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RESEARCH ARTICLE

Metal mixtures in pregnant women and umbilical cord blood at urban populations—Rio de Janeiro, Brazil

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Abstract

This study aims to assess interrelationships between serum lead (Pb), cadmium (Cd), arsenic (As), and mercury (Hg) concentrations in pregnant women in their third trimester and umbilical cord blood, while inter-metal correlations were also determined. This study is part of the PIPA project (Childhood and Environmental Pollutant Project), whose pilot study was carried out from October 2017 to August 2018 and will be presented here. Blood samples were obtained from 117 mother-umbilical cord pairs and analyzed concerning metal concentrations. A positive correlation was found between metal concentrations in mother and cord blood ($R > 0.7$, $p < 0.001$). The results indicate that mother metal concentrations are able to determine child metal concentrations ($p < 0.001$). The correlations between maternal blood metal concentrations were positive for all assessed metals except for As and Hg. The strongest correlations in this matrix were observed between Cd and Pb ($R = 0.471$ $p = 0.000$), Cd and Hg ($R = 0.425$ $p = 0.000$), and Pb and Hg ($R = 0.427$ $p = 0.000$). Umbilical cord correlations were lower compared to mother blood correlations. In general, the four analyzed metals displayed significant correlations to serum concentrations in both maternal and cord blood.

Keywords Environmental child health · Heavy metals · Environmental exposure · Birth cohort · Cord blood · Urban population

Introduction

Several environmental pollutants can affect perinatal health, leading to fetal development consequences and implications reflected at birth, such as prematurity and low weight, as well as childhood and adulthood implications (Yıldırım et al. 2019). In this regard, lead (Pb), cadmium (Cd), arsenic (As), and mercury (Hg) have been identified as potential toxic elements concerning human reproductive system (Flora et al. 2011). Fetal exposure to these metals during gestation may interfere with fetal development, as these elements are able to cross the placental barrier and interfere with fetal formation and growth (ATSDR 2007; Sabra et al. 2017).

According to the World Health Organization (2010), these metals are considered one of the most important public health problems among environmental chemicals, due to their adverse health effects and environmental distribution, as they are widely applied in industrial processes and in daily population routines (Zhou et al. 2018). Food, water, and air pollution are among the main exposure routes (Gundacker and Hengstschläger 2012). In addition, these metals display the ability to remain in the environment for long periods of time and may lead to prolonged and gradual population exposure, which may not result in immediate adverse health effects but, instead, in long-term effects (Zhou et al. 2018).

In addition to low-concentration and long-term exposure effects to an isolated metal, the effects of exposure to a combination of metals have been identified as a major challenge for environmental health studies (CDC 2004). Epidemiological studies find it difficult to investigate this combined action, both concerning the identification of the

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most appropriate statistical method and with regard to known metal toxicology characteristics, variable behavior, and chemist collinearity (Taylor et al. 2016). One of the key points in this regard is that the occurrence of toxic effects depends on the modes of interaction between the constituent metals of the mixture and the target site in the organism (Pan et al. 2018). Rai et al. (2010) observed that combined exposure to As, Cd, and Pb in rats may lead to a synergistic effect concerning several dysfunctions in the test subjects. In humans, some studies have pointed to synergistic metal effects in child neurodevelopment (Kim et al. 2009; Wasserman et al. 2011; Pan et al. 2018).

Assessing the interrelationships between serum metal concentrations in mother-baby pairs during pregnancy may aid in investigating the possible combined effects of these metals on fetal development, birth, and child development. In this context, this study aims to study serum Pb, Cd, As and Hg interrelationships in pregnant women in their third trimester and in their babies' umbilical cord blood, as well as intermetal correlations.

Methodology

Study area

This study is part of the PIPA project (Childhood and Environmental Pollutant Project), which proposes to conduct a prospective cohort study to investigate the effects of environmental pollutant exposure on child health. The PIPA project is under development at the Federal University of Rio de Janeiro Maternity School (ME-UFRJ), located in southern Rio de Janeiro, in southeastern Brazil.

This maternity ward attends low-risk pregnant women referred by the basic health units in the area (50% of births) and high-risk pregnant women referred from other areas in the municipality and other state municipalities (50%). The total population of pregnant women attended each year is of about 2000–2500.

