Prenatal exposure to metals and neurodevelopment in infants at six months: Rio Birth Cohort Study of Environmental Exposure and Childhood Development (PIPA Project).

Monica Seefelder de Assis Araujo (✉ monica.seefelder@nutricao.ufrj.br)

UFRJ: Universidade Federal do Rio de Janeiro <https://orcid.org/0000-0002-6352-9943>

Nataly Damasceno de figueiredo

UFRJ ME: Universidade Federal do Rio de Janeiro Maternidade Escola

Jorge Fonte de Rezende Filho

UFRJ ME: Universidade Federal do Rio de Janeiro Maternidade Escola

Joffre Amim Junior

UFRJ ME: Universidade Federal do Rio de Janeiro Maternidade Escola

Marlos Melo Martins

UFRJ ME: Universidade Federal do Rio de Janeiro Maternidade Escola

Santos Alves Vicentini Neto

FIOCRUZ: Fundacao Oswaldo Cruz

Lisia Maria Gobbo dos Santos

FIOCRUZ: Fundacao Oswaldo Cruz

Silvana do Couto Jaco

FIOCRUZ: Fundacao Oswaldo Cruz

Volney Magalhães Camara

UFRJ FM: Universidade Federal do Rio de Janeiro Faculdade de Medicina

Ronir Raggio Luiz

UFRJ: Universidade Federal do Rio de Janeiro

Amaldo Prata Barbosa

UFRJ ME: Universidade Federal do Rio de Janeiro Maternidade Escola

Carmen Ildes Rodrigues Froes Asmus

UFRJ ME: Universidade Federal do Rio de Janeiro Maternidade Escola

Research Article

Keywords: Environmental child health, Environmental exposure, Heavy metals, Neurodevelopment, Umbilical cord blood

Posted Date: July 23rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-734023/v1>

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Abstract

The PIPA Project is a prospective birth cohort study based in Rio de Janeiro, Brazil, whose pilot study was carried out between October 2017 and August 2018. Arsenic (As), cadmium (Cd), lead (Pb), and mercury (Hg) concentrations were determined in maternal (n = 49) and umbilical cord blood (n = 46). The Denver Developmental Screening Test II (DDST-II) was applied in 50 six-month-old infants. Metals were detected in 100% of the mother and newborn samples above the limits of detection. Maternal blood lead concentrations were higher in premature newborns (GM: 5.72 µg/dL; p = 0.05). One-third of the infants (17–33%) exhibited at least one fail in the neurodevelopment evaluation (fail group). Maternal blood arsenic concentrations were significantly (p = 0.02) higher in the "fail group" (GM: 11.85 µg /L) compared to infants who did not fail (not fail group) (GM: 8.46 µg /L). Maternal and umbilical cord blood arsenic concentrations were higher in all Denver Test's domains (except personal/social) in the "fail group", albeit non-statistically significant. These findings indicate the need to further investigate the toxic effects of prenatal exposure to metals on infant neurodevelopment.

1. Introduction

Metals are significant environmental pollutants and may originate from natural sources or as a result of human activities (Jaishankar et al., 2014). The Agency for Toxic Substances and Disease Registry (ATSDR) lists arsenic (As), cadmium (Cd), lead (Pb) and mercury (Hg) in the Priority Substance List, based on a combination of frequency, toxicity and potential for human exposure (ATSDR, 2017).

Chronic low-dose exposure to these metals may cause toxic human health effects (Moraes et al., 2012). Environmental exposure to heavy metals can occur through inhalation (indoor and outdoor air pollution) or ingestion of contaminated food and water (Goyer, 1996, Tchounwou et al, 2012). Some metals, such as mercury and lead, are known neurotoxic elements (Schofield, 2017). Neurotoxic metals may represent a risk for child neurodevelopment during critical early life periods (Dórea, 2020). Fetal brain development during pregnancy, for example, is susceptible to the action of neurotoxic substances (Schofield, 2017), as the placental barrier is not completely impermeable to the passage of harmful substances, including heavy metals (Caserta et al, 2013). Several studies have reported an association between metal exposure during pregnancy and early childhood and impaired cognitive function in children (Lanphear et al., 2005; Bellinger, 2008; Jurewicz, Polanska and Hanke, 2013; Liu et al., 2014).

In Brazil, few studies have investigated metals in maternal and umbilical cord blood (Rosalem, 2004; Santos et al, 2007; Amaral et al., 2010; Rudge et al., 2011; de Assis Araujo et al, 2020). In one study carried out with 117 newborns in the city of Rio de Janeiro, Southeastern Brazil, de Assis Araujo et al. (2020) observed As, Cd, Pb and Hg concentrations above the limit of detection (LD) in all maternal and umbilical cord blood samples and Pb concentrations near 5µg/dL in 25% of the investigated newborns (de Assis Araujo et al.; 2020).

