

# Heavy Metals Can either Aid or Oppose the Protective Function of the Placental Barrier

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## Abstract

**Citation:** Abdel Hameed ER, Shehata MA, Waheed H, Abdel Samie OM, Ahmed HH, Sherif LS, Ahmed A.. Heavy Metals Can either Aid or Oppose the Protective Function of the Placental Barrier. Open Access Maced J Med Sci. <https://doi.org/10.3889/oamjms.2019.709>

**Keywords:** Heavy metals; Maternal blood; Cord blood; Placental permeability

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**Received:** 12-Jul-2019; **Revised:** 23-Aug-2019; **Accepted:** 24-Aug-2019; **Online first:** 30-Aug-2019

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**Funding:** This was a part of a research project, funded by the National Research Centre 10th research plan, Egypt (Grant No. 11010140)

**Competing Interests:** The authors have declared that no competing interests exist

**BACKGROUND:** In developing countries, toxic heavy metals are a threatening catastrophe to human health, particularly in the vulnerable group of pregnant mothers and their fetuses. Fortunately, the placenta can be a protective barrier to the fetuses.

**AIM:** To explore the relationship between serum lead, cadmium and arsenic levels in pregnant mothers and their newborns, to address the placental barrier in this situation.

**METHODS:** A cross-sectional study was conducted on 100 pregnant mothers at the time of labour and their newborns. Serum cadmium, lead, and arsenic levels were measured using the Inductively Coupled Plasma Mass Spectrometry.

**RESULTS:** All the studied heavy metals concentrations showed a significant elevation in the maternal blood relative to the cord blood. There was a significant association between the maternal lead and both fetal lead and arsenic. Meanwhile, a negative but insignificant correlation was recorded between the maternal cadmium and each of the fetal cadmium, lead, and arsenic.

**CONCLUSION:** The study findings indicated a weak relation between maternal and fetal blood heavy metals, except for the influence of maternal lead, so it can be assumed that the placental barriers are partially protective against those toxic pollutants, putting into consideration the influence of their different natures.

## Introduction

Environmental contamination with heavy metals is considered as a public health problem in Egypt. Their progressive contamination of the soil and water are increasing to an alarming rate [1]. Besides, the growing industrial development and disorganised urbanization, contribute to the raised levels of heavy metals in the urban environment of our country [2].

Prenatal exposure to environmental contaminant may occur through the placenta and the umbilical cord. It has been widely evidenced that the protection provided by the placental barrier is not complete, as several harmful agents can pass through it, like some drugs and toxic agents [3].

Nowadays, toxic heavy metals are considered as major sources of the progressively growing

problem of environmental pollution. Cadmium, lead, and arsenic are all toxic heavy metals present in the surrounding environment almost always together as co-occurrences [4]. Collectively, they reach our bodies through the air, food, and water, with a special referral to cadmium, whose main entry source, is smoke [5].

Several studies have investigated the passage of these contaminants from the mother to the fetus, and their influence on the health of pregnant mothers and their fetuses where they can affect growth and development [6], [7].

They are all neurotoxic besides their other hazards, mostly due to the oxidative stress [8]. Fortunately, on the other side, they can induce the synthesis of low molecular weight proteins, rich in cysteine, named metallothioneins (MTs) at the placenta. These, in turn, are protective to the fetus against the different stressful conditions exemplified

by heavy metals, oxidative damages and inflammation. They can regulate cell growth differentiation repair and apoptosis. Moreover, they are a pillar for immune regulation and are protective against immune-mediated apoptosis [9].

The purpose of this study was to identify the relation between serum lead, cadmium and arsenic levels in pregnant mothers and their newborn's cord blood, to justify the function of the placental barrier in this condition.

