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Heavy metals and placental fetal-maternal barrier: a mini-review on the major concerns

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Abstract. – BACKGROUND: Heavy metals (HMs) are environmental contaminants with toxic properties for wildlife and humans. The placenta is a privileged organ that, along with the fetal membranes and amniotic fluid, enables growth and development of the fetus during the physiological pregnancy. It also acts as a filter reducing the passage of harmful substances, protecting the embryo and then the fetus from exposure to pollutants. The placental barrier is not completely impermeable to the passage of harmful substances; indeed, HMs were detected not only in placental tissues, but also in amniotic fluid and umbilical cord blood. The amniotic fluid can be considered as a valuable marker of prenatal exposure to exogenous factors, and as an indicator of the integrity of placental barrier. The effect of an intrauterine exposure to heavy metals has been amply evaluated during the last decades. Several studies investigated the exposure to HMs in order to evaluate the mechanism of placental transfer and the impact on fetuses and later children's health. In particular, the early exposure to Pb, Hg, and Cd was correlated to infant health effects, such as neurological, developmental, and endocrine disorders. The aim of this mini-review is to summarise the current state of knowledge about the interaction between HMs and placental barrier, considering possible implications on fetal health.

Key Words:
Heavy metal, Lead, Mercury, Cadmium, Placental barrier, Pregnancy.

Introduction

The increasing pollution originated from industrialization exposes the entire population to several toxic agents such as heavy metals, organic hydrocarbons, and pesticides[1]. Therefore, the overall population may undergo a daily exposure to these pollutants through several pathways, including inhalation of contaminated air, consumption of contaminated drinking water, exposure to contaminated soils or industrial waste, or consumption of contaminated food[2,3]. Several substances which share the ability of interfering with the female reproductive system are possibly implicated in the development of gynecological pathologies[4]. Hence, considering reproductive health as a continuum from gamete production and fertilization through to intrauterine and postnatal development of progeny, a crucial role could be attributed to these pollutants in the loss of endocrine and metabolic balance in a such delicate stage[4,5]. For instance, epidemiological studies documented an association between agricultural occupation and the incidence of infertility, congenital malformations, miscarriage, low birth weight, small-for-gestational-age birth, preterm delivery and stillbirth[6]. Heavy metals (HMs) are environmental contaminants with toxic properties for wildlife and humans[7-9]. In this view, studies are required to investigate the factors contributing to early exposure to HMs and to determine how placental transfer of these toxic compounds may affect fetuses and later children's health.

Fetal exposure to environmental factors occurs through the amniotic fluid (AF), the placenta, and the umbilical cord. It has been widely demonstrated that the placental barrier is not completely impermeable to the passage of harmful substances, such as drugs or toxic agents[10]. Since the AF is similar to fetal plasma composition from 10 to 20 week of gestation, it can be considered as a valuable marker of prenatal exposure to exogenous factors, and as an indicator (especially until the 20th week of gestation) of the integrity of placental barrier[11,12]. Whereas data on high-level exposure to the HMs are well known for animals and humans[13-16], evidences on the effects of the environmental exposure on the placental fetal-maternal compartment are limited.

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The aim of this mini-review is to summarize the current state of knowledge about the interaction between HMs and placental barrier, considering possible implications on fetal health.

We reviewed the international literature in order to identify papers focusing on heavy metals and fetal-placental barrier. PubMed, Medline and Google scholar databases were searched for English language studies by using the following key words: heavy metals, environment, pollution, cadmium, lead, mercury, arsernic, placenta, amniotic fluid, fetal health, birth outcomes, fetal neurotoxicity.

