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ESTIMATE OF PRENATAL EXPOSURE TO MERCURY THROUGH UMBILICAL CORD MATRICES

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ABSTRACT

Mercury concentrations in maternal and fetal tissues are used as biomarkers of prenatal exposure, however, some doubts remain regarding the matrix that can best express exposure during pregnancy. The purpose of this study was to verify the correlation of total mercury concentration between the different matrices of the umbilical cord. The study included 278 umbilical cords from pairs of mothers and newborns attended to delivery at the Itaituba/Pará/ Brazil, Public Maternity Hospital.The Total mercury concentrations (TotalHg) were determined in cord tissue (TC), in vein blood (VB) and arteries blood (AB) of the umbilical cord separately, by atomic absorption spectrophotometry. Maternal data including sociodemographicand weekly frequency fish intake and newborn outcomes arepresented. The mercury concentration measured in cord umbilical tissue in wet weigth showed strong correlation with those found in vein blood and arteries bloodsuggesting that the matrices from cord umbilical analyzed separately or together by the methodology used in this study can be used in studies that evaluate prenatal exposure to mercury.

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INTRODUCTION

The biomarkers of exposure to mercury during pregnancy are useful for assessing child neurodevelopment, especially in site where the consumptionof fish and seafood is the food base of the population. Several matrices of maternal and fetal tissues are used to estimate prenatal exposure, including maternal hair(1), umbilical cord blood (2), umbilical cord tissue(3–5) and placenta (6). Umbilical cord blood has long been considered better biomarker of fetal exposure to methylmercurythan maternal blood and hair (2,3). Studies involving analyzes of total mercury(TotalHg) and methylmercury (MeHg) in blood and umbilical cord tissue have shown that the chemical presentation in the umbilical cord side is almost entirely in methylated form, suggesting that the placenta does not constitute amaternal-fetal barrier for this compound (7). In the last decade,the most reliable biomarker of prenatal exposure to mercury for child growth and development studies continues to be investigated in different maternal and fetal matrices, however, the results were not as expected, even with the use of statistical strategies to guide the choice of the most accurate biomarker (8). Correlation of TotalHg concentrations in umbilical cord tissue and blood was demonstrated by Dalgard*et al,* (1994), Grandjean*et al,* (2005); Needhan*et al*(2011); Sakamoto *et al*, (2013, 2016) (3–5,9,10). These studies used cord tissue in dry weight and wet weight,and a blood sample without defining the original compartment. Kozikowaska*et al* (2013) also found a correlation between TotalHg concentrations in cord tissue in wetweight, however, with cord vein blood (11). Prenatal exposure to mercury is associated with frequent eating of fish contaminated with methylmercury during pregnancy (12). This habit is common in fishing and riverside communities (13). In Brazil, there is evidence of prolonged exposure to mercury in region with gold mining activity and in riversides communities involving women of reproductive age (13)and children with scholar old (14).However, there are few studies evaluating prenatal exposure using the umbilical cord as

biomarker. Santos *et al*, (2007) evaluated the levels of exposure to mercury using umbilical cord blood (without identification of the collection site) whose results demonstrated a correlation between the concentrations of TotalHg in cord blood and those of maternal blood (15). The studies that evaluated umbilical cord blood in general don't let it be clear if was used a mixture of umbilical cord bloodsince they do not specify the origin, if from vein and umbilical arteries blood. It is admit that the blood contained in the cord vessels does not mix and the matrix (tissue) has low lipophilic potential and there becomes an ideal matrix for determining prenatal exposure (10). In addition, it is an accessible and easyto handle specimen. Understanding the dynamics of substance exchanges in the maternal-fetal circulation becomes more complex when it comes to toxic compound, including mercury. In the case of prenatal exposure to methylmercury, the concentrations in each compartment of the umbilical cord can contribute to clarifying the biomarker that best expresses prenatal exposure to mercury. In this contex, the study investigated the correlation of TotalHg concentrations between the different matrices of the umbilical cord to identify the validity of each as a biomarkerof exposure during pregnancy.

MATERIAL AND METHODS

Study design: Cross-sectional study involving pairs of mothers and newborns carried out at the Maternity from Itaituba Regional Hospital, located at the headquarters of the municipality of Itaituba in the State ofPará. This hospital is a reference for the municipalities in the Itaituba region (trairão, Novo Progresso, Rurópolis) in the clinical, tropical diseases, surgery and maternal and child care.