Study population

A pilot study was conducted from October 2017 to August 2018 at ME-UFRJ. All pregnant women over 16 years old who participated in an Orientation Seminar held at the ME-UFRJ during a 2-month period were invited to participate in the pilot study (209). A total of 142 pregnant women agreed to participate and signed the consent form. A total of 135 births occurred during the study period. Biological samples were obtained from 117 mother-baby pairs. A questionnaire was applied to collect sociodemographic, clinical and metal exposure information, followed by maternal blood sampling. At birth, umbilical cord blood and clinical information concerning the newborn were collected. Metal concentration analyses were performed on 117 mother-umbilical cord pairs and this population has been considered for this study.

Biological samples

Mother blood and umbilical cord collections were performed by a previously trained maternity nursing team. Vacuum scalps and vacuum tubes containing EDTA were used collect mother blood. Cord blood was collected during delivery. Blood samples were stored between 2 and 7 °C for up to 48 h and were then transported to the laboratory, where they were stored in a freezer at − 4 °C until analysis.

The blood analyses were performed at the laboratory of the National Institute for Quality Control in Health (INCQS), at the Oswaldo Cruz Foundation (FIOCRUZ) by inductively coupled plasma source mass spectrometry (ICP-MS). After thawing, 0.5 mL of each sample was diluted with demineralized water to 10 mL. Subsequently, 1.0 mL of 65% nitric acid (HNO_3) were added and the samples were the heated at 80 °C in a water bath for 2 to 3 h, to ensure complete organic matter digestion. The limits of quantification (LOQ) and limits of detection (LOD) for each element were as follows: 0.01 μg/L and 0.003 μg/L for arsenic, 0.006 μg/L and LOD 0.002 μg/L for cadmium, 0.02 μg/L and LOD 0.007 μg/L for mercury, and 0.05 μg/L and LOD 0.015 μg/L for lead. For lead, metal values were converted to μg/dL.

Statistical analyses

The characteristics of the participants were described, such as mother's age, per capita income household, schooling, passive and active smoking, birth weight, gestational age, and babies' sex. These characteristics were considered possibly confounding variables, and we observed the relation regarding the mothers' and babies' metal concentrations. For continuous variables, the Spearmen correlation coefficient has been used, and for categoric variables, ANOVA.

Geometric means and respective 95% confidence intervals were calculated for the descriptive analyses of metal concentrations in maternal and umbilical cord. Considering that the detected metals presented a positive asymmetric distribution, the geometric means best describes the central tendency of the variable, since it calculated based on algorithmized values (Daly and Bourke 2000). The 25th, 50th, 75th, and 95th percentiles are also presented. To describe the metal distribution pattern, skewxness and kurtosis values were calculated and the Kolmorogov-Smirnov test was performed.

The nonparametric Spearman correlation coefficient was applied to evaluate the mother-baby metal correlations. A scatterplot displaying the correlation and equality lines was constructed for each metal. A linear regression was performed to assess the ability to predict umbilical cord metal concentrations using maternal blood metal concentrations as the predictor variable. Among confounding variables, passive smoking and active smoking were considered, since it presented statistical significance when evaluating the association with the concentration of some metals ($p < 0.05$).

To evaluate intermetal correlations between metal concentrations, the nonparametric Spearman correlation coefficient was applied.

Ethical considerations

The PIPA project is coordinated by the Federal University of Rio de Janeiro in partnership with the Oswaldo Cruz Foundation, approved by the Maternity Research School (no. 2,092,440) and the Oswaldo Cruz Foundation (no. 2,121,397) Ethics Committees.

Results

Among pregnant women who participated of this analysis ($n = 117$), all reside in the urban Rio de Janeiro area, with an average age of 28.46 years (SD 7.12). The average per capita household income was of US$ 160.50 (SD US$ 105.82), 73% were non-white, and 83% presented over 10 years of schooling. Passive smoking was reported by 43.2% of the pregnant women and active smoking during pregnancy, by 9.2%, alcohol consumption during pregnancy was reported by 48.2% of pregnant women.

None of them reported developing occupational activities which could lead to a higher metals' exposure.