Principal Heavy Metals Involved in Human Health

The term "heavy metal" has been increasingly used in literature during the last twenty years in reference to environmental pollution and toxicity of chemical compounds. According to the review written by Duffus in 2002[17], there is no authoritative definition of HMs in the relevant literature. However, they are traditionally defined on the basis of their density. Prasher et al[7], in 2009, defined HMs as chemical elements with a specific gravity that is at least five times the specific gravity of water. Although there is no clear definition of "heavy metal", density is often considered to be the major factor. Thus, HMs can be defined as chemical compounds having a specific density[8] of more than 5 g/cm^3. In small quantities, certain HMs are essential nutrients for a healthy life, belonging to the so-called "essential elements" group (e.g. iron, copper, cobalt and zinc). These elements are naturally present in specific foods (i.e. seafood, fruits and vegetables)[11]. Due to the industrialization era, anthropogenic sources of HMs, such as pollution, have been introduced to the ecosystem. Arsenic, beryllium, cadmium, chromium, lead, manganese, mercury, nickel, and selenium are some of these so called HMs (due to their high relative atomic mass) which persist in nature and can cause damage or death in animals, humans, and plants even at very low concentrations[8]. The available literature reported as potential causes of different long-term effects the exposure to antimony (Sb), arsenic (As), beryllium (Be), cadmium (Cd), cesium (Ce), chromium (Cr), cobalt (Co), copper (Cu), gallium (Ga), gold (Au), iron (Fe), lead (Pb), manganese (Mn), mercury (Hg), nickel (Ni), platinum (Pl), silver (Ag), trillium (Te), thallium (Tl), strontium (Sr), uranium (U), vanadium (V) and zinc (Zn)[18,19].

HMs are detrimental for human health through several exposure pathways and multiple biological targets; thus, the accurate study of this pathogenetic mechanism is one of the major issues in the assessment of toxicological risk in the environment[11,20]. HMs can damage human health through an oxidative cell stress (e.g. Cd, Cr, Pb, As)[11,21,22], neurological damage (e.g. Pb, Hg)[23,24], DNA injury (e.g. As, Cr, Cb)[22,25,26], altered glucose (As)[27], or calcium (Cd, Pb)[28,29] metabolism, and they can interfere with essential elements (Cd, Hg)[30.31]. HM exposition affects a broad range of targets, such as immune[32], neurological[33,34], renal[21,35], endocrine[27], and reproductive health[4,6,11,36,37]. Moreover, human health damage could be the result of an endocrine disruption due to HM, such as cadmium[38,39].

HMs have been shown to adversely affect placental functions[40]. During pregnancy, the placenta behaves as a very active transporter of essential elements (calcium, copper, zinc, and iron), and toxic elements (cadmium, mercury, nickel) to the developing fetus[41-43]. Placenta acts as a selective fetal-maternal barrier allowing nutrients and oxygen to pass in the fetus, and possibly preventing potentially harmful compounds from crossing[44]. It is, however, demonstrated that HMs can pass through the placenta and eventually accumulate in fetal tissue. In the subsequent section the main properties of the placental barrier will be analyzed and HMs involved in the maternal-fetal deregulation will be described.

Heavy Metals and fetal-Maternal Balance: the Placenta Model

The placenta is a privileged organ that, along with the fetal membranes and AF, enables growth and development of the fetus during the physiological pregnancy[45]; it establishes an interface between maternal circulation and the fetus and it regulates the transport of gases, nutrients and waste products[46]. It also acts as a filter reducing the passage of harmful substances, protecting the embryo and then the fetus from exposure to pollutants. The detoxification process is also ensured by macromolecular proteic complexes expressed on the cell membranes in the placenta. They act as transporters, bringing unwanted substances back into the maternal circulation, and as filterers agents, preventing the passage of harmful agents. If these activities are pursued through the binding of toxic agents, some placental functions may be altered, such as the transport of certain elements that are essential for both the growth and the development of the fetus[30,47].

Placental tissue has been used in clinical studies as a readily available specimen, as an alternative to the more invasive matrices such as maternal plasma or AF[48]. Moreover, due to its reliability, it has been defined by some authors as a dual biomarker for toxic metals in order to assess both maternal and fetal health[44].

In the last decades several studies investigated possible interactions between toxic elements and placental tissue: today, it has been widely demonstrated that several toxicants and drugs are transferred by the placenta to the product of conception (Figure 1)[49,50]. In particular, several HMs, such as lead, mercury and cadmium are known to alter the delicate maternal-fetal balance, potentially causing long-term damage to the newborns[40,51].

At the end of the first trimester of pregnancy, the extravillous trophoblast invades the tunica muscolaris in the arterioles spiralis; thus, an effective maternal blood flow is established in the intervillous space.

