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Research

Prenatal Exposure to Mercury and Adverse Birth Outcomes in Rio de Janeiro, Brazil: Rio Birth Cohort Study (PIPA Project)

Angelica dos Santos Vianna[1)], Volney de Magalhaes Camara[1)], Nataly Damasceno de Figueiredo[2)], Carmen Ildes Rodrigues Froes Asmus[2)]

[1)]Public Health Studies Institute (IESC), Federal University of Rio de Janeiro (UFRJ), Brazil
[2)]Maternity School (ME), Federal Unversity of Rio de Janeiro (UFRJ), Brazil

ABSTRACT

Background: Mercury (Hg) is a highly toxic environmental pollutant, with studies of its prenatal exposure indicating adverse birth outcomes such as low birth weight, preterm delivery, and microcephaly. Therefore, we analyzed prenatal Hg exposure levels and their relationship with birth outcomes in pregnant women living in an urban area in the city of Rio de Janeiro.
Subjects and Method: A cross-sectional study nested in the prospective birth cohort (PIPA Project) was conducted at the Federal University of Rio de Janeiro Maternity School from October to November 2017. A total of 117 mother-infant pairs were evaluated. The sampling technique used convenience sampling. The independent variables encompassed maternal and cord blood Hg levels, while the dependent variables were birth weight, birth length, head circumference (neonatal anthropometrics), and Apgar score at 1 and 5 minutes. The Hg levels were analyzed using inductively coupled plasma-mass spectrometry, and dependent variable data were obtained through medical records. Multiple regression models were applied using the SPSS.
Results: The detection rate of maternal and cord blood was 100%, with medians of 0.76 and 0.91 µg/L, respectively. A strong correlation between maternal and cord blood Hg levels was observed ($r= 0.70$; $p<0.010$), as well as an inverse association between cord blood Hg and Apgar score at 1 and 5 minutes ($b=-0.47$; $p<0.010$; $b=-0.34$; $p<0.010$) after adjusting for covariates.
Conclusion: Our study provided preliminary evidence that Hg exposure was associated with a worse Apgar score at 1 and 5 minutes. However, the relevance of this finding requires further evaluations due to its potential clinical implications concerning newborn health.

Keywords: Mercury, Maternal exposure, Apgar Score, Anthropometry

Correspondence:
Angelica dos Santos Vianna. Federal University of Rio de Janeiro (UFRJ). Avenida Horacio Macedo sem numero – Proximo a Prefeitura Universitária da UFRJ. Ilha do Fundao – Cidade Universitária. ZIP Code: 21941-598, Rio de Janeiro, RJ, Brazil. Email address: angelica-@iesc.ufrj.br

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BACKGROUND

Mercury (Hg) is a widely distributed in the environment, release from both natural (e.g., volcano outgassing) and anthropogenic (e.g., industrial settings) sources. Considered one of the ten most toxic substances globally, it has no known physiological function in humans (Vigeh et al., 2018). Its adverse effects on health are of significant concern in all its three forms (elemental, inorganic, and organic), especially the most predominant organic form, methylmercury (MeHg), a

known neurotoxicant that readily crosses the placenta and the fetal blood-brain barrier, posing a particular threat to fetus development (Garcia-Esquinas et al., 2013). The main source of MeHg exposure is through the dietary route, primarily through fish and shellfish intake, and its consumption by pregnant women may lead to adverse birth outcomes (Taylor et al., 2016).

Fetuses and children present critical windows, where their developing organs and systems, immature detoxification mechanisms and augmented absorption rates compared to adults make them both susceptible and vulnerable to environmental threats (Pelroth et al., 2017). Adverse birth outcomes related to prenatal Hg exposure include low birth weight, microcephaly, and preterm birth (Karagas et al., 2012; Ramon et al., 2009; Xu et al., 2016). Most studies, however, have focused on populations displaying relatively high exposure levels based on high fish and shellfish consumption (Ding et al., 2013). Nevertheless, in the last two decades a growing body of research has explored the effects of lower Hg levels on a variety of health outcomes in both adults and children. In this regard, the potential impact of this level of exposure on fetal development is still uncertain, although there is suggestive evidence of negative effects (Karagas et al., 2012).

The city of Rio de Janeiro is the second most populous in Brazil (6.72 million), and the sixth in the American continent (IBGE, 2012; UN, 2018). The entire local popularation lives in the urban area, with a 22% estimate of slum habitation (IBGE, 2012).