The birth characteristics observed were 57.9% male, 42.1% female, 9.1% premature (less than 37 weeks of gestation), and 7.8% weighing less than 2500 g, and 7.0% were small for the gestational age (Table 1). Mother's age, schooling, average per capita income, and alcohol consumption do not show any relation to metal concentration in mothers and babies, as well as birth outcomes (Table 1).

The detection rates for Pb, As, Cd, and Hg were 100% in both maternal and cord blood. The geometric mean Pb concentration in pregnant women was of 3.74 μg/dL, and 25% of the samples presented values above 5.46 μg/dL, while the geometric mean concentration in umbilical cord blood was of 3.85 μg/dL, with 25% of the samples presenting values above 4.92 μg/dL. The geometric mean Hg concentrations were very close between pregnant women and umbilical cord samples (about 1.0 μg/L). A geometric mean of over 10.00 μg/dL in maternal and cord blood was observed for As (Table 2). As concentrations in maternal and cord blood presented a normal distribution ($p = 0.077$). The same was also observed for maternal Pb concentrations ($p = 0.081$), while a positive asymmetry was observed in cord blood ($p = 0.000$). Cd and Hg displayed positive asymmetry in both maternal and umbilical cord blood (Table 2). Pb and As concentrations in both maternal and cord blood displayed a greater distribution around the median, with few outliers, while Cd and Hg concentrations were close to the limit of detection, with a higher number of outliers (Figs. 1 and 2).

A positive correlation was detected between metal concentrations in mother and umbilical cord blood. As and Hg displayed the highest correlations (Spearmen correlation $r = 0.712$, $p = 0.000$, and $r = 0.701$, $p = 0.000$, respectively) (Fig. 3). The results of linear regression adjusted to passive and active smoking indicate that the mother metal concentrations could determine part of the child metal concentrations (26% and 40%). Mother As concentration explained approximately 40% of the observed umbilical cord concentration variation (As $R^2_a = 0.408$, $p = 0.000$). Mother Pb and Cd concentrations explained approximately 30% of the observed umbilical cord concentration variation (Pb $R^2_a = 0.308$ $p = 0.000$; Cd $R^2_a = 0.292$; $p = 0.000$). Hg displayed the lowest determination capacity, of around 26% ($R^2_a = 0.257$ $p = 0.000$).

The correlations between maternal blood metal concentrations were positive for all elements, except for As and Hg. The strongest correlations in this matrix were observed between Cd and Pb ($R = 0.471$, $p = 0.000$), Cd and Hg ($R = 0.425$, $p = 0.000$), and Pb and Hg ($R = 0.427$, $p = 0.000$). As was correlated only to Cd in cord blood. Compared to mother blood correlations, umbilical cord correlations were lower, where the Pb and Hg ($R = 0.377$, $p = 0.000$) and Cd and Pb ($R = 0.340$ $p = 0.000$) associations displayed lower correlation strengths. As and Hg displayed a weak negative correlation in this matrix ($R = -0.18$, $p = 0.052$) (Tables 3 and 4).

Discussion

In the present study, serum Pb, As, Hg, and Cd concentrations above the LOD were identified in all analyzed mother-cord pairs. Ettinger et al. (2017) when assessing 2000 mothers in Canada, reported lower As detection rates in maternal blood in the third pregnancy trimester and in umbilical cord blood, of 87.3% and 49.1%, respectively (LOD = 0.225 μg/L). Considering that metals are widely distributed in the environment, efforts have been made in recent decades in developed countries to achieve decreased concentrations and, consequently, decreased population exposure (Forns et al. 2014; NHANES Report 2009). Saravanabhavan et al. (2016) reported decreased As, Hg, and Cd detection rates in an adult urban population in Canada over three consecutive trienniums (2007–2009, 2009–2011, and 2012–2013). Throughout this period, Cd detection rates decreased from 97.1 to 88.5% (LOD 0.004 μg/L), while Hg detection rates decreased from 88.4 to 63.0% (LOD 0.1 μg L).