In humans, the placenta barrier is mainly composed by three components: syncytiotrophoblast (that covers the surface of chorionic villi, delimiting the intravillous space), cytotrophoblast (subjacent to the syncytiotrophoblast and supported by a basal lamina) and fetal endothelial cells. Together, these three elements separate fetal blood from the intravillous space[53].

The cytotrophoblast, until the 12th week of gestation, is made up of a continuous layer of cuboidal cells; since the second trimester of pregnancy, it becomes discontinuous. This leads to the formation of the so-called "vasculosyncytial membrane", in which syncytiotrophoblast comes in close with fetal endotheliocites. These structural changes of the chorionic villi facilitate the fetal-maternal transport of nutrients, gases, and exogenous molecules[53,54], and are responsible for a thinning of the fetal-placental barrier.

Thickness of the placental layers is one of the most important determinants that affects permeability and bi-directional transfer of substances in the maternal-fetal district[53,54].

Another determining factor in the permeability to exogenous substances is the presence of membranous transport mechanisms. According to the previous literature, they can be briefly summarized as: passive transport, in which energy consumption is not contemplated (i.e. osmosis, simple diffusion); active transport, in which molecules are transported through the cellular membrane against a concentration gradient, employing energy; vesicular transport, in which macro-molecules are adsorbed or repelled from the cells by the microvilli caption[40].

To date, several authors have investigated about toxicokinetics and toxicodynamic properties of main HMs in the human placenta[40].

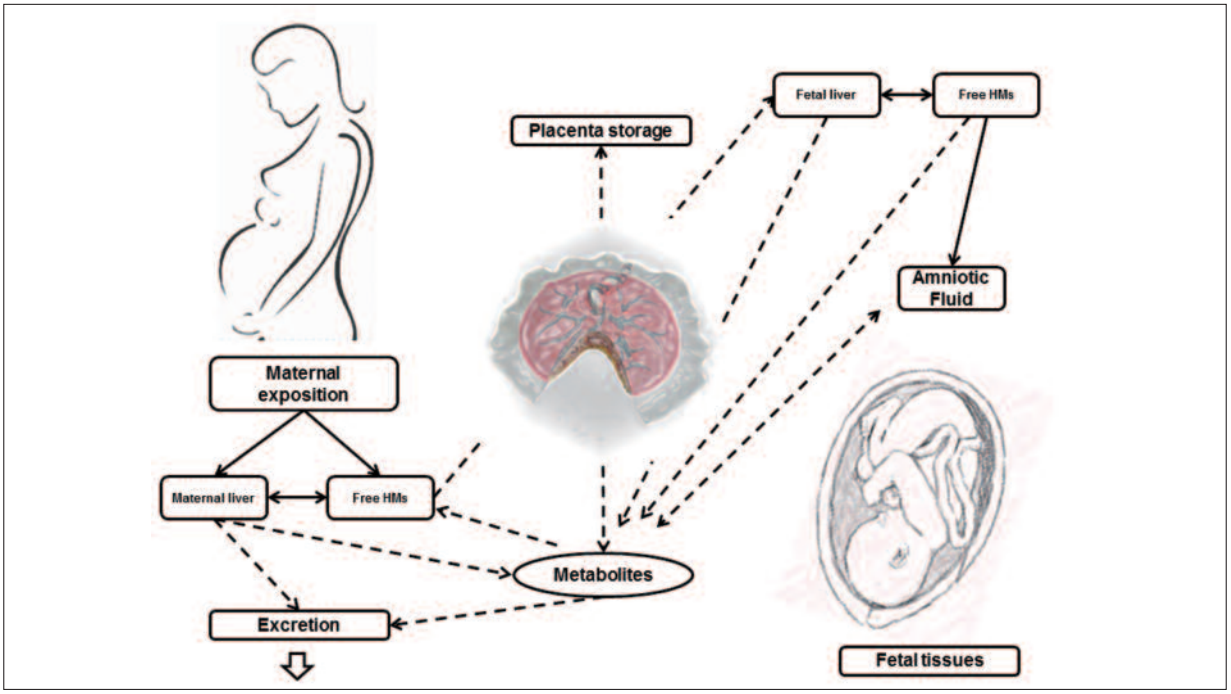

Figure 1. Interactions and passage of heavy metals between maternal circulation and the fetus through the placenta.