The Rio Birth Cohort Study on Environmental Exposure and Child Development (PIPA Project) is a prospective cohort study conducted at the Federal University of Rio de Janeiro Maternity School, in the city of Rio de Janeiro, southeastern Brazil, aiming at the investigation of the effects of environmental pollutants on maternal and child health. A pilot study (PIPA Pilot study) was carried out between September 2017 and August 2018, with 142 pregnant women enrolled in and 135 children born at the Federal University of Rio de Janeiro Maternity School (Asmus et al, 2020). This study investigates potential associations between metal concentrations in maternal and umbilical cord blood and newborn neurological development among the PIPA pilot study population.

2. Material And Methods

2.1 Study area

The PIPA Pilot Study was carried out for 12 months, from September 2017 to August 2018, at the UFRJ Maternity School (UFRJ Maternity). The UFRJ Maternity is located in the South zone of the city of Rio de Janeiro and is a reference maternity hospital for the delivery of eight family health centers (CSFs) responsible for the prenatal care of populations living in low-income communities in this city zone. It is also a reference for the monitoring of high-risk pregnancies in the Rio de Janeiro public health system.

2.2 Study population

A total of 135 children were born at the UFRJ Maternity between October 2017 and February 2018 during the PIPA Pilot Study. Five dropouts occurred, so 130 newborns were eligible for follow-up visits. In this assessment, the study population comprises all children that returned for a follow-up visit in the sixth months, totaling 58 infants (44.6%). The infants were evaluated using the Denver Developmental Screening Test II (DDST-II). Exclusion criteria comprised children admitted to the intensive care unit during the neonatal period, birth weight < 2.5 kg, gestational age < 34 weeks and mother drugs use during pregnancy. After these exclusions, the study population comprised a total of 50 (38.5%) children (Fig. 1).

2.3 Arsenic, cadmium, lead and mercury determinations

Arsenic, Cd, Pb and Hg in maternal blood samples collected during the third trimester of pregnancy and umbilical cord blood collected during delivery were analyzed employing the inductively coupled plasma mass spectrometry technique (ICP-MS), at the National Institute for Quality Control in Health (INCQS) laboratory, at the Oswaldo Cruz Foundation (FIOCRUZ). The limits of quantification (LQ) for As, Cd, Pb and Hg were, respectively 0.01 µg/L, 0.006 µg/L, 0.05 µg/L and 0.02 µg/L, while the limits of detection (LD) were 0.003 µg/L, 0.002 µg/L, 0.015 µg/L and 0.007 µg/L, respectively. The sample collection and analysis procedures have been previously described by Asmus et al (2020).

2.4 Denver Development Screening Test II (DDST-II)

Infant neurodevelopment was assessed using the Denver Developmental Screening Test II (DDST-II). The DDST-II is the 1992 revised version of the Denver Screening Test developed by Frankenburg and Dodds in

1967 (Frankenburg, Dodds and Archer, 1992). The DDST-II used herein is the version translated into Portuguese. The Brazilian Society of Pediatrics recommends this test to monitor child development (Pinto et al, 2015). The DDST-II can be applied by health professionals directly to the child or through its parents or guardians. The purpose of this tool is to screen neuromotor development, evaluating children from zero to six years old regarding their ability to perform tasks organized in four neurodevelopmental domains: “Personal-Social”, “Fine Adaptive Motor”, “Gross Motor” and “Language”. Each task is represented by a bar that indicates the age in which task compliance is performed by 25%, 50%, 75% and 90% of children. A score is given to each task evaluated, as follows: “pass, fail, refuse, no opportunity” (Frankenburg, 1996).

For all newborns, a follow-up appointment at sixth months was scheduled, when the DDST-II was applied for neurodevelopment assessment, in the presence of the mother by a specially trained examiner who was unaware of the child's developmental history and of the metal levels at the time of the test.

All “fail” and “refuse” scores were considered as “fail.”, and “no opportunity” and “pass” scores were considered to “not fail.”

2.5 Statistical analyses

A descriptive analysis of participants characteristics was performed. Frequency distributions for categorical variables and arithmetic mean and median for the continuous variables were calculated. The geometric means, 25th, 50th, 75th, 90th and 95th percentiles and the minimum and maximum values of the pollutant concentration levels were calculated for the maternal and umbilical cord blood samples.

Spearman's correlation or non-parametric comparisons (Mann-Whitney) or parametric (Student) tests were used to evaluate continuous variables and Chi-squared or Fisher tests were used for categorical variables. All data were analyzed using the SPSS v.21 software.