## Material and Methods

A cross-sectional study that was conducted in the period from September 2016 to June 2017, 100 pregnant mothers and their newborns were recruited at the time of labour [10]. They were chosen randomly from those attending AL-Galaa Teaching Hospital as a research project, funded the by National Research Centre 10<sup>th</sup> research plan, entitled "immunological profile in cord blood and growth assessment of the newborn about maternal exposure to environmental contaminant". (Grant No. 11010140), which was approved by the Medical Ethical Committee of the National Research Centre (Registration No.16-295).

All mothers gained comprehensive and clear knowledge about the aim of our work, and written consents were signed before enrollment.

The mother's ages ranged between 18 and 40 years. Neonates were of both sexes. Pregnant mothers with a history of chronic diseases or major illnesses during pregnancy were excluded. Neonates with any apparent congenital abnormalities, genetic, metabolic or neurological problems were also excluded.

### The following data were collected

- Sociodemographic data about mothers included age, social status, economic responsibility, water source availability, sanitary disposal, smoke exposure and education.

- Food frequency questionnaire (FFQ) for dietary assessment of the different foodstuff.

- Gestational age, type of labour, history of delivery problems and chronic diseases.

- Maternal anthropometric measurements of weight in kilograms (kgs) height in centimetres (cm).

- Neonatal Apgar scoring, at one and five minutes, was measured to assess neonatal condition at birth.

- Neonatal anthropometric measurements of weight (kgs), height (cm), head circumference and

mid-upper arm circumference (MAC) in cm were all taken.

### Blood sample collection

Five ml of blood were collected from mothers, whether in normal or section delivery at the time of labour and put in 3 free EDTA tubes. Another 5 ml of blood were collected from the cord blood during delivery before placental separation and put in free EDTA tubes.

These blood samples were for measuring the cadmium, lead, and arsenic levels in mothers and umbilical cord of fetus using inductively coupled plasma mass spectrometry, as shown in a previous study [10].

### Statistical analysis

The analysis was performed using SPSS version 21 (SSPS Inc., Pennsylvania, USA). Mean  $\pm$  SD, median and interquartile ranges were used to present quantitative data. While frequencies and percentages used for qualitative data. Mann Whitney U test was used for comparison between groups. Pearson's correlation analysis was carried out to evaluate the association between variables.  $P < 0.05$  value was considered as significant.

## Results

A total of 100 mothers with their infant (46 males and 54 females) were analyzed for the current study; their mean age was  $26.25 \pm 5.44$  years. The study population had no history of occupational exposure to toxic elements, and they were all living in an urban environment. None of the mothers was active smokers, while about 80% were passive smokers. Table 1 shows the demographic characteristics of our target population

**Table 1: General characteristics of the study population**

Categorical variables	Category	N (%)
Maternal Age	below 20 years	8 (8%)
	20-30 years	63(63%)
	More than 30 years	29 (29%)
Type of delivery	Normal delivery	55 (55%)
	Cesarean section	45 (45%)
Newborn's gender	Male	46 (46%)
	Female	54 (54%)
Vegetables intake	1 / week	27 (27%)
	3 / week	55 (55%)
	> 3 / week	17 (17%)
Fruits intake	1 / week	44 (44%)
	3 / week	38 (38%)
	> 3 / week	17 (17%)
Animal proteins intake	1 / week	59 (59%)
	3 / week	35 (35%)
	> 3 / week	5 (5%)
Continuous variables	Mean	SD
Gestational age	37.04	2.1
Newborn Weight	2.9	0.64

As shown in Table 2, all the studied heavy metals concentrations displayed significant

enhancement in the maternal blood serum versus to the cord blood serum.

**Table 2: Heavy metals concentrations in maternal and cord blood sera**

	Maternal					Fetal					Z	P
	Mean	SD	25th	Percentile 50th Median	75th	Mean	SD	25th	Percentile 50th Median	75th		
Lead (µg/ml)	23.56	36.1	0.30	12.84	19.7	13.15	22.2	0.05	5.5	13.2	-2.84	0.005*
Arsenic (µg/L)	60.86	527.2	1.08	2.30	7.7	3.43	7.5	0.499	0.98	2.72	-4.66	0.000*
Cadmium (ng/ml)	20.59	155.9	0.35	1.35	7.1	1.95	3.2	0.15	0.60	1.6	-3.14	0.002*

\* Significant at  $p < 0.05$  level.