Lead was found to easily cross the placental barrier, by means of passive diffusion[55]. It has been reported a positive correlation[56]. Similarly, a positive correlation was observed in the majority of the studies, between placental and cord blood levels[56]. Concerning toxicodynamics, lead may alter calcium-mediated cellular processes in syncytiotrophoblasts: according to Goyer et al, lead seems to precipitate, along with calcium, in the microvilli around the trophoblast[55,57]. This lead storage observed in syncytiotrophoblast cells seems to be related to a reduced cytocrome oxidase activity[58].

The role of placenta as a barrier for mercury is not completely clear: the cellular uptake of this heavy metal appears to be related to its chemical structure[40,57]. It has been observed that mercury vapor and methyl mercury easily pass the placenta, respectively using passive transport and amino-acid carriers[59]; instead, inorganic mercury is more commonly accumulated in placenta, limiting the amount that reaches the fetus[60]. The toxicity caused by mercury in placenta implies deregulation in hormonal secretion, amino acid transfer, oxygen consumption and membrane fluidity[40].

Available studies showed that cadmium accumulates in the placental tissues: indeed, placental levels of this metal are related with maternal but not with cord blood levels[56]. In terms of toxicokynetics, it has been described a correlation between cadmium placental level and the expression of placental metallothionein (MT)[46]. MT is a small protein synthetized in maternal tissues and the placenta; it retains cadmium in the placental tissue preventing the passage to the fetal compartment. The increasing expression of MT, therefore, seems to be a protective mechanism of the placental barrier, against the passage of this toxic agent in the fetal compartment. On the other hand, the increase in MT leads to an alteration in the zinc transport from placental circulation to the fetus, thus diminishing the placental permeability to this essential element[46,61]. Cadmium also affects endocrine hormone synthesis (e.g. placental progesterone or leptin), alters trophoblast cell migration, induces early decidualization of human endometrial stroma cells[40].

Detection of Heavy Metals in Amniotic Fluid

AF, the protecting liquid contained in the amniotic cavity, is an essential component for fetal development and maturation during pregnancy[62]. The AF prevents mechanical insults and provides nutrients necessary for the maintenance of fetal wellbeing[38].

AF originates from the filtration of maternal plasma through the fetal membranes into the amniotic cavity. However, the fetus itself is responsible for the synthesis of AF: up to the 20-25th weeks of gestational age, when keratinization of fetal skin occurs, the AF composition is also the result of fluid transudation across the fetal skin. Moreover, starting approximately from 11 week of gestational age, AF also stems from fetal urine, with a small contribution by the lungs. It is mainly composed by water and electrolytes (99%), together with glucose, lipids from the fetal lungs, proteins and flaked-off fetal epithelium cells.

Thus, AF is the result of the delicate balance between both fetal and maternal compartments. Because free diffusion occurs bidirectionally between the AF and the fetus across fetal skin, placenta and umbilical cord from 10 to 20 weeks of gestation, AF composition becomes similar to fetal plasma during this period[11].

Several evidences considered the AF as a valuable marker of prenatal exposure to drugs and an indicator of the placental barrier function[12].

Nevertheless, the available data on dietary and environmental impact on the AF composition are limited, and insufficient to establish reference values[11,50].

In a previous study we evaluated the presence of HMs in 25 human AF samples obtained from amniocentesis in order to demonstrate an early fetal *in-utero* exposure. We found that Be, Ag, Ba, Pb, Sr, Cu, Mn, Sn, Sb, Te, Tl, As, Co, Zn and Se are present in AF between 15 and 18 weeks of gestation. In particular, Mg, Ag, Tl, Ba, Be, Sb and Zn were present at high levels in more samples. In contrast, Hg, Pd, Sc and Ni were absent in AF[11]. Considering that all women were nonsmokers, with no occupational exposure, and similar life-styles and eating habits, the detection of HMs in AF the study mentioned above apparently remained unknown. In addition, the newborn Apgar score and birth weight at delivery resulted within the normal range, despite the detected concentration of HMs[11].