The Rio Birth Cohort Study (PIPA Project) is prospective research study in development in the city of Rio de Janeiro and aims to investigate the effects of environmental pollutants on maternal-child health. A pilot study was carried out between September 2017 and August 2018 (PIPA Pilot study) evaluating prenatal exposure to chemicals, including Hg, and their association with adverse effects on birth outcomes and during the infant's first six months of development.

In this context, this assessment investigated potential associations between prenatal Hg exposure and birth outcomes in pregnant women taking part of the PIPA pilot study.

SUBJECTS AND METHOD

1. Study Design

This study was a cross-sectional study nested in the Rio Birth Cohort Study of Environmental Exposure and Childhood Development (Projeto Infancia e Poluentes Ambientais PIPA Project). It was conducted at the Rio de Janeiro Federal University (UFRJ) Maternity School, a reference hospital for all types of pregnancies (including high-risk pregnancy monitoring) and belongs to the Rio de Janeiro public health system, from October to November 2017.

2. Population and Sample

The population in this study were all pregnant women over the age of 16 in the third trimester referred to the UFRJ Maternity School and those presenting high-risk pregnancies in the metropolitan Rio de Janeiro area. The convenience sampling was used. Out of 209 eligible pregnant women, 142 accepted the invitation, 131 deliveries occurred at UFRJ Maternity School, and 117 mother-neonate pairs had complete data to be included in the final statistical analysis.

3. Study Variables

The dependent variables were Apgar score at 1 and 5 minutes and neonatal anthropometrics, including birth weight, birth length, and head circumference. The independent variables encompassed maternal and cord blood Hg levels.

4. Operational Definition of Variables

The Apgar scores at 1 and 5 minutes are a rapid methods of assessing the clinical status of the newborn and they were categorized into two (≤ 6 and ≥ 7).

The birth weight (g), birth lenght (cm), and head cirumference (cm) were the neonatal anthropometrics measured immediately after birth. The birth lenght was categorized according to baby sex (for male: less than 46.30 or above it, and for female: less than 45.30 or above it), and the head circumference (cm) was categorized according to baby sex (for male: less than 31.90 or above it, and for female: less than 31.50 or above it).

The maternal and cord blood Hg levels reflected the exposure of the participants to Hg and were presented as numerical variable (continuous).

5. Study Instruments

The collection of social-demographic and lifestyle data was performed through an enrollment questionnaire administered to the mothers. Infant sex, birth date, delivery method, gestational age, Apgar score at 1 and 5 minutes and neonatal anthropometrics were obtained from medical records. Data on prior medical history, current health behavior, and clinical estimates of gestational age (ultrasound and last menstrual period) were also obtained.

Maternal 3rd trimester whole blood and umbilical cord blood were collected in 20 mL K2 EDTA tubes. The umbilical cord blood, comprising a mixture of venous and arterial umbilical blood was collected during newborn delivery. Samples were stored at 2°C–7°C, for a maximum of 48 h until transportation in isothermal boxes containing recyclable ice to the National Institute of Quality Control in Health Laboratory (INCQS), belonging to the Oswaldo Cruz Foundation (FIOCRUZ), where they were frozen at -4°C until metal content determinations. Chemical analyses werperformed using the inductively coupled plasma-mass spectrometry (ICP-MS) technique. Samples (0.5 mL) were first diluted with demineralized water to 10 mL, followed by the addition of 1.0 mL of 65% nitric acid (HNO_3). Specimens were then heated to 80°C in a water bath for 2–3 h in order to ensure complete organic matter digestion. The limit of quantification (LOQ) for mercury was 0.02 µg/L, while the limit of detection (LOD) was 0.007 µg/L.

6. Data analysis

Univariate analysis use kolmogorov smirnof, Bivariate analysis use Mann-Whitney U-test and Kruskal-Wallis tests were used to assess differences in Hg concentrations and other continuous variables. Spearman's correlation was used to examine potential correlations between birth factors, maternal and cord blood Hg levels, fish consumption, and maternal blood Hg levels. The Chi square test was employed to test the relationship between maternal blood Hg levels, transformed into tertiles, with potential Hg sources, thimerosal-containing vaccine and fish and shellfish intake. Multivariate analyis use linear regression

7. Research Ethics

The present study was conducted after approval from the UFRJ Maternity School (reference number: 2.092.440) and FIOCRUZ (reference number: 2.121.397) ethics committees. Written informed consents were obtained from all participants after explaining the purpose and procedure of the study, privacy protection, the right to refuse to participate, and withdrawal from the study at will. Survey participation was strictly voluntary.

