and showed its toxic effects causing mitochondrial dysfunction, morphological changes, and eventual apoptosis [35]. Most of the studies were conducted on mice, rats, and zebrafish showing its association with genetic expression alterations and phototoxicity [36, 37]. Mouse model studies have also shown its influence on inhibiting central nervous system development by using nanoparticles by altering gene expression [38].

4.14 Boron (B)

It is a black-brown metalloid, rarely occurring element in the Earth's crust. The highest quantity of boron is found in Turkey. It is used in fiberglass, polymer, and the ceramic industry. It has insecticidal and mild antimicrobial properties. Given its plant cell strengthening properties, it is used in small amount as fertilizer but there is a lack of substantial evidence to suggest its essential role in the human body. It is suggested to be required for bones in wound healing. It has been reported to have antioxidant property as well. Its higher maternal serum concentration has been observed to be associated with smaller and low-birth-weight babies [39]. The main source of boron exposure is drinking water. Small boronated particles are widely used in the industry, agriculture, and even cosmetics. There is no evidence to suggest its mutagenic effects but there is some evidence suggesting its association with developmental defects such as testicular toxicity [40].

4.15 Arsenic (As)

It is a metalloid, grey-colored chemical commonly used in the industry. It is also found in yellow and black colors. It is used in car batteries and ammunition with lead. Arsenic contamination is a major health issue in many countries such as Pakistan, China, and Bangladesh. It is toxic to many bacteria, viruses, and fungi and thus has become famous for wood preservation. Arsenic is a trace element required for some functions in the human body; however, its higher exposure in particular food and drinks results in many harmful effects on the body. It has been labeled as carcinogenic. An interesting study was reported from Chile where there was a particular pattern of bladder cancer. Eventually it was found that the patients were exposed in arsenic in utero. Arsenic has been reported to be associated with DNA damage in a cohort study [41]. There has been a strong association of arsenic exposure in prenatal life and development of cancer and diabetes later in life [42, 43]. A summary of the studies on arsenic is presented in Table 1. There has been association with still birth and high mortality. Due to the low birth weight, small size, and less developed immunity of babies, they are at higher risk of infections resulting in high mortality and morbidity among infants.

4.16 Indium (In)

It is a silvery white post-transition metal used in the industry. It gets entry into the human body by injection, ingestion, and inhalation. There is no known physiological role of indium but it is used as indium 111 in radiotracer for the movement of labeled proteins in white blood cells. Mostly the exposure is occupational; as a result of its

potential toxic effects, the per day work limit is restricted to 8 hours. There is limited data available on human subjects but studies on rats showed inhibitory effects of indium on chondrogenic ossification of the bones. In addition a study also suggested that the concentration of indium in the fetus was half of the mother's due to the placental barrier [44].

5 Metals with Limited Evidence of Effects on Human Intrauterine Development and Body Functions

There are some rarely occurring metals which do not come in contact with human beings and even rarer when it comes to pregnant women. These metals are listed in Table 2. The available literature on these metals is mainly derived from animal studies including mice, rats, and zebrafish. Some studies also used goats, frogs, and shrimps as well. The evidence of their effects on growing humans is rare. Moscovium is a synthetic short-lived element produced in the laboratory. It is a manmade element without much of known uses. Livermorium (Lv) is a highly radioactive synthetic element made from shower curium on calcium. It is very short lived (61 ms) and is produced in the laboratory; thus, there is a thin chance of exposure in prenatal life. Polonium is measured in the placenta (i.e., 27.8 pg/100 gm), 80 times higher than the recommended concentration when diet taken is high in polonium. The main source of polonium is animal meat. Antimony has shown an inverse relationship between umbilical cord blood level and birth weight. Gold was studied on mice and rats which have shown toxicity of gold on reproductive organs (i.e., ovary and uterus) [45]. Gold nanoparticle exposure at early pregnancy was associated with abortions in mice [46]. Germanium is a grayish white metalloid commonly used as transistor in making electronic items. It is not considered to be used in human body systems and it is reported to be toxic to the kidneys when orally ingested in soluble form. In Japan it is used in making polyethylene terephthalate (PET) bottles. As naturally occurring germanium is found in small quantity, less likely exposure at mass is expected. However, its synthetic compounds such as germanium chloride irritate the eyes and skin on exposure, and when inhaled, it causes irritation of the throat and lungs.