Only few studies reported the detectable concentration of HMs in amniotic fluid.

Hall et al[63] in 1983 evaluated 97 AF samples, between 16 and 19 weeks of gestation, finding a mean Ba concentration, ranged from < 2 to 49 μg/L; in the study above mentioned, we found a similar Ba concentration, ranged from 0,877 to 47,494 μg/L[11]. Morover, Kosanovic et al[64], in

2002, determined the AF concentration of cadmium and selenium using atomic absorption spectrometry in 37 normotensive and 23 hypertensive women during the last trimester of pregnancy in relation to their smoking status. In the AF, tobacco smoking caused significant differences in cadmium and selenium concentrations between smokers and nonsmokers. In both the normotensive and the hypertensive women, selenium concentration was found to be significantly higher in AF of non-smokers women, if compared to smokers; conversely, cadmium concentrations in AF were significantly higher in subgroups of smokers compared to non-smokers.

An Italian study[65] performed in 2003 showed a positive, even not significant correlation between the presence of detectable mercury (Hg) concentration in human AF, and number/surface areas of dental amalgam fillings of pregnant women. Moreover, neither adverse pregnancy nor negative neonatal outcomes were observed.

Effects of Heavy Metals on Neonatal Outcomes

Prenatal life should be considered the phase of the human development in which fetal cellular division and differentiation occur. Despite adults, the fetus is highly susceptible to subtle teratogens at low exposure levels that do not significantly compromise the clinical status of the pregnant woman[66]. If exposure takes place during the organogenesis, HMs could produce permanent structural and anatomical changes. Alternatively, when the exposure occurs after the end of the organogenesis it might result in functional consequences. The immune, respiratory, and central nervous systems are also susceptible to postnatal exposures because they are immature at birth and characterized by a prolonged period of postnatal maturation[67].

The effect of an intrauterine exposure to HMs has been amply evaluated during the last decades. In particular, several studies correlated the early exposure to Pb, Hg, and Cd with infant health effects, such as neurological[68], developmental[69], and endocrine disorders[70] (Table I). There is less evidence on adverse fetal effects of Cr and Mn.

The fetal nervous tissue is more susceptible to injuries caused by toxic agents than the adults'one. The physiological brain development process consists in the migration of neurons along precise pathways from their points of origin (cells of dorsal ectoderm) to their final positions and in the establishment of specific networks with other cells[71]. A disruption of the nervous developmental process could deeply interfere with the events mentioned above. Even though the human brain continues to develop postnatally, a damage of the fetal anatomical structures has low chances of a later spontaneous recovery and the consequences could, therefore, be permanent[72,73].

Prenatal exposure to methyl mercury and lead could cause neurodevelopmental disorders and subclinical brain dysfunction[68].

Recent studies showed the effect of the prenatal exposures to reduced concentrations of methylmercury. A decrease in intelligence quotient (IQ) and changes in behaviour in children born to women with high concentrations of mercury were detected[74].

A large multicenter maternal-birth cohort study evaluated the widely debated association between cord blood total mercury levels and both mental and psychomotor development children (n=1.683). Infant neurodevelopment was assessed around age 14 months by the Bayley Scales of Infant Development. A doubling in total mercury levels did not show an association with mental or psychomotor developmental delay. Further analyses suggested a negative association between prenatal exposure to total mercury and psychomotor development among female infants[75].

It has also been showed that prenatal cadmium exposure adversely affects children's IQ[76]. Tian et al[76] analyzed the effect of maternal cadmium exposure on pregnancy outcome (n= 109) and development in the offspring at age 4.5 years. The placental, whole blood, and cord blood levels of cadmium were determined and, then, children at 4.5 years of age evaluated with detailed questionnaire surveys, anthropometric measurements and specific IQ tests. Data revealed a significant negative correlation between cord blood cadmium level and fetus development. Low birth weight (less than 2.500 g) and lower IQ test results were detected significantly more frequently in infants with higher cord blood cadmium than in those exposed to lower levels of cord blood cadmium.