3. Results

Arsenic, Cd, Pb, and Hg were above the LQ in all maternal blood and umbilical cord blood samples (Table 1). A significant positive correlation was observed between all metal concentrations in maternal and umbilical cord blood, as previously described by Figueiredo et al. (2020).

Mean mother age was 28.54 years old (SD $\pm$ 7.07), with a mean *per capita* income of US\$ 257.00 (SD $\pm$ 167.38) and median of 14 years of schooling; 71.4% of the mothers were non-white, 36.7% reported exposure to tobacco (personal and second-hand exposure) and 50.0% consumed alcohol during pregnancy. A statistically significant positive correlation between maternal age and cord blood concentrations were observed for Hg ($r = 0.34$; 0.02) and Pb ($r = 0.29$; 0.05). Non-white pregnant women presented higher geometric Cd means in maternal blood ($p = 0.04$) and cord blood ($p = 0.08$) compared to white women (Table 2).

Mean birth weight was 3.3 kg (SD $\pm$ 0.5 kg) and median gestational age was 39 weeks (range: 36-41 weeks), 62.0% (n=31) of all infants were male, 11.1% (n=5) were small for gestational age (SGA) and 6.0% (n=3), premature (IG 34 - 37 weeks). The geometric Pb mean in maternal blood (5.72 μ g / dL; p = 0.05) and in cord blood (7.23 μ g/dL; p = 0.16) was higher in premature babies. An inverse correlation trend was observed between gestational age and Cd concentrations in maternal blood (-0.25; p = 0.08) and in umbilical cord blood (-0.21; p = 0.16) (Table 3).

In the sixth month follow-up visit, 50 eligible children were evaluated with regard to the four neurodevelopmental Denver Test's domains. Most (33 -66.0%) did not fail in any domain ("not fail" group) and 17 (33.0%) children failed in one or more domains ("fail" group). No differences were observed concerning maternal sociodemographic characteristics and birth characteristics between the "fail" and "not fail" groups (Table 4).

Comparisons between the metal concentrations geometric means in maternal blood and cord blood between the "fail" and "not fail" groups in the sixth month are displayed in Table 5. The geometric means for maternal blood As were significantly higher in the "fail group" compared to the "not fail group" (p=0.02). The maternal and cord blood As concentrations were higher also in the "fail group" for the fine adaptative motor (p=0.27), language (p=0.36), and gross motor (p=0.07) Denver Test's domains, (Table 6), albeit non-significantly. No significant results were observed for the other metals between the "fail" and "not fail" groups and each DDST-II domain.

4. Discussion

To the best of our knowledge, this study is the first in the city of Rio de Janeiro to investigate prenatal exposure to As, Cd, Pb and Hg and the neurodevelopment of children up to 6 months of age.

Maternal and umbilical cord blood geometric means for As were higher in the "fail" group for DDST-II in the six month, statistically significant for maternal blood. Some studies have investigated the effect of prenatal exposure to As on neurological infant development. Liang et al. (2020), in a prospective Chinese birth cohort study (Ma'anshan Birth Cohort-MABC) on 2315 six-month-old infants, observed associations between umbilical cord serum As concentration (median = 1.89 μ g /L) and suspected developmental delay in the personal-social domain (Liang et al, 2020). Wang et al. (2018), in a cross-sectional study carried out in Shanghai (n = 892), observed that newborns with a low neonatal behavioral neurological assessment (NBNA) score exhibited higher concentrations (median, interquartile range) of umbilical cord As (3.93, 1.27–8.21 μ g/L) than those with a high NBNA score (0.61, 0.23–1.50 μ g/L). Tolins, Ruchirawat, & Landrigan, (2014), concluded in a review study that intrauterine exposure may be associated with neurodevelopment deficits, even at exposure levels below current safety guidelines (10 μ g/L in drinking water), with manifestations detected only later in life. Those authors also observed that certain factors, such as sex, concomitant exposures and exposure time, modify developmental As neurotoxicity.

No associations between fails in the neurodevelopment domains and maternal or cord blood Cd, Pb, and Hg concentrations in our study population were observed. Nevertheless, in a systematic review study,

Asmus et al (2016) reported a body of studies demonstrating associations between high child exposure to Hg in the Brazilian Amazon and poor neurobehavioral assessment results. Marques et al (2007, 2009), evaluated the neuromotor development of 82 six-month-old children, in the Brazilian Amazon and observed an inverse and significant correlation between hair Hg contents and neurodevelopment delay ($r = -0.333$; $p = 0.002$) (Marques et al, 2007; Marques et al, 2009; Asmus et al, 2016).