RESULTS

1.Univariate Analysis

One-hundred and seventeen mother-infant pairs were evaluated. The median age of the mothers was 27 (IQR= ±12.00), and 76

(66.10%) of them had ≥13 years of schooling, 58 (54.40%) earned a salary of up to three Brazilian minimum wages (R$ 2,811.00 or USD 848.22), and 87 (75.70%) were married. Concerning life and eating habits, 86 (74.80%) were not smokers, 71 (61.70%) used to drink alcohol beverage, 46 (40%) ate up to two servings of lean fish and 43 (46.10%) of oily fish. In contrast, 73 (63.50%), and 53 (46.10%) did not ate any canned tun and shellfish, respectively. Regarding the vacines containing thiomerosal, 61 (53%) had at least one during pregnancy. None was occupationally exposed to Hg. Finally, 55 (47.80%) had been at least one time pregnant, 39 (33.90%) had normal body mass index (BMI), and 43 (37.40%) gained less than 10 kg during pregnancy.

Concerning newborn infant characteristics, 65 (56.50%) were male, 64 (57.70%) were delivered through caesarean, and 104 (90.40%) had gestational age ≥ 37 weeks. The medians for birth weight, body length and head circumference were respectively, 3240.00 g (IQR= 646.50), 48.50 cm (IQR= 2.50), and 34.0 cm (IQR= 2.00). Concerning Apgar scores (AS) at 1 and 5 minutes, 103 (89.60%) and 109 (94.80%) had AS ≥ 7, respectively (Table 1).

Table 1. Sample Characteristics

Characteristic	N (%)	Median ± IQR
Age (years)		27.00 ± 12.00
< 18	4 (3.50%)	
18 - 34	81 (70.40%)	
≥ 35	29 (25.20%)	
Education (years of schooling)		14.00 ± 2.70
< 10 (lower secondary)	6 (5.20%)	
10-12 (upper secondary)	30 (26.10%)	
≥ 13 (postsecondary and tertiary)	76 (66.10%)	
Monthly household income (US$)		755.90 ± 498.90
up to 1 Brazilian minimum wage (≤ 282.74)	6 (5.20%)	
> 1 to 3 Brazilian minimum wages	52 (45.20%)	
≥ 4 Brazilian minimum wages	39 (34.00%)	
Marital status		
Single	23 (20.00%)	
Married/Living as married	87 (75.70%)	
Smoking during pregnancy		
Yes	6 (5.20%)	
Living with smoker	19 (16.50%)	
No	86 (74.80%)	
Alcohool consumption		
Yes	71 (61.70%)	
No	37 (32.20%)	
Seafood consumption (servings/week)		
Lean fish		
None	37 (32.20%)	
up to 2sv/week	46 (40.00%)	
> 2sv/week	26 (22.60%)	

Continue.

Oily fish		
None	32 (27.80%)	
up to 2sv/week	53 (46.10%)	
> 2sv/week	25 (21.70%)	
Canned tuna		
None	73 (63.50%)	
up to 2sv/week	33 (28.70%)	
> 2sv/week	0 (0.00%)	
Shellfish		
None	53 (46.10%)	
up to 2sv/week	44 (38.30%)	
> 2sv/week	13 (11.30%)	
Vaccine containing thimerosal		
Yes	61 (53%)	
No	54 (47%)	
Occupational mercury exposure		
Yes	0 (0%)	
No	115 (100%)	
Parity		
0	29 (25.20%)	
≥ 1	55 (47.80%)	
Pre-pregnancy BMI*		
Underweight (< 18.5 kgm-2)	7 (6.10%)	
Normal (18.5 to 24.9 kgm-2)	39 (33.90%)	
Overweight (25.0 to 29.9 kgm-2)	35 (30.40%)	
Obese (≥ 30.0 kgm-2)	19 (16.50%)	
Gestational weight gain		
< 10 kg	43 (37.40%)	
10-15 kg	35 (30.40%)	
> 15 kg	27 (23.50%)	
Birth variables		
Sex		
Male	65 (56.50%)	
Female	47 (40.90%)	
Method of delivery		
Vaginal	50 (43.50%)	
Caesarean	64 (55.70%)	
Outcomes variables		
Gestational age		38.60 ± 1.80
< 37 weeks	10 (8.70%)	
≥ 37 weeks	104 (90.40%)	
Birth weight (g)		3240.00 ± 646.50
Male		3252.50 ± 523.30
Female		3277.60± 519.80