Study population: The sample size was calculated based on the record of 1,499 deliveries, including normal and cesarean deliveries in 2017, at the Itaituba Regional Hospital based on the records of the Live Birth Information System(SINASC) of the Health Brazil Ministry. Thus, the sample was composed for 278 of 313 pairs mothers and newborns together with the umbilical cord. The sample selection was random and the samples were then collected in the months of june,july and september of 2018 and april, june and july 2019. Pairs of mothers and newborns attended at delivery at the Maternity Hospital of Itaitubachildren under years old 13 years old were excluded, indigenous mothers and newborns , mothers who gave birth to twinchildren, mothers presenting complications during or after delivery,patients with hypertension, uncontrolled diabetes and with vertical transmission infectious diseases, such as syphilis, HIV, viral hepatitis (B and C). Also, mothers of newborns with malformations did not participate, mainly in the funicular vessels. Mothers aged 13 to 17years participated after their consent with the formalization Informed Consent signed by the parents or guardians.

Collection of information related to mother and newborn: After formal authorization through the Informed Consent Form to participate in the study, a form was applied to record sociodemographic, reproductive and current pregnancy data (age, occupation, color skin, education, habits, comorbities, gestacional age and delivery conditions) and on newborns (anthropometric data and birth conditions). Some information was completed with the records contained in the medical record of the parturient and her newborn.Information was also obtained on the weekly frequency of fish intake based on the protocol used by Nordberg *et al*, 1991, as follows: Category I, no fish intake. Category II: < two fish meals / week. Category III: 2 - 4 fish meals / week. Category IV: > 4 fish meals / week.

Umbilical cord collection and processing for TotalHg analysis: Immediately, after delivery, the umbilical cord was separated from the placenta with stainless steel scissors after clamping at two points on the cord, one performed near insertion placenta and the other 10centimeters (cm)distant of the first obtaining a segment of umbilical cord of 10centimeters extension.Then, this segment was placed in a plastic bag, identified by code and placed in a thermalbox with dry ice and immediately afterwards placed in a frizzer at -4o C and later for freezing at -80o C until processing sample. In the laboratory, the cord segments were removed from the frizzer, the excess external ice removed and subjected to transversal cuts. Two cross-sections were obtained from each cord segment. The first including tissue vein and umbilical arteries, identified by cord tissue (CT) , the second was divided into two others, one of which included tissue and vein, identified by VB and the other containing tissue and arteries umbilical cord identified by (AB) Figure 1.

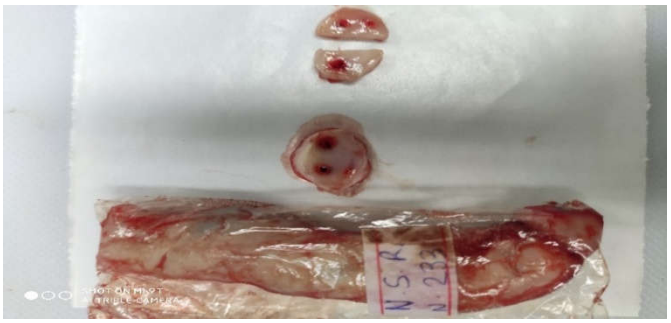


Figura 1. Umbilical cord in three cuts (CT, VB, AB)

Then, the samples were weighed in an amount of approximately 0.5grams and placed in quartz boats over a 1:1 mixture of sodium carbonate and calcium hydroxide, and then covered with a layer of aluminum hydroxide and then placed in quartz furnace of the automatic mercury meter commercially know as Mercury Analyzer (MA), model SP-3D of Nippon Corporation-Japan.The samples were heated at 850 ^{o}C for about eight minutes and the mercury involved is trapped in a gold trap. Immediately, after combustion, the amalgamed mercury is released and measured by atomic absorption spectrophotometry with amalgamation in gold foil. The equipment washandled according to the manufacturer's instructions. Before the toxicological analysis, the TotalHg quantification method in the umbilical cord matrices was subjected to a validation test according to Brazil (2017) and Brazil (2011). All procedures strictly followed the recommendations of the pos-validation method. In summary: Calibration curve (Y=0.7642X - 0,4446 R2= 0,9938. Linearity for THg concentrations in a series of eight points showed Correlation coefficient R2: 0.993, based on Anvisa's acceptance criterion (R2 > 0.990) to be considered linear. The concentration range considered was 5 to 200pp. Detection limit (DL) 1.15ppm and quantification limit (QL) 5ppm (experimental) and 1.86ppm (statistical methods). The results are expressed in µg/g (ppm) in wet weight.