Table 1 Mothers and babies characteristics and correlation with metal concentration

Characteristics		Description	Mothers *p* value				Babies *p* value			
			As	Pb	Hg	Cd	As	Pb	Hg	Cd
Mother	Mother's age	Average 28.46 (SD 7.12)	0.74	0.87	0.79	0.61	0.87	0.93	0.76	0.78
	Schooling	83% > 10 years	0.59	0.60	0.92	0.66	0.85	0.93	0.82	0.68
	Non-white (color)	73%	0.97	0.47	0.07	0.08	0.59	0.74	0.28	0.19
	Average percapta household	Average US$160 (SD 105.82	0.27	0.85	0.17	0.27	0.61	0.67	0.16	0.54
	Passive smoking	43.2%	0.44	0.57	0.46	0.54	0.10	0.57	0.02*	0.39
	Active smoking	9.2%	0.97	0.29	0.87	0.75	0.66	0.04*	0.49	0.93
	Alcohol consumption	48.2%	0.26	0.24	0.82	0.24	0.62	0.11	0.33	0.47
Birth	Sex	Male 57.9%	0.78	0.15	0.94	0.53	0.78	0.30	0.27	0.12
	Premature	9.1%	0.69	0.12	0.15	0.77	0.18	0.97	0.90	0.67
	Birth weight < 2500 g	7.8%	0.52	0.83	0.23	0.54	0.47	0.50	0.85	0.85
	Small for gestational age	7.0%	0.68	0.94	0.43	0.48	0.64	0.76	0.87	0.40

Spearman correlation for mother' age, schooling years, average per capita household, birth weight. ANOVA for color, passive smoking, active smoking, alcohol consumption, babies' sex, prematurity and small for gestational age

*Variables with *p* value < 5 were considered for adjust of metals concentration between pairs mother-baby

The main concerns regarding the possible toxic effects of long-term exposure to metals are aggravated by their occurrence in the most vulnerable human formation and development stages, such as the intrauterine period and the first 5 years of life. In the present study, Pb, Cd, As, and Hg concentrations in umbilical cord blood were detectable in all samples, indicating transplacental mother-infant transfer, as pointed out in other studies.

No safe environmental exposure parameters are set for Pb (ATSDR 2008). Exposure to relatively low levels is already considered toxic and may lead to potential human health effects, especially when this occurring during early life stages, such as fetal formation and development (Sanders et al. 2015). The US Center for Disease Control and Prevention (CDC) considers 5 μg/dL the limiting blood Pb concentration in children. Levels above this value may lead to toxic child health effects. However, some studies have found neuromotor and cognitive development alterations in children with blood concentrations below this value, corroborating that no safe Pb exposure limits exist (Bellinger 2008).

Hg and Cd distribution patterns in maternal blood indicated values close to the LOQ for these elements (LOQ Hg = 0.02 μg/L; LOQ Cd = 0.006 μg/L). The main non-occupational Hg exposure source is fish and shellfish consumption (Ruggieri et al. 2017), while the main Cd exposure source is smoking. A high number of pregnant women in the present study, approximately 40% of the population, reported passive or active smoking. In addition to smoking, other Cd sources have also been reported, such as contaminated water and vegetables, and roots contaminated by soil and irrigation water (Mezynska and Brzóska 2017).

Lead and As presented values more widely distributed around the central measures. Exposure to As occurs mainly through fish, rice and poultry consumption of (ATSDR 2007).

Table 2 Metal concentrations in pregnant women's blood and umbilical cord blood

Metal	Sample	Geometric means (95% IC)	P25	P50	P75	P95	KS *p**	Skewness	Kurtosis
As (μg/L)	Maternal blood	10.27 (9.37–11.18)	8.90	11.13	12.81	17.99	0.077	1.98	9.73
	Umbilical cord	10.31 (9.75–10.93)	8.65	10.71	12.78	15.88	0.978	0.18	− 0.23
Pb (μg /dL)	Maternal blood	3.74 (3.40–4.12)	2.38	3.75	5.46	7.96	0.081	1.97	5.39
	Umbilical cord	3.85 (3.53–4.19)	2.87	3.69	4.92	11.54	0.001	2.54	7.11
Hg (μg/L)	Maternal blood	1.00 (0.85–1.18)	0.56	0.76	1.44	6.76	0.000	3.13	11.24
	Umbilical cord	1.11 (0.97–1.27)	0.68	0.91	1.63	5.14	0.000	2.00	3.49
Cd (μg/L)	Maternal blood	0.30 (0.29–0.53)	0.19	0.37	0.83	9.28	0.000	4.58	24.55
	Umbilical cord	0.41 (0.32–0.52)	0.22	0.37	0.84	4.67	0.000	4.92	25.83