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Birth length (cm)		48.50± 2.50
Male (AGA)		48.30 ± 2.20
< 46.30	7 (10.80%)	
≥ 46.30	55 (84.60%)	
Female (AGA)	47.90 ± 3.80	
< 45.60	5 (10.60%)	
≥ 45.60	38 (80.90%)	
Head circumference (cm)		34.00 ± 2.00
Male		34.10 ± 1.50
Microcephalic (≤ 31.9)	2 (3.10%)	
Normocephalic (> 31,9 – 37)	61 (93.80%)	
Female	33.40 ± 1.80	
Microcephalic (≤ 31.5)	5 (10.60%)	
Normocephalic (> 31,5 – 36.2)	38 (80.90%)	
1-min Apgar score		
≤ 6	11 (9.50%)	
7-10	103 (89.60%)	
5-min Apgar score		
≤ 6	5 (4.40%)	
7-10	109 (94.80%)	

2. Bivariate Analysis

The maternal and cord blood medians were 0.76 (IQR= 0.88) and 0.91 (IQR= 1.14), respectively. Hg levels in cord blood were higher when compared to maternal blood in the median (1.2 times). A statistically significant difference in the cord blood Hg median was observed for birth length (p= 0.09) and head circumference (p= 0.02) in boys, birth weight (p= 0.03), and 1-minute (p= 0.01) and 5-minute (p= 0.08) Apgar scores (Table 2).

Table 2 Descriptive statistics of mercury levels in maternal and cord blood (n=117)

Blood sample	Median	IQR	p	Range	P25	P75
Hg maternal blood (µg/L)	0.76	0.88	0.590	0.33-13.32	0.56	1.44
Hg cord blood (µg/L)	0.91	1.14		0.35-6.38	0.67	1.81

Table 3 Descriptive statistics of mercury levels in maternal and cord blood and associations with birth outcomes (n=117)

Birth outcomes	Hg cord blood (µg/L)					
	Median	IQR	p	Range	P25	P75
Sex						
Male	0.92	1.09	0.84	0.35-5.50	0.63	1.63
Female	0.85	1.30		0.42-6.38	0.68	1.80
Gestational age						
< 37 weeks	0.67	2.60	0.41	0.37-6.28	0.53	2.83
≥ 37 weeks	0.92	1.04		0.35-6.38	0.68	1.63

Continue.

Birth outcomes	Hg cord blood (µg/L)					
	Median	IQR	p	Range	P25	P75
Birth weight (g)						
< 2500	0.54	1.01	0.03	0.37-3.90	0.51	0.99
≥ 2500	0.93	1.29		0.35-6.38	0.69	1.98
Birth length						
Male (AGA)						
< 46.30 cm	0.54	0.64	0.09	0.37-2.75	0.42	1.05
≥ 46.30 cm	0.92	1.20		0.35-6.38	0.70	1.81
Female (AGA)						
< 45.60 cm	0.87	1.43	0.66	0.51-3.90	0.55	1.32
≥ 45.60 cm	0.91	1.45		0.35-6.38	0.68	2.05
Head circumference						
Male						
Microcephalic (≤ 31.9 cm)	0.39	NC	0.02	0.37-0.42	0.37	0.42
Normocephalic (> 31.9 – 37 cm)	0.91	1.40		0.35-6.38	0.68	1.98
Female						
Microcephalic (≤ 31.5 cm)	2.16	2.65	0.48	0.51-3.90	0.73	2.64
Normocephalic (> 31.5 – 36.2 cm)	0.89	0.82		0.35-6.38	0.66	1.32
1-min Apgar score						
≤ 6	2.62	3.54	0.01	0.62-6.28	1.45	4.43
7-10	0.87	0.65		0.35-6.38	0.66	1.30
5-min Apgar score						
≤ 6	2.62	3.26	0.08	0.62-5.61	1.03	4.11
7-10	0.89	0.66		0.35-6.38	0.67	1.48

A significant positive correlation was observed between Hg maternal and cord blood (r= 0.70; p< 0.010), while no correlation between the fish and shellfish intake sum and Hg maternal blood was detected (r=-0.086;p=0.360)(Table3).