Statistical analysis: Maternal sociodemographic and neonatal characteristics were analyzed descriptively.Mercury concentrations in umbilical cord matrices CT, VB and AB were described as median and minimum, maximum concentrations. Mann-Whitney test was used to verify difference betweenTotalHg concentration in CT, VB and AB

matrice. Spearman'S correlation was used to analyze the correlation between TotalHg concentration in the different matrices from umbilical cord. A*pvalue* of 0,05 was considered significant. All statistical analysis were performed using Biostat 5.0 (Ayres *et al*, 2011).

Ethical Aspects: The protocol of this study followed the ethics guidelines of Resolution 466/2012 of the National Health Council/ Ministry of Health of Brazil and was approved by the Ethics Committee of theTropical Medicine Nucleus from Federal University of Pará, Brazil with number: 2.520.602.

RESULTS

Between june2018 to July 2019, a total of 278pairs of mothers / newborns were attented to delivery at the Maternityat Itaituba Hospital General from State of Pará, Brazilian Amazonian. Of these, 29 did not accept to participate and 06 did not meet the inclusion criteria. Two hundred, seventynine (278) parturients with their newborn respective were included in the studyafter providing written consent to participle in this research.

Characteristics of study population: Participating women had a median age of 22 years old, ranging from 12 to 44 years, with 4,8% under 18years of age. Most were brown 96.3%; performed household activities 80.3% , 69.5% said they were married and 49,8% were poorly educated.

Tabela 1. Maternal and neonatal characteristics

Maternal characteristics	Median (min-max) or %	N
Age (yearsold)	22 (12-14)	
< 18	40	(4,8)
≥ 18	230	(85,2)
Color /race		
Parda	262	(96,3)
Niger	06	(2,2)
Branca	04	(1,5)
Marital status		
Married /stable union	173	(69,5)
No married	77	(16,1)
Education		
Low	139	(49,8)
Median	104	(37,2)
High	22	(7,9)
Occupation		
Do lar	224	(80,3)
Others	48	(17,2)
Fish consumption		
<2 times /wk	172	(61,7)
≥ 2 times /wk	93	(33,3)
Neonatal characteristics		
Sex		
Male	120	(45,8)
Female	142	(54,2)
Birth weigth(g) n:262	3.000 (1.860 – 4.390)	
Low birth weigth (<2.500)		
Yes	18	(6,9)
No	244	(93,1)
Birth length (cm) n:262	50 (35 – 55)	
Low birth length (< 40cm)	1	(0,4)
Yes	261	(99,6)
No		
Birth head circunference(cm) (n:262)	34 (24 – 38)	
Low birth head circumference(<33cm)	18	(6,9)
Yes	244	(93,1)
No		

Categories according Nordberg*et al*, 2000 (adapted).

A total of these women, 61.7% reported consuming less than two weekly meals of fish, being categorized in the low consumption group. Two hundred and sixty-one (261) mother had information about their newborns, 53.8% newborns were girls and 46.2% boys. The median and birth weight variations were 3000g (1860g – 4390g) with 6.9% showing low weight. The median height was 50cm (35-55cm) with 0,4% showing low height, and the circumference of the head 34 (24 – 38 cm) with 6,9% low head circumference. Table 2 shows the TotalHg concentrations in different matrices of the umbilical cord. The median concentrations were 0.0014µg/g, 0.0009µg/g and 0.0009µg/g respectively in the CT, VB and AB. The minimum concentration was the same in all cord matrices (under detection limit) and the maximum concentration was 0.3700µg/g, 0.1800µg/g and 0.2500µg/g respectively in CT, VB and AB. The comparison of the TotalHg concentrations between the cord matrices performed using the Mann Whitney Test showed a highly significant difference in the TotalHg concentrations in TC and VB ($p<0.000$) in the concentrations in TC and AB ($p <0.000$), however, no there was a significant difference in VB and AB Total concentrations ($p > 0.05$). This results suggest that TotalHg concentration in CT and VB are good biomarkers of prenatal exposure.