Several papers discuss the influence of HMs on birth anthropometric measures[57,69,77-79]. In particular, a recent study[80] assessed the association between exposure to HMs (lead, cadmium and mercury) during pregnancy and birth outcomes in 1578 women aged 16-50 years. The levels of lead, cadmium and mercury were measured in umbilical cord blood, maternal blood and the placenta. Cadmium had the most noticeable effect on several measures of birth outcome. Crown-heel lengths,

Table I. Source of exposure, reproductive effects and fetal-neonatal outcomes of cadmium (Cd), lead (Pb) and mercury (Hg).

Heavy metal	Pathways of exposures	Reproductive effects	Fetal effects	Neonatal effects
Cadmium	Food chain (flour, rice, wheat, sugar; seafood) Cigarette smoking	Sperm quality alterations Sexual potency reduction Interfarence with the placental progesterone production and gonadic steroidogenesis	IUGR	Reduced QI Low birth weight and SGA Reduced neonatal lenght Reduced APGAR Score
Lead	Tobacco smoking Pb compounds manipulation and preparation Petrol additives Points, enamels Air pollution	Oxidative damage Decreased sex drive, impotence Sperm quality alterations Hormonal changes Menstrual disorders	Miscarriage/stillbirth IUGR Low-birth weight Preterm delivery Mental restriction Congenital malformations	Hematological changes (WBCs development alteration) Poorer Mental Development Index Reduced QI impairment in hearing and motor development Learning disabilities Attention deficit disorders
Mercury	Food (fish) Industrial sources (chlor-alkali industry, pulp andpaper industry, hospital and laboratory instrumentation containing elemental mercury) Food preservatives, cosmetics preservatives Photo labs Insecticides, pesticides, fungicides	Sexual potency reduction Sperm quality and quantity alterations Increased risk of testicular cancer Lowered testosterone levels Menstrual disorders	Miscarriage/stillbirth Nervous system dysfunction	Birth defects Neurodevelopmental mental retardation Hearing deficiences Learning disabilities Autism Reduced QI

Apgar 5-minute scores, birth weights and small for gestational age (SGA) births below the 10th percentile were influenced by cadmium levels in the umbilical cord. In addition, crown-heel length and placental thickness were affected by cadmium levels in maternal blood. Authors did not found associations between lead in maternal blood, umbilical cord blood and placental tissues with birth outcomes. Only lead levels in maternal blood influenced placental thickness. In both umbilical cord and maternal blood, mercury was marginally associated with placental thickness and placental weight, respectively. On the contrary, placental mercury significantly influenced head circumference, Apgar 5-minute scores and cord length.

Cadmium high levels of exposure could alter endocrine function, causing various reproductive problems[81]. It could interfere with the production of placental progesterone which in turns could impair steroidogenesis and consequently have an effect on fetal growth and development[82].a

An observational study correlated cadmium levels in cord whole blood sampled from 24 women at the time of delivery to the levels of thyroid stimulating hormone (TSH) and free thyroxin (fT4) in the neonatal blood sampled at 4-6 days postpartum. A significant negative correlation was observed between Cd concentrations in cord blood and TSH concentration in neonatal blood. These data suggested the possible effect of in utero Cd exposure on thyroid hormone status of newborns and that Cd exposure[83].

Ji et al[84] demonstrated that exposure to cadmium during late pregnancy could alter gonadic steroidogenesis in male offspring.

Conclusions

It has been widely demonstrated that some HMs (i.e. lead, cadmium, mercury) can cross the placenta barrier, accumulating in AF and/or in fe-

tal tissues. The *in-utero* exposure to these pollutants has been correlated to infant health consequences, like developmental, neurological, or endocrine disorders.

Considering the inability of the human maternal fetal-placental unit to totally prevent the fetus from exposure to HMs, recognition of risk factors, such as an inappropriate diet, occupation and living conditions, has led to evidence-based programs of prevention.

The paucity of studies on exposure to HMs during pregnancy does not allow us to support a definitive conclusion. Further studies are needed to expand knowledge on the developmental effects of most HMs in the human fetal-placental unit.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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