The correlations between maternal and fetal heavy metals are shown in Table 3; a significant positive association was recorded between the maternal lead and both fetal levels of lead and arsenic. There was also an insignificant negative association between maternal cadmium concentrations and the cord blood serum levels of cadmium, lead and arsenic

**Table 3: Correlation between maternal and neonatal heavy metals**

		Fetal Pb	Fetal As	Fetal Cd
Maternal Cd	r	-0.007	-0.001	-0.018
	P - Value	0.944	0.992	0.859
Maternal Pb	r	0.718	0.593	-0.010
	P - Value	0.000	0.000	0.919
Maternal As	r	-0.047	0.022	-0.042
	P - Value	0.642	0.827	0.679

\* Significant at  $p < 0.05$  level.

## Discussion

The protective function of the placental barrier against some toxic heavy metals was assessed in the present study, by evaluating the relationship between levels of arsenic, cadmium and lead in the maternal and cord blood, we observed statistically significantly higher concentrations of all mentioned heavy metals in maternal blood serum than in cord blood serum.

In comparison to other recent studies, concentrations of the above-mentioned heavy metals were assessed in Malaysia in maternal and cord blood; they observed significantly lower levels of lead and cadmium but not arsenic in cord blood than in maternal blood [11]. Our findings were also in partial agreement with those of Zhuo et al., [12] who reported higher concentrations of lead and cadmium in a maternal blood clot in comparison to an umbilical cord blood clot, but again arsenic levels showed insignificant differences. These investigators also stated that the barrier function of the placenta works most effectively with cadmium. Simultaneously, our findings indicate that the placental barriers act as a partial defence against those agents especially arsenic and cadmium.

On the opposite side, the finding of this research indicated that maternal blood cadmium levels correlated negatively, but insignificantly with the

umbilical cord blood levels of cadmium, lead, and arsenic. The oxidative stress which cadmium in poses should mal-affect the placental barrier, which in turn should allow more levels of toxic metals to pass to the fetus. However, the observed negative correlation in this study could be ascribed to the capability of the maternal cadmium, even at relatively low doses, to act as a powerful driver of metallothioneins synthesis at the placental barrier [13], [14]. MTs are proteins of low molecular weight and abundant in cysteine; they can hinder the passage cadmium from the mothers to their fetuses in several ways. It is worth mentioning that MTs, however, do not completely stop the movement of Cd from mothers to their fetuses [14], but Cd had been considered a more potent inducer of MTs in comparison to other heavy metals [15].

Several recent types of the research reported results consistent with ours where they found out that the placenta works as a strong barrier against Cd passage to the fetuses whose umbilical cord blood Cd levels were significantly lower than those of mothers' blood ( $P < 0.001$ ) [11], [16].

On the other hand, this study found a highly significant positive correlation between the maternal lead levels and the fetal lead and arsenic levels. In accordance, previous work demonstrated that lead and arsenic have positive correlations with each other [17], [18]. Moreover, both metals showed a synergistic action [19].

Also, a recent meta-analysis mentioned a positive association in most of the included studies, between placental lead level and that of cord blood [20]. The easy transfer of lead across the placental barriers by a passive diffusion process was documented previously [3]. Also, lead was declared to be detrimental even at low levels of exposure [21]. It is crucial to emphasise that lead was documented to induce oxidative stress through various mechanisms, causing structural injury and perturbation of various vital functions at the cellular level [22], [23].

Meanwhile, both lead and arsenic impair nitric oxide production, which is a known endothelial relaxing agent, leading to increased reactive oxygen species (ROS) generation [24], causing deterioration to the vascular endothelium, and this will end in vasoconstrictions [25]. Accordingly, we assume that they impair blood and nutritional supplies to the foetus via hampering the placental barrier proper function, and hence there will be no proper detoxification.