Table 4. Spearman correlation

	Hg maternal blood	
	r	p
Hg cord blood	0.70	0.010
Fish and shellfish intake sum	-0.09	0.360

Table 5. linear regression analysis

Birth outcomes	Prenatal exposure Cord blood Hg levels (µg/L)	
	β (95% CI)	p-value
Birth weight (g)	-0.12 (-151,19 to 55.73)	0.360
Birth length (cm)	-0.04 (-0.79 to 0.59)	0.780
Head circumference (cm)	-0.03 (-0.39 to 0.31)	0.810
1 minute Apgar score	-0.47 (-0.79 to -0.30)	0.010
5 minutes Apgar score	-0.34 (-0.54 to -0.11)	0.010
n observation= 85		
Adj R-Squared= 0.648		
p< 0.100		

3. Multivariate Analysis

The five multiple linear regression models indicated an inverse association between Hg cord blood and Apgar scores at 1 (b= -

0.47; 95%CI= −0.79 to −0.30; p< 0.010) and 5 (b= -0.34; 95%CI= −0.54 to −0.11; p< 0.010) minutes, with statistical significance. However, no association was found with neonatal anthropometrics (Table 5).

DISCUSSION

The findings reported herein revealed Hg exposure in all participants and both a strong correlation between maternal and cord blood, and a negative Hg cord blood association with Apgar scores at 1 and 5 minutes. Other associations observed and already reported in the literature were gestational age, birth weight and length (positive) (Callaghan et al., 2010), pre-gestational BMI and Apgar score negative (Zhu et al., 2015).

Hallmark studies on fetus and newborn susceptibility to prenatal Hg exposure are available, for example on the poisoning episodes in Japan and Iraq (Bose-O'Reilly et al., 2010; Patel et al., 2019). In Brazil, most reports concerning prenatal Hg exposure relate to Amazonian communities, which often exhibit relatively high exposure levels due to the large amounts of Hg-contaminated fish and shellfish consumption (Dutra et al., 2012; Hacon et al., 2000; Santos et al.,2007). On the other hand, studies assessing this kind of exposure and its effects on Brazilian urban area birth outcomes are still lacking. In this sense, our results are the first to provide information on blood Hg concentrations in a mother-infant pair sample in an urban area such as the city of Rio de Janeiro.

All evaluated biomatrices from all study participants contained Hg, indicating maternal exposure to Hg during pregnancy, at least in the third trimester when the blood samples were obtained. In urban areas, the main exposure sources comprise air pollution from fossil fuel combustion (especially coal), industrial settings, waste incinerators and contaminated water and food intakes (McLagan et al., 2018). Concerning the latter, contaminated fish and shellfish are the main source of methylmercury exposure (WHO, 2007). In the present study, occupational exposure (zero cases), fish intake, and vaccines (p>0.05) were ruled out as potential Hg sources. Air pollution from the presence of Hg-emitting industrial activities and the open dumping and landfill discarding of fluorescent lamps are potential exposure sources. To a lesser extent, Amazon deforestation and biomass burning, responsible for a higher amount of global Hg and road traffic emissions, may be another possibility. These sources emit Hg into the atmosphere, which then may travel hundreds of miles with the wind, creating a global issue (Crespo-Lopez et al., 2021; Won et al., 2007).

Low median Hg levels were observed in both biomatrices. These findings are similar to those reported in other studies in urban areas worldwide, where fish and shellfish intake was low (Arbuckle et al., 2016; Gundacker et al., 2010; Jedrychowski et al., 2007; Mendez et al., 2020; Morello-Frosch et al., 2016; Rollin et al., 2009; Taylor et al., 2016). Despite low median Hg levels detected in our study, 6.84% and 2.56% of the investigated maternal and cord blood samples, respectively, were above the Hg reference dose equivalent of 5.80 μg/L established by the U.S. Environmental Protection Agency (EPA), with higher levels potentially increasing the risk of adverse effects on pregnancy outcomes (US EPA,2007; Pinheiro et al., 2020). However, the maternal Hg results reported herein were two-fold higher compared to the U.S. National Health and Nutrition Examination Survey (NHANES) for 1999-2010, consisting of women aged 16 to 49 (NHANES: 3.45%) (US EPA, 2012).