*Kolmogorov-Smirnov test

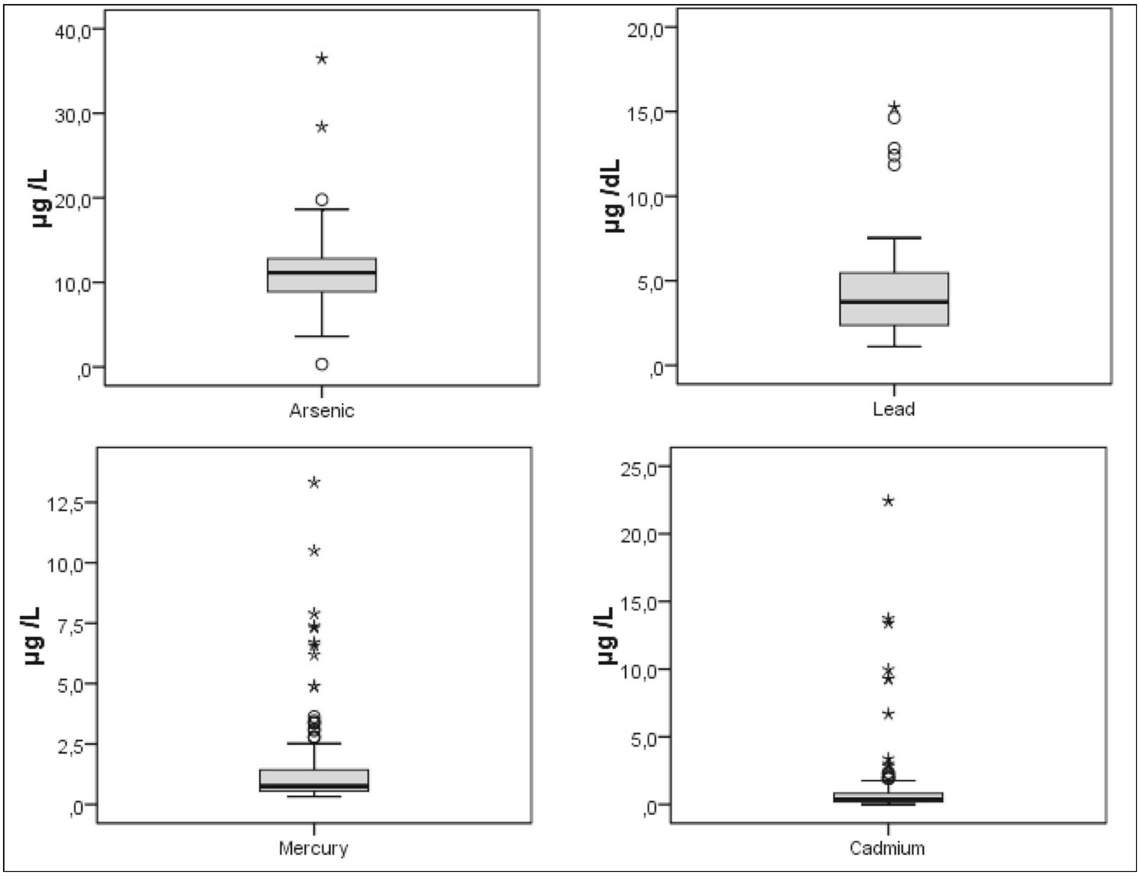


Fig. 1 Metal concentrations in maternal blood

A study conducted in southern and southeastern Brazil reported the presence of As in certain types of fish consumed by the population, in concentrations up to 23.5 mg/kg (Avigliano et al. 2019). Another study conducted on the Brazilian coast verified As concentrations ranging from 42.5 to 238 mg/kg in different species consumed by humans (Gao et al. 2018). In addition to fish, birds are also an important source of As (ATSDR 2007). Birds fed arsenic-containing feed may accumulate this metal in their body. However, rice and beans are noteworthy among As-containing food items as a daily consumption foodstuff in the Brazilian population (Ciminelli et al. 2017). Another As source is the ingestion of contaminated water (ATSDR 2007).