Table 2. Mercury concentration (µg/g) in differents matrices of the umbilicalcord

Descriptives parameters	THg CT	THg VB	THg AB
Mean	0,0082	0,045	0,0053
Median	0,0014	0,0009	0,0009
Variance	0,0010	0,0000	0,0010
Standartdeviation	0,3480	0,1622	0,0228
Minimum	0,0000	0,0000	0,0000
Maximum	0,3700	0,1800	0,2500
interval	0,3700	0,1800	0,2500
Intervalo interquartílico	0,0000	0,0000	0,0000

Mann Whitney: CT and VB: p<0,000 z: - 4,680; CT and AB: p<0,000 z:-4,727; VB and AB: p>0,05 z: -0,022.

The correlation of TotalHg concentrations between the different cord matrices is shown graphs 1,2 and 3. There was a significant difference between TotalHg concentration in the CT and VB (n:278, r: 0.7292, p<0.0001); TotalHg concentration in CT and AB (n:278, r: 0.7791, p<0.0001) and TotalHg concentration between VB and AB (n:278,rs: 0.8529, p<0.0001).

Figure 1: Correlation (r Pearson) between THg concentration CT and VB.

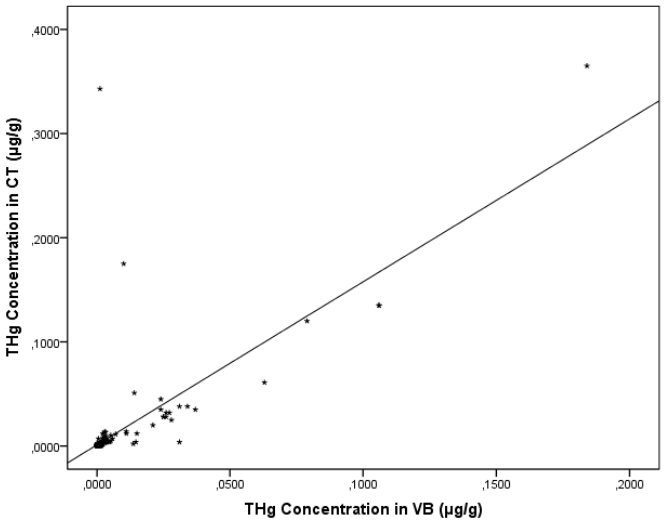


Figure 2. Correlation (r Pearson) between THg concentration CT and AB.

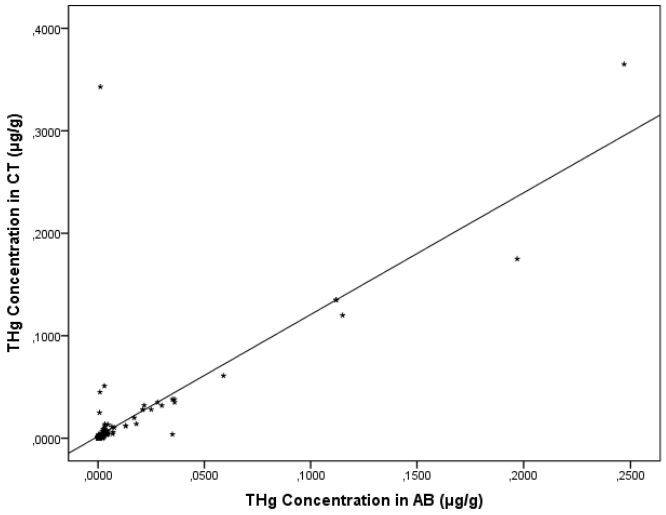
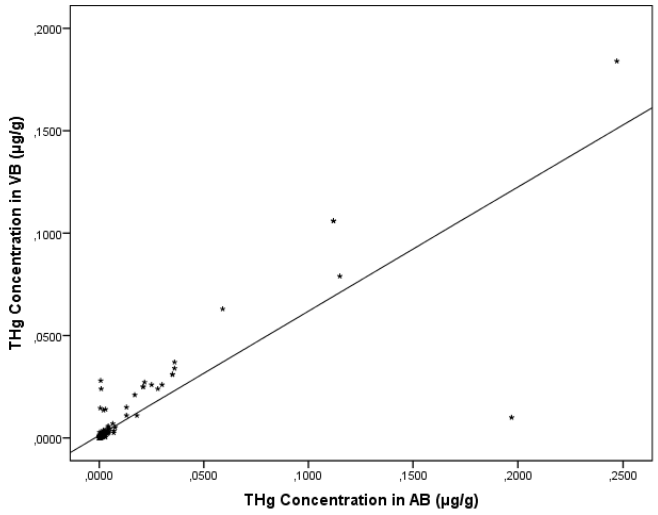


Figure 3. Correlation (r Pearson) between THg concentration VB and AB.