In addition, the positive correlation

found for Hg between maternal and cord blood (ρ=0.70, p<0.010) indicates its transfer across the placental barrier, in line with previous studies (Song et al., 2016; Santos et al., 2007; Channa et al., 2013; Jedrychowski et al., 2007; Sakamoto et al., 2010). This is one of two most important Hg transfer route from mother to offspring. The first occurs during pregnancy, via the placenta, and the second, after birth, through breastfeeding (Song et al., 2016). Moreover, median Hg levels in cord blood were 1.2 fold higher than in the maternal blood, in agreement with results reported for Japan, Poland and Spain (Kim et al., 2011), probably because of the easy transfer of MeHg through the placenta due to special amino acid transporter characteristics, high MeHg affinity to fetal hemoglobin, and higher hemoglogin concentrations in newborns compared to mothers (Pinheiro et al., 2020; Kim et al., 2014).

The Apgar score (AS) is employed worldwide to assess neonatal status at birth. Many factors can influence its results, including maternal sedation or anesthesia, gestational age (prematurity) and neonatal weight (ACOG, 2015; Yang et al., 2019). In a scenario of low Hg exposure levels, our results suggest that cord blood Hg levels are negatively associated to AS at 1 and 5 minutes for both premature and to term infants. This topic has been only sparingly investigated and it is still unclear whether prenatal Hg exposure is a risk factor for this score. Out of the seven studies that have evaluated this subject, most were carried out in relatively high Hg exposure level scenarios due to fish intake, gold mining, or suicide attempts (Romero et al., 2016; Bank Nielsen et al., 2019; Gokoel et al., 2020; Pugach et al., 2009; Courchia et al., 2018), two observed positive associations (OR= 1.18; 95%CI 1.04 to 1.35; p= 0.010) (Al-Saleh et al., 2013); a 9.80% increase, p< 0.050 (Romero et al., 2016), and three found no associations (adjusted OR= 0.76; 95%CI 0.50 to 1.14; p= 0.177; OR= 0.57; 95%CI 0.22 to 1.46; p= 0.242; adjusted slope coefficient= -0.01; p= 0.980, respecttively) (Bank-Nielsen et al., 2019; Gokoel et al., 2020; Rahbar et al., 2015). Other two studies were case report (Pugach et al., 2009; Courchia et al., 2018). These conflicting results may be attributed to differences in populations, maternal fish intake habits, evaluated biomatrix and statistical power level (Al-Saleh et al., 2013; Bank-Nielsen et al., 2019; Rahbar et al., 2015).

On the other hand, associations displaying no statistical significance between prenatal low-level Hg exposure and neonatal anthropometrics were also observed herein, which may be attributable to the small sample size assessed in this study. Epidemiological investigations concerning this subject are, however, limited and have yielded inconclusive results. Furthermore, most focused on relatively high Hg exposure level scenarios, due to high fish and shellfish intake (García-Esquinas et al., 2013; Taylor et al., 2016; Ding et al., 2013). Differences in scenario exposures, the biomatrices used to assess Hg exposure (cord blood, maternal hair), statistical approaches and lack of negative confounding factors through fish model adjustment may prevent adequate comparisons between studies (Karagas et al., 2012; Choi et al., 2008).

One of the major strengths of this study lies in the fact that it is the first of its kind to be carried out in an urban Brazilian area, providing information on blood Hg concentrations in mother-infant pairs. Therefore, our findings may be employed as a reference for monitoring Hg levels in the study environment.

Some study limitations must be

acknowledged, such as the relatively small sample size, so the reported findings may be difficult to generalize. Furthermore, as in most studies, blood Hg levels were determined at a single time point, which may not accurately reflect exposure throughout the entire critical fetal growth window. Additionally, some factors associated with Apgar scores, such as the delivery duration, especially longer second labor stage durations, and maternal sedation or anesthesia, were not included in the regression model as this information was not available. Finally, other possible confounders that we were unable to adjust for may also have affected the results, although we did account for many others in our analyses.

To the best of our knowledge, this is the first study to provide information on Hg levels and birth factors associated to its exposure in an urban Brazilian area with a susceptible group subset comprised by mother infant pairs. The relevance of our findings requires further evaluation due to their potential clinical implications on infant health. As several other epidemiologic factors also influence birth outcomes, the results of this pilot project will be validated by ongoing analyses of the larger PIPA study cohort.

AUTHOR CONTRIBUTION

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.

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CONFLICT OF INTEREST

The authors do declare that there is no conflict of interest.

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