Human exposure to Pb occurs through different industrial sources (Capitani et al. 2009), poorly maintained residential paintings, contaminated dust and soil and vehicle emissions (Freitas et al. 2007). Pb present in the atmosphere and soil can also be deposited in water, leading to contamination (Silva et al. 2018). A study assessing water samples from different cities in Brazil, including Rio de Janeiro, found Mn, Cd and Pb in concentrations above the limits set by the National Environment Council (Ramalho et al. 2000). Contaminated water and soil can lead to food contamination, while other sources are also noted, such as alcoholic beverages, cosmetics, toys, herbal medicines and others, depending on the individual' work, housing and consumption circumstances (Capitani et al. 2009).

The metal distributions in umbilical cord blood displayed a distribution pattern similar to that of maternal blood except for Hg, whose pattern was more elongated compared to the maternal pattern. Placenta permeability to these metals leads to intrauterine exposure (Freire et al. 2018; ATSDR 2007). This transfer occurs in different amounts and is higher in the case of Hg (Lauwerys 1978) whose concentration in umbilical cord blood may reach up to twice the values compared to maternal blood, which may indicate active Hg transport to the fetus (Gundacker and Hengstschläger 2012), corroborated by the results reported here.

Additionally, as observed in Fig. 3, this study indicates positive correlations for the four metals analyzed in the mother-baby pairs. Other studies have previously reported correlations between these metals in maternal and cord blood. Al-Saleh et al. (2011), in a study conducted in Saudi Arabia with 1574 pregnant women, reported a positive correlation coefficient for Pb and Hg in mother and umbilical cord blood, of, respectively, $R = 0.456$ ($p < 0.001$) and $R = 0.202$ ($p < 0.001$). Sabra et al. (2017), in a study conducted in Barcelona, Spain, with 178 mother-infant pairs, identified a