DISCUSSION

The current study involved women and her childbirth attended in a reference maternity to region of Itaituba, in the Brazilian Amazon. The sociodemographic characteristics of the mothers were similar to those found in other poor Brazilian regions, an important percentage of teenage pregnancies, brown women, responsible for household activities and with low education.

According to Martinez *et al* (2011), early pregnancy is more frequent in places with lower gross domestic product (GDP) per capital, higher poverty rate, lower human development index (HDI) and higher percentage of individuals with a social vulnerability index(16). Prenatal exposure to mercury through the diet is mainlyrelated to the consumption of fish and seafood during pregnancy. The risk of this exposure is greaterfor the fetus than for mothers and increases with the frequency of consumption of fish (17).In the present study the majority (61,7%) of the participating mothers reported low fish consumption during pregnancy. This canbe explained by the fact that the Maternity Hospital in the study is a reference for the Itaituba region, which is home to other groups, such as farmers, worker and self-employed peoplewho do not have the habit of frequent intake of fish. There was no neonatal death. Most newborns had anthropometric measurements within the reference limits. The changes occurred in 6,9% with weight below 2500grams, 0.4% short stature and 6.9% head circumference below 33cm.

Several factors are associated with low birth weight and microcephaly including maternal exposure to mercury, however the mothers in this study hadlow levels of exposure, which were consistent with the low fish intake during pregnancy. The measures of weight, height and head circumference were lower in newborns in the current study than those found by Cunha *et al* (2018) in others children, also in the Amazon region, however , they were similar to those found in children exposed to mercury in the Aveiro river region, in Portugal(Alves et al, 2017)(12,18).Some studies showed alterations in anthropometric measures in stillbirth with TotalHg concentration above 5,8µg/L in cord blood, which is safe limit to risk prenatal (19,20). Different techniques for processing and analyzing maternal-fetal tissue matrices have been used to estimate prenatal exposure (3,9,21,22). In this study, umbilical cord matrices (tissue, vein and arteries) were used together and separately, in wet weight to determine mercury concentrations and estimate prenatal exposure. Low levels of TotalHg were found in the different umbilical cord matrices. These findings are consistent with the eating habits of the population studied, where 61.7% did not consume fish or consumed less than two meals for week. On the other hand, the concentrations were determined in wet weight, which can express lower levels than in dry weight (3,9). Concentrations below the detection limit were observed in the CT, VB and AB, and the maximum concentrations varied, being higher in the CT when compared with the TotalHgconcentrations in VB and AB. No difference occurred in the comparation of the TotalHgconcentrations between VB and AB. Concentrations of total mercury in cord blood of individuals who do not eat fish are normally in the range of 0.5 – 5.0µg/g. In cases of high fish consumption, values higher than 10µg/L are frequently occurring. The reference value for mercury in cord blood based on the USEPAs reference dose is 5.8µg/L(23).In this study the mercury concentration was analyzed in matrices of umbilical cord tissue with cord blood and there was no casewith levels above 5.8µg/g. The low frequency of consumption of fish may explain the low concentrations of TotalHg in all matrices of the cord. Levels close to those found in this study were found in the vein blood of umbilical cord (0.027µg/L) in a study involving Nigerian parturient (24).