Silicon is the most commonly occurring metalloid in the Earth's crust, with a blue-grey crystal solid texture. It is used in the construction industry and making of electronic devices. It is considered as an essential trace element in the human body because of its use in bone strengthening and the formation of elastin and cartilage which is a key component of major vessels (i.e., aorta). This is the most widely occurring element and exposure is very common. Inhaled silicon causes lung irritation resulting in silicosis, an occupational disease. However, exposure in utero is less well studied. Cerium is a soft silvery white, rare-earth metal. Cerium oxide is widely distributed in nature and humans get easily exposed. A number of studies have been conducted to explore the effects of growing fetuses. However, the studies used animals including mice to study contact. There are studies suggesting

Table 2 Summary of metals with limited evidence on human subjects

(a) Metals with toxicity evidence from animal and in vitro studies			
S#	Name of metal	Tissues studied	Target organ/system
01	Beryllium	Chicken, human lung cell lines	Inhibits fibroblast in lung tissue
			Affects in vitro phalangeal growth of chicken
02	Californium	Mouse, rats	Carcinogenesis
03	Antimony	Fetal urine concentration	High fetal urine concentration was seen in pre-mature infants
04	Scandium	Nothing	
05	Titanium	Mouse, zebrafish	Increased risk of phototoxicity, genotoxicity, brain developmental anomalies
06	Gallium	Mouse, zebrafish, pulmonary cell lines	Limited evidence on zebrafish embryo toxicity
07	Polonium	Guinea pig, goat, rat, mice	Polonium crosses the placenta
08	Ruthenium (Ru)	Limited information	Used in diagnostic and treatment process but no studies on its effects on developing human
09	Palladium (Pd)	Cell lines, zebrafish	1. Anti-angiogenic activity
			2. Zebrafish embryo showed expression of metal-induced genes and antioxidant enzyme downregulation
(b) Metals with no evidence of toxicity on humans			
01	Rubidium		
02	Strontium		
03	Rhodium		
04	Praseodymium		
05	Neodymium		
06	Holmium		
07	Erbium		
08	Lutetium		
09	Hafnium		
10	Rhenium		
11	Iridium		
12	Platinum		
13	Francium		
14	Radium		
15	Actinium		
16	Protactinium		
17	Uranium		
18	Plutonium		

toxic effects on testicular development and impairment of lung development. However, its rare occurrence indicates less exposure to human beings; therefore, it is less likely to cause toxic effects in masses. Gadolinium is a silvery white earth metal used as a contrast medium for MRI. The pure form is highly toxic but the toxicity of the

chelated form is negligible. Although there is limited data available suggesting the toxicity of gadolinium in developing human beings or pregnant women, the FDA recommends its use with caution due to the risk of gadolinium deposition disease.

6 Conclusion

Metals have various effects on the human body ranging from normal physiological effects to detrimental effects on body systems. Lead, aluminum, mercury, lithium, arsenic, cadmium, and vanadium are reported to be toxic when a fetus is exposed. They not only have effects on the fetus by reducing birth weight but also produce long-term effects. The nervous system appears to be the most affected system in utero followed by the cardiovascular system. Other systems such as gastrointestinal, biliary, genitourinary, endocrine, and immune are not well studied.

The expanding exposure of metals during prenatal period and the working environment making pregnant women exposed to rarer metals warrant further research not only on frequently occurring metals but also on rarer elements to predict their detrimental effects and make strategies for prevention.

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