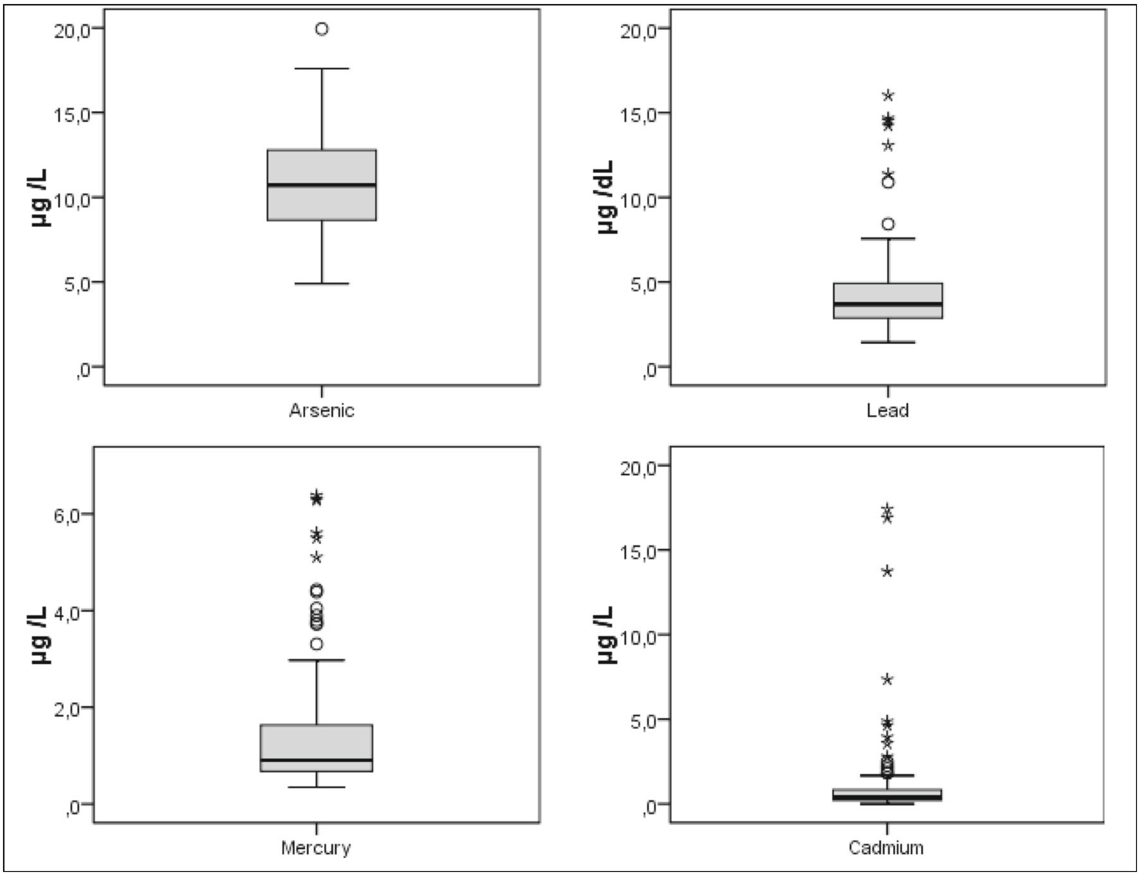
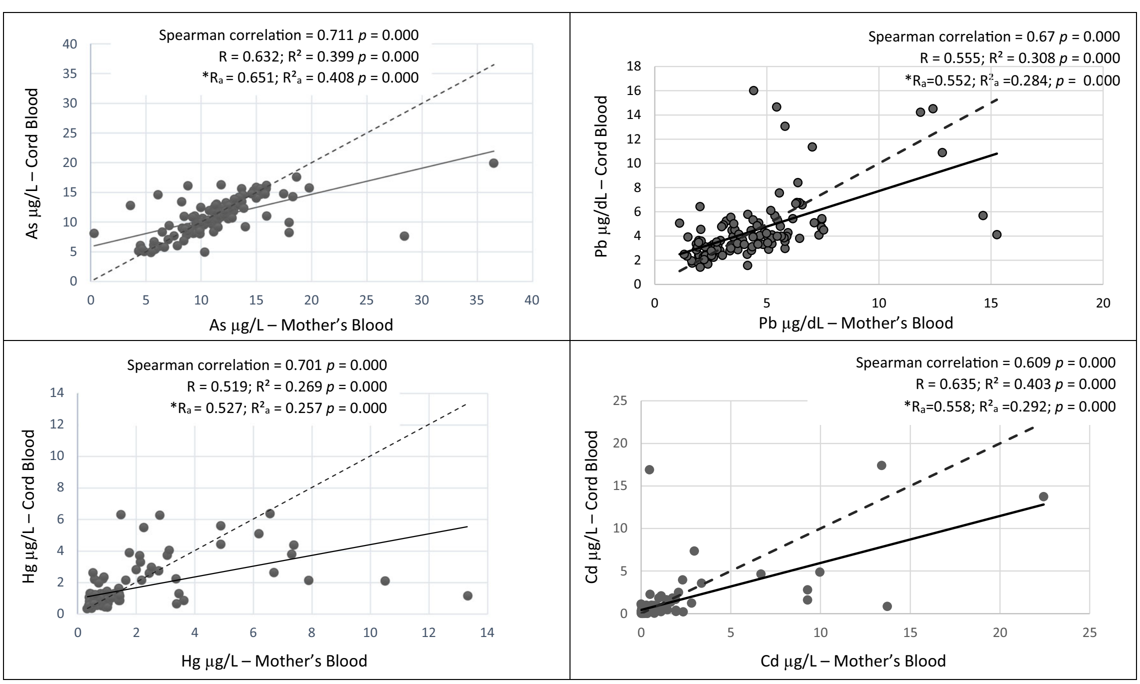


Fig. 2 Metal concentrations in maternal in umbilical cord blood



_ _ _ _ _ Equality Relationship Line
_______ Correlation line
*R_a and R^2_a – R and R^2 by Linear regression adjusted for Passive smoking and active smoking

Fig. 3 Correlation between metal mother's blood and umbilical cord concentrations

Table 3 Correlation matrix between mother's blood metal concentrations

Metals	As	Cd	Pb	Hg
As correlation coefficient (*p*)	1			
Cd correlation coefficient (*p*)	0.244* (0.008)	1		
Pb correlation coefficient (*p*)	0.233* (0.012)	0.471* (0.000)	1	
Hg correlation coefficient (*p*)	− 0.025 (0.785)	0.425* (0.000)	0.427* (0.000)	1

*The correlation is significant (two ends)

positive correlation between serum mother and fetus blood Cd levels ($r = 0.4$, $p < 0.001$). Ettinger et al. (2017) found a positive correlation between As concentrations in mother blood in the third trimester of pregnancy and in umbilical cord ($r = 0.29$) in Canada. These results suggest possible umbilical cord blood metal predictability from maternal blood concentrations during pregnancy. In the present study, Cd and Hg concentrations in mother blood explained approximately 40% of the results observed in the umbilical cord ($R^2 = 0.403$ and $R^2 = 0.399$, respectively). This determination capacity was lower for Pb and As ($R^2 = 0.308$ and $R^2 = 0.269$) (Fig. 1).