In conclusion, based on the present findings, it seemed that arsenic and lead might have a synergistic effect, causing derangement of the barrier function of the placenta. However, this function is partially effective regarding the transfer of arsenic and cadmium but less effective against lead. Importantly, cadmium showed a weak protective action mostly attributed to MTs action, but that needs to be clarified in further future research.

## Acknowledgement

The author would thank all participants and their parents.

## References

- Mohiuddin KM, Ogawa YZ, Zakir HM, Otomo K, Shikazono N. Heavy metals contamination in water and sediments of an urban river in a developing country. *International journal of environmental science & technology*. 2011; 8(4):723-36. <https://doi.org/10.1007/BF03326257>
- Issa AB, Yasin K, Loutfy N, Ahmed MT. Risk assessment of heavy metals associated with food consumption in Egypt: A pilot study. *J Clin Exp Tox*. 2018; 2(1):10-19.
- Caserta D, Graziano A, Monte GL, Bordi G, Moscarini M. Heavy metals and placental fetal-maternal barrier: a mini-review on the major concerns. *Eur Rev Med Pharmacol Sci*. 2013; 17(16):2198-206.
- Nampoothiri LP and Gupta S. Biochemical effects of gestational coexposure to lead and cadmium on reproductive performance, placenta, and ovary. *J Biochem Molecular Toxicology*. 2008; 22(5). <https://doi.org/10.1002/jbt.20246> PMID:18972398
- Taylor CM, Golding J and Emond AM. Moderate prenatal cadmium exposure and adverse birth outcomes: a role for sex-specific differences? *Paediat Perinatal Epidemiol*. 2016; 30(6):603-611. <https://doi.org/10.1111/ppe.12318> PMID:27778365 PMID:PMC5111596
- Sabra S, Malmqvist E, Saborit A, Gratacós E, Roig MD. Heavy metals exposure levels and their correlation with different clinical forms of fetal growth restriction. *PloS one*. 2017; 12(10):e0185645. <https://doi.org/10.1371/journal.pone.0185645> PMID:28985223 PMID:PMC5630121
- Hameed ER, Shehata MA, Ahmed HH, Sherif LS, Elnady HG, Waheed H. Relation of Heavy Metals in Cord and Maternal Blood to Neonatal Anthropometric Indices. *Journal of Clinical & Diagnostic Research*. 2019; 13(3).
- Sankhla MS, Sharma K and Kumar R. Heavy metal causing neurotoxicity in human health. *International Journal of Innovative Research in Science, Engineering and Technology*. 2017; 6(5).
- Jakovac H, Grebić D, Mrakovcic-Šutić I, Rukavina D, Radošević-Stašić B. Expression of metallothioneins in placental and fetal tissues in undisturbed and PGM-Zn treated syngeneic pregnancy. *AJBIO*. 2015; 3:1-7. <https://doi.org/10.11648/j.ajbio.s.2015030202.12>
- Abdel Hameed ER, Sherif LS, Ola M, AbdelSamie OM, Ahmed HH, Ahmed A, et al. Mercury materno-fetal burden and its nutritional impact. *Open Access Macedonian Journal of Medical Sciences*. 2018; 6(9):1652-58. <https://doi.org/10.3889/oamjms.2018.364> PMID:30337982 PMID:PMC6182524
- Sakai N, Alsaad Z, Thuong NT, Shiota K, Yoneda M, Mohd MA. Source profiling of arsenic and heavy metals in the Selangor River basin and their maternal and cord blood levels in Selangor State, Malaysia. *Chemosphere*. 2017; 184:857-65. <https://doi.org/10.1016/j.chemosphere.2017.06.070> PMID:28646768