Estimation of exposure to mercury using the different umbilical cord matrices separately, had not yet been performed. This is the first study that analyzes the TotalHg concentrations in the umbilical cord in veinand arteries, together and separately, in wet weight. Kozikowski*et al*, (2013) analyzed the CT matrix in wet weight and found a lower median TotalHg concentration (0.008µg/g) than that found in cord blood (8µg/L), a different result to that found in current study, whose concentrations were measured in blood of the vein and arteries separately, in µg/g. In both comparations,TotalHg concentrations in CT were higher than VB and AB(11). The TotalHg concentration found on umbilical cord tissue (CT) includes the mercury contained in the vein blood and arteries blood. It is assumed that the levels found in tissue (CT) represent the concentrations of TotalHg that is carried to the fetusthough the amount that returns from the fetus to the placenta. Currents results suggest that the concentrations of TotalHg found on CT and VB better reflect prenatal exposure. As the venous and arterial blood do not mix, the concentration of the methylmercury compound released into the venous circulation of the umbilical cord may not be same as the concentration that returns from the fetus to

the placenta. Little is known about the ability of the fetal organism to retain more or less mercury (25). In a study comparing TotalHg concentrations in umbilical cord tissue (CT) using samples in dry weight and wet weight, the concentration in the CT was 0.210µg/g in wet weight while in dry weight it was 0.024µg/g. The authors recommend the use of umbilical cord in dry weight as a measure of prenatal exposure, however when wet weight is used a correction factor of 30% should be taken into account in relation to umbilical cord blood and maternal hair (3).

Few studies have evaluated exposure to mercury through umbilical cord tissue. Those who analyzed demonstrated a significant correlation with TotalHg concentrations in cord blood. With the exception of Sakamoto *et al* (2016), the other studies did not mention the origin of the blood collected (Dalgard*et al,* 1994; Grandjean*et al*, 2005; 2016)(5)(9)(3). Dalgard*etal*, (1994) analyzed 12 samples of umbilical cord in dry weight (lyophilized) to verify the association of TotalHg and MeHg concentrations with umbilicalcord blood. Grandjean*et al* (2005)through a structural equation model found an imprecision between these two exposure biomarkers in 30%(3,26). The inaccuracy of the dry weight concentration was less than the parameter based on wet weight and concluded that the analysis of mercury in the umbilical cord can be used as a measure of prenatal exposure to methylmercury since it is considered an adjustment factor for this inaccuracy. Sakamoto *et al* (2016) evaluated CT in dry weight and wet weight to correlate the concentrations of TotalHg and MeHg in cord blood and concluded that the concentrations in CT dry weight correlated better with those found in cord blood than using the CT in wet weight. They also found a correction factor of 22.37 for the correlation between TotalHg concentration in umbilical cord tissue and umbilical cord blood. In all studies that used CT and correlated with cord blood there is no reference as to whether the blood was from the vein or arteries or from both compartments of the umbilical cord, which differs from the present study that compared and associated TotalHg concentrations between the different compartiments of the cord(7).

The correlation between TotalHgconcentrations in the differentumbilical cord matrices wet weight has not been evaluated. The results showed a strong correlation between the concentrations in CT with those of VB and CT versus AB.Kozikowska*et al* (2013) found a strong correlation between TotalHg concentration in cord tissue and cord blood in wet weight, however, there is no reference as to the tested blood collection site, whether from vein, umbilical arteries or the mixture of the two(11). Some studies have evaluated the correlation between TotalHg in CT in dry weight , with concentrations in cord blood and have shown a strong correlation between these matrices(3,7,26). These authors recommended the use of tissue in dry weight as biomarker to evaluate prenatal exposure to mercury and suggest that the measurement in wet weight can be used, as long as adjustment or correction factor is used. Some limitations were found in achieving the proposed objectives: the study included a 278pairsof mothers and newborns with umbilical cord constituting 88,6% of the calculated sample, which was 310 pairs. This limitation was due to difficulties in preserving part of the collected sample. Another difficulty was the lack of recording some information obtained in the hospital records of some parturient and their respective newborns and the difficulty in obtaining them immediately after delivery. Despite these difficulties, the main objective of the study was achieved. The correlation of TotalHg concentrations in the different cord matrices was demonstrated. The analysis of TtotalHg in segments of the umbilical cord in wet weight proved to be viable and showed a significant correlation between them.

Conclusion

The results of the current study showed low levels of exposure to mercury in mothers and her newborns, which were consistent with the low intake of fish in the diet of this population. The THg concentrations found in umbilical cord tissue (CT) in wet weight showed strong correlations with those in vein blood (VB) and in arteries blood of umbilical cord. The umbilical cord tissue by the methodology used can be indicated as a useful biomarker for the assessment of prenatal exposure due the facility obtaining, processing and analyzing the sample, and can be recommended for others studies, especially for region of significant exposure to mercury.

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