In general, the population is simultaneously exposed to multiple metals that may be toxic to human health. However, evidence on the combined effect of exposure to these metals is still limited (Goodson III et al. 2015; Grandjean and Landrigan 2014). This interaction may vary depending on the site of action and assessed effect (Sanders et al. 2015), and varied statistical analysis techniques with different limitations have been applied (Taylor et al. 2016). In the present study, correlation analyses between metals in maternal blood identified higher positive correlations between Pb and Cd ($R = 0.471$, $p = 0.000$), Cd and Hg ($R = 0.425$, $p = 0.000$) and Hg and Pb ($R = 0.427$, $p = 0.000$). Positive correlations between Pb and Cd, Cd and Hg, and Pb and Hg were also observed in umbilical cord albeit correlations weaker, while Hg and As displayed an inverse relationship (Table 2).

Interaction processes between metals can occur both at their absorption level and concerning specific effects (Goyer 1997). Their absorption can also be altered by competition with essential nutrients such as iron and calcium. The gastrointestinal absorption of Cd can vary between 5 and 8%; however, in cases of low dietary calcium and iron intake, this absorption may be higher, also noted for Pb (Klaassen, 2001).

A birth cohort evaluated the effects of environmental exposure and diet during pregnancy on fetal and child development in different areas of Spain, with the participation of 302 children. The study assessed fetal exposure through the placenta and cognitive functions and motor neurodevelopment disorders at ages 4 and 5, and noted a synergistic interaction between Pb and As when assessing effects on overall cognitive score at 5 years old ($\beta = -16.47$ 95% CI -30.45–2.49) (Freire et al. 2018). Interaction effects between Pb and As (McDermott et al. 2011) and combined exposure to Pb, As, Hg, and Cd (Pan et al. 2018) on childhood neurodevelopment have been described. Animal studies have shown that Pb and As share a similar mechanism of action in brain development (Rai et al. 2010), so combined exposure during central nervous system development could lead to a toxic synergistic effect (Freire et al. 2018). Pb, Hg, As, and Cd present not only the ability to overcome the transplacental barrier, leading to fetus exposure, but also the blood-brain barrier (Ruggieri et al. 2017). Identifying the interaction processes between metals from environmental exposure and their consequent effects on fetal and child development is of the utmost importance (Zhou et al. 2018).

The results of this study point to a combined exposure condition to the investigated metals, while also corroborating transplacental exposure, despite a relatively small sample number.

Conclusions

Detectable Pb, As, Cd, and Hg concentrations were found in all maternal and cord blood samples assessed in the present study. A moderate to strong positive correlation was found

Table 4 Correlation matrix between umbilical cord blood metal concentrations

Metals	As	Cd	Pb	Hg
As correlation coefficient (*p*)	1			
Cd correlation coefficient (*p*)	0.220* (0.017)	1		
Pb correlation coefficient (*p*)	0.160 (0.084)	0.340* (0.000)	1	
Hg correlation coefficient (*p*)	− 0.18 (0.052)	0.438* (0.000)	0.377* (0.000)	1

*The correlation is significant (two ends) between all metals in mother and umbilical cords blood, corroborating their ability to cross the placenta. Metal concentrations in maternal blood may be indicative of umbilical cord blood concentrations. In general, the four analyzed metals showed significant serum concentration correlations in both maternal and cord blood, which highlights the need to evaluate the effects of combined action on fetal development and childhood. Further studies are required to evaluate the possible effects of early exposure to this metal combination.

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Compliance with ethical standards

The PIPA project is coordinated by the Federal University of Rio de Janeiro in partnership with the Oswaldo Cruz Foundation, approved by the Maternity Research School (no. 2,092,440) and the Oswaldo Cruz Foundation (no. 2,121,397) Ethics Committees.

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