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Review Article

Umbilical Cord Tissues as Matrices to Predict Prenatal Exposure to Mercury - Review

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Abstract

Mercury prenatal exposure can be estimated through mercury concentrations in different maternal/fetal biological matrices. However, questions have been raised regarding the accuracy of umbilical cord matrices as biomarkers of that exposure. The aim of the present study was to verify the potential of umbilical cord matrices as prenatal exposure biomarkers to mercury and their uses in studies of correlation and association with outcome at birth and with neurodevelopment. For such, we have searched different databases for primary scientific articles using the following terms: methylmercury/total mercury and umbilical cord blood, methylmercury/total mercury and umbilical cord tissue; methylmercury/total mercury in umbilical cord and child growth/neurodevelopment. We found 55 articles about that topic, but only 34 articles met the following inclusion criteria. In general, the studies showed that concentrations of total mercury and methylmercury in umbilical cord blood were higher than those found in maternal blood and umbilical cord tissue and that cord tissue concentrations were better correlated with cord blood concentrations than maternal blood concentrations. Methodological differences among the studies were found regarding the collection of umbilical cord blood and the processing of the cord tissue samples for analysis. In the majority studies that used these matrices as mercury, exposure biomarkers have not verified association with anthropometrics or neurodevelopment. Factors inherent to the placenta and differences in the collection and analysis methods among the studies analyzed may explain the uncertainties regarding the definition of the best biomarker of prenatal exposure to mercury.

INTRODUCTION

Prenatal exposure to metals is a concern for maternal-fetal health due to the effects of toxicity on birth outcomes [1-4]. Mercury has been the most widely studied metal since the tragedies that occurred in Minamata and Niigata- Japan in the 1950s and 60s, and the tragedy in Iraq in the 1970s due to the consumption respectively of fish, seafood and bread contaminated by organomercury compounds [5]. These episodes resulted in numerous cases of congenital poisoning with serious neurological damage, such as deafness, blindness, cerebral palsy and different degrees of delayed psychomotor development [5].

The adverse effects of prolonged exposure to low concentrations of mercury have also been recorded in populations with a history of fish intake in other parts of the world, such as the Faroe Islands [6-9].

Mercury exposure during pregnancy can be determined using biological matrices as exposure biomarkers, such as maternal hair and blood, umbilical cord blood and tissue (10), nails, meconium and placenta [11,12]. The quantification of mercury in hair during the pregnancy is very used because its collection and storage are simple and provides information about mercury exposure during pregnancy through segmental analysis considering a monthly growth rate of one centimeter; in addition there are reference limiar established in 10μg/g [5].

Maternal blood is less used, perhaps because it is a procedure that involves biological and traumatic risks. Umbilical cord matrices including umbilical cord tissue and cord blood have been used to estimate prenatal exposure. The collection and analysis procedures of the different matrices are diverse. There are studies that used venous cord blood [8,13], others do not identify the cord vase from the sample collected, suggesting the mixture of blood present in the arteries and the umbilical vein [3,14-17]. Some evaluated exposure using cord tissue in dry weight and/or wet weight [2,6,10,18,19].

The biomarker that best expresses prenatal exposure still needs to be discussed. Knowledge of maternal-fetal circulation contributes to a better interpretation of intrauterine fetal exposure to mercury.

Methylmercury (MeHg), exposure generally occurs due to the frequent consumption of fish and seafood, which is a common habit in fishing communities. Once ingested, approximately 90% of MeHg is absorbed by the digestive tract. Before being distributed to the tissues through the bloodstream, this compound combines with sulfhydryl groups and gains a greater affinity for cysteine, with which it forms L-cysteine-methylmercury, the chemical structure that is similar to that of methionine. In this form, MeHg crosses the blood-brain and fetal-placental barriers [5].

Maternal blood arrives in the intervillous space of the

placenta via the spiral arteries through gaps that cross the cytotrophoblastic layer. The blood flows slowly around the chorionic villi, enabling the exchange of substances between the mother and fetus. From the capillaries of the villi, fetal blood rich in oxygen passes to the veins of the chorionic plate and, from there, to the umbilical vein, which is a large blood vessel that transports oxygen-rich blood and nutrients, but also transports toxic substances to the fetus [20]. The oxygen-poor blood that leaves the fetus passes through the umbilical arteries and crosses the chorionic plate through the arteries, returning to the placenta. Considering that the venous blood and arterial blood do not mix, the concentration of metal released into the venous circulation of the umbilical cord may not be the same as the concentration that returns from the fetus to the placenta [20].

The placenta offers a protective barrier to many compounds for the safe development of the fetus by reducing the input of xenobiotics from the mother to the fetus. However, the placenta facilitates the passage of other compounds to the fetal compartment. The physicochemical properties of toxicants, such as lipid solubility, polarity and molecular mass, determine transference rates through the placenta [21].