Birth conditions and nutritional status are known to interfere in child neurodevelopment (Halpern et al., 1996; Costa et al., 2015; Hirvonen et al., 2017; Allotey et al., 2018). Halpern et al. (1996), in a study carried out in the city of Pelotas, southern Brazil, with 1362 one-year-old children, observed the occurrence of neurodevelopmental failures through the application of the DDST-II, inversely associated with birth weight. Higher birth weights were observed herein in the “not fail” group, although not statistically significant.

We report herein a positive correlation between maternal age and Pb (0.29; $p = 0.05$) and Hg (0.34; $p = 0.02$) levels in umbilical cord blood (Table 2). Other studies have also reported that maternal age is associated with higher Pb and Hg levels in umbilical cord blood (Bjerregaard & Hansen, 2000; Arbuckle et al, 2016; Bocca et al, 2020; Hadavifar et al, 2020). This may be due to the accumulation of these metals in the body (Bocca et al, 2019). The higher Hg and Pb concentrations in umbilical cord compared to maternal blood can be attributed to increased glomerular filtration rates during pregnancy, resulting in higher renal elimination (Selevan, Kimmel & Mendola, 2000). A significant positive correlation was observed between As, Cd, Pb, and Hg concentrations in maternal and umbilical cord blood, as previously described by Figueiredo et al (2020).

The maternal and cord blood geometric means for Cd were higher in the non-white ethnic group, significant only for maternal blood. Some studies suggest that higher biological Cd levels may be associated to a more socioeconomically vulnerable population, including lower socioeconomic favored ethnicities (Lewin et al, 2017; Bulka et al 2019), as is the case of the non-white population in Brazil.

Associations between gestational age and metal concentrations has been investigated in many studies (Ettinger & Wengrovitz, 2010; Kumar et al, 2017; Ashrap et al 2020). In the present assessment, maternal blood Pb concentrations were significantly higher in preterm children (gestational age > 34 weeks and < 37 weeks). No associations were observed between maternal or cord blood As concentrations and gestational age.

No significant associations were observed between mother age, income, education, ethnicity or tobacco or alcohol use and the “fail” and “not fail” groups. The differences between the results reported herein and other studies may be due to sample size, metal concentrations, the type of test used to assess neurodevelopment and the influence of sociodemographic factors and lifestyle (Bellinger, 2009). The long-term development of the investigated children may alter the results, as other areas of child development will be better analyzed with a longer observation time.

A limitation of this study comprises the individual analysis of each metal without considering their potential interactions and the small number of participants. Despite this, these findings provide information on environmental prenatal exposure to metals and potentially adverse neurodevelopment effects on newborns, encompassing sociodemographic and lifestyle data.

Conclusion

This study provides evidence of associations between As concentrations in maternal blood and fails in infant DDST-II. Continuous monitoring of neurotoxic substance concentrations in women at reproductive age is paramount to establish preventive measures to eliminate or minimize the risk of fetal exposure during pregnancy. Longer-term development studies may reveal other associations. Future investigations should aim to demonstrate the possible neurodevelopment effects of prenatal exposure to environmental pollutants on child health and identify potential exposure sources.

Declarations

Acknowledgements The authors would like to acknowledge the UFRJ Maternity School team for the broad support of the PIPA project and the study participants for their contributions.

Author Contributions All the authors participated in the conception and design, or analysis and interpretation of the data, drafting the article or revising it critically for important intellectual content. All the authors approved the final version. This manuscript is original research and has not been submitted to, nor is under review at, another journal or other publishing venue.

Funding Funding was received from the Brazilian Government: National Council for Scientific and Technological Development (Grant No. 409275/2018-2), Science and Technology Department (Grant No.404168/2019-1), Surveillance Health Secretary (Grant No. 733663/19- 002), and Ministry of Health and the Carlos Chagas Filho Foundation for Supporting Research in the State of Rio de Janeiro (Grant No. E-26/010.001894/2019).

Conflict of interest The authors do not have any competing or conflicts of interest.

Ethical Approval This research involved human participants and all procedures were approved by the Federal University of Rio de Janeiro (UFRJ) Maternity School Ethics Committee (reference number: 2.092.440) and the Fiocruz Foundation Ethics Committee (reference number: 2.121.397).

Informed Consent All participants signed an informed consent before any procedure was performed.

Consent for Publication All the authors agree with the publication of this manuscript.

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Tables

Due to technical limitations, Table 1,2,3,4, 5 and 6 are only available as a download in the Supplemental Files section.

Figures

Figure 1

Selection process of the study population.

Supplementary Files

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