- Zhou C, Zhang R, Cai X, Xiao R, Yu H. Trace elements profiles of maternal blood, umbilical cord blood, and placenta in Beijing, China. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2019; 32(11):1755-61. <https://doi.org/10.1080/14767058.2017.1416602> PMID:29228828
- Benitez MA, Mendez-Armenta M, Montes S, Rembao D, Sanin LH, Rios C. Mother-fetus transference of lead and cadmium in rats: involvement of metallothionein. *Histology and histopathology*. 2009; 24(10):1523.
- Jacobo-Estrada T, Santoyo-Sánchez M, Thévenod F, Barbier O. Cadmium Handling, Toxicity and Molecular Targets Involved during Pregnancy: Lessons from Experimental Models. *Int J Mol Sci*. 2017; 18(7):1590. <https://doi.org/10.3390/ijms18071590> PMID:28737682 PMID:PMC5536077
- Gundacker C and Hengstschlager M. The role of the placenta in Fetal exposure to heavy metals. *Wien. Med. Wochenschr*. 2012; 162:201-206. <https://doi.org/10.1007/s10354-012-0074-3> PMID:22717874
- Jeong KS, Ha E, Shin JY, Park H, Hong YC, Ha M, Kim S, Lee SJ, Lee KY, Kim JH, Kim Y. Blood heavy metal concentrations in pregnant Korean women and their children up to age 5 years: Mothers' and Children's Environmental Health (MOCEH) birth cohort study. *Science of the Total Environment*. 2017; 605:784-91. <https://doi.org/10.1016/j.scitotenv.2017.06.007> PMID:28679122
- Zota AR, Schaidler LA, Ettinger AS, Wright RO, Shine JP, Spengler JD. Metal sources and exposures in the homes of young children living near a mining-impacted Superfund site. *J Expo Sci Environ Epidemiol*. 2011; 21:495-505. <https://doi.org/10.1038/jes.2011.21> PMID:21587306 PMID:PMC3161168
- Henn BC, Ettinger AS, Hopkins MR, Jim R, Amarasiriwardena C, Christiani DC, Coull BA, Bellinger DC, Wright RO. Prenatal arsenic exposure and birth outcomes among a population residing near a mining-related superfund site. *Environmental health perspectives*. 2016; 124(8):1308-15. <https://doi.org/10.1289/ehp.1510070> PMID:26859631 PMID:PMC4977047
- Ram AS, Reddy KP, Girish BP, Supriya C, Reddy PS. Arsenic aggravated reproductive toxicity in male rats exposed to lead during the perinatal period. *Toxicology research*. 2018; 7(6):1191-204. <https://doi.org/10.1039/C8TX00146D> PMID:30510688 PMID:PMC6220733
- Esteban-Vasallo MD, Aragones N, Pollan M, López-Abente G, Perez-Gomez B. Mercury, cadmium, and lead levels in human placenta: a systematic review. *Environmental health perspectives*. 2012; 120(10):1369-77. <https://doi.org/10.1289/ehp.1204952> PMID:22591711 PMID:PMC3491942
- Tiwari S, Tripathi IP, Tiwari HL. Effects of lead on Environment. *International Journal of Emerging Research in Management & Technology*. 2013; 2(6).
- Mathew BB, Tiwari A, Jatava SK. Free radicals and antioxidants: A review *Journal of Pharmacy Research*. 2011; 4(12):4340-4343.
- Jaishankar M, Tseten T, Anbalagan N, Mathew BB, Beeregowda KN. Toxicity, mechanism and health effects of some heavy metals. *Interdiscip Toxicol*. 2014; 7(2):60-72. <https://doi.org/10.2478/intox-2014-0009> PMID:26109881 PMID:PMC4427717
- Ellinor DC. Arsenic, reactive oxygen, and endothelial dysfunction. *Journal of Pharmacology and Experimental Therapeutics*. 2015; 353(3):458-64. <https://doi.org/10.1124/jpet.115.223289> PMID:25788710
- Jennrich P. The influence of arsenic, lead, and mercury on the development of cardiovascular diseases. *ISRN Hypertension*. 2012; 2013. <https://doi.org/10.5402/2013/234034>