Methylmercury is actively transferred from the mother to the fetus through the placenta by the amino acid transport system [21]. Due to its high affinity for the immature nerve tissue and the fact that it is slowly eliminated, mercury causes damage to the fetus brain. Therefore, a diet based on the frequent consumption of fish during pregnancy can increase the risk of fetal exposure to mercury, consequently exerting a negative impact on child growth [17,22], and neurodevelopment [3,8,9,23].

Few studies have used total Hg concentration in umbilical cord matrices to assess prenatal exposure and to verify the association with child growth and psychomotor development to the detriment of the non-invasive collection procedure and the practicality of handling this material.

The aim of the present study was to verify the potential of umbilical cord matrices as prenatal exposure biomarkers to mercury and their uses in studies of correlation and association with outcome at birth and with neurodevelopment.

METHODS

For the present review, a survey was performed of the scientific literature for the identification of relevant primary studies that evaluated biomarkers of prenatal exposure to mercury, particularly those that used matrices of the umbilical cord (venous blood and/or arterial blood and/or umbilical cord tissue) published in scientific periodicals in English or Portuguese between 1980 and 2019. Searches were conducted in the Pubmed, ScienceDirect and Google Scholar databases using the following terms: methylmercury/total mercury and umbilical cord blood, methylmercury/total mercury and umbilical cord tissue; methylmercury/total mercury in umbilical cord and child growth/neurodevelopment.

We found 55 articles topic related, but only 31 primary studies were included for meeting the following inclusion criteria: original articles on prenatal exposure to mercury, correlation studies involving mercury concentration between the umbilical cord matrices (venous blood, arterial blood and cord tissue) and maternal blood, studies based on the association between mercury concentration in cord umbilical matrices as exposure biomarkers with changes in the growth and development of children exposed to methylmercury in the prenatal period.

Review studies, abstracts presented at scientific events for which the full article could not be obtained, studies involving animal models, studies on occupational exposure and studies on exposure to inorganic mercury or other organic mercury compounds were excluded. The results were analyzed and compared to the pertinent, updated literature.

A total of 31 articles related to the research question were found, including 22 correlation studies: 15 umbilical cord blood (UCB), versus maternal blood (MB), and seven umbilical cord blood (UCB), versus umbilical cord tissue (UCT), and 14 association studies, among which seven umbilical cord blood (UCB) versus birth outcomes and seven umbilical cord blood (UCB), versus neurodevelopmental (Figure 1).

DISCUSSION & CONCLUSION

The correlation between total Hg/MeHg in umbilical cord blood (UCB), and maternal blood (MB), are shown in Table 1.

Most studies on the correlation of total Hg/MeHg concentrations in UCB and MB showed a strong correlation with the highest concentrations of total Hg in UCB [8-10,13-17,24-29]. However, the majority of these studies did not make clear the origin of the umbilical cord blood collection, whether it had been from the cord vein or cord artery separately, or from the blood mixture.

Two studies found total Hg concentration in umbilical cord blood lower than in the maternal blood [30,31]. The first study looked at total Hg concentration in a mixture of venous and arterial cord blood, the second looked at a blood sample obtained from the umbilical cord vein. Agbonlahor et al. (2018), studying 200 pregnant Nigerian women found a significantly higher mean concentration of total Hg in MB (0.068 ± 0.003μg/L) than that found in the umbilical cord venous blood (0.027 ± 0.001μg/L) at the time of birth (ratio: 2.52; p-value < 0.0001).

In a study involving 77 pregnant women in Seville, Spain, concentrations of total Hg and MeHg were analyzed in both venous and arterial blood of the umbilical cord. The mean concentration did not differ from each other and these concentrations were significantly correlated with the ones found in the MB. The coefficient of variation was higher in the arterial blood than in the venous blood of the umbilical cord [32]. These results differ from those of the majority of studies using mercury in UCB as a biomarker.

Physiologically, blood in the cord vein is different from the blood that circulates in the umbilical cord arteries. In this context, measurements of total Hg and/or MeHg concentrations should be analyzed separately, since that may influence the interpretation of the prenatal exposure results.

Higher concentrations of total Hg in UCB compared to MB suggests the inability of the placental barrier to retain metals, such as mercury. Several hypotheses can be raised to explain

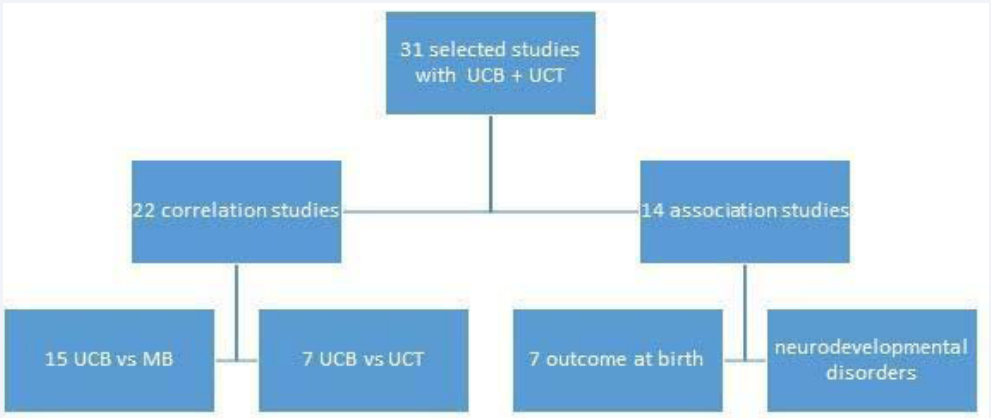

Figure 1 Schematic model of the studies selection process.

Table 1: Mercury concentration in umbilical cord blood (UCB) and maternal blood (MB) as biomarkers of prenatal exposure to mercury.

Authors	Country	Sample number	UCB Mean / geometric mean ± SD (minimum-maximum)	MB Mean / geometric mean ± SD (minimum-maximum)	Correlation
Kuntz et al, 1982	Estados Unidos	57	TotalHg:1.15 ± 0.18ng/L	TotalHg:1.21 ±0.14ng/L	r:0.23 p<0.09
Soria et al. (1992)	Seville, Spain	25 24	TotalHg(a): 6.82±2.95 TotalHg(v): 6,43±3.61	TotalHg: 6.23 ± 1.89	r: 0.7226 p < 0.01 r:0,3680 p<0,10
Ong et al. (1993)	Singapore	28	TotalHg:18.8 ± 8.01 MeHg: 8.82 ± 5.39	TotalHg: 15.8 ± 6.85 MeHg: 5.46 ± 4.59	r = 0.58 p < 0.005
Walker et al. (2006)	Canada	UCB/402 MB/385	TotalHg:5.8µg/L TotalHg: 2.7 µg/L ± ND (ND-75.8) MeHg:4.9µg/ MeHg:2,5g/L ND (0.0-70.2)	TotalHg:2.96 TotalHg: 1.66 ± ND (ND-33.9) MeHg: 2.20 MeHg:1,30 ± ND (0.0-29.3)	r = 0.90 p < 0.0001
Jedrychowsk et al. (2007b)	Poland	313	TotalHg:1.093 ±0.675 µg/L	TotalHg:0.833 ±0.681 µg/L	rs= 0.62, 95% CI(0.55-0.69)
Santos et al. (2007)	Tapajós, Brazil	1510	TotalHg 16.68 ± 17.16 µg/L	TotalHg: 11.53 ± 11.30 µg/L	r = 0.8019 p = 0.0001
Rudge et al. (2009)	South Africa	62	*TotalHg median: 1.22 µg/L Min-Max (0.1-9.7) µg/L	*TotalHg median: 0.65 µg/L Min-Max(0.1-8.8) µg/L	r-sq = 76.9 p < 0.0001
Sakamoto et al. (2010)	Kumamoto, Japan	81	TotalHg: 0.077 ± 0.021ng/g	TotalHg: 0.053 ± 0.021ng/g	r = 0.91
Al Saleh et al, 2011	Saudi Arabia	1393	TotalHg:3.354 ±2.673	TotalHg:3.005 ± 6.319	r=0.202 p : 0
Channa et al. (2013)	South Africa	350	TotalHg: 0.84µg/L (0,21-18.37)µg/L	TotalHg: 0.60 µg/L (0,15-12,3)µg/L	r = 0.728 p < 0.001
García-Esquinas et al. (2013)	Spain	UCB/108 MB/140	TotalHg:6.72 µg/L 95% CI(5.74-7.82)µg/L	TotalHg:3.90 µg/L 95%CI(3.38-4.50)	r = 0.57 p < 0.001
Soong et al. (2016)	Korea	127	TotalHg: 5.46 ± 2.41 µg/L	TotalHg: 3.12 ± 1.36µg/L	r = 0.829 p < 0.001
Huang et al, 2017	Taiwan/ China	145	TotalHg: 5.0 TotalHg: 2.5µg/L ±7.3µg/L	TotalHg: 3.6 TotalHg: 2.1µg/L ±3.9µg/L	r=0.76 p<0.0001
Agbonlahor, Emokpae and Evbuomwan (2018)	Nigeria	300	TotalHg: 0.027 ± 0.001 µg/L	TotalHgT: 0.068 ± 0.003 µg/L	MB vs. UCB 2.52
Viget et al. (2018)	Japan	334	TotalHg: 10.15 ±7.74 µg/L	TotalHg: 4.97 ± 3.25 µg/L	r = 0.974 p < 0.001

Legend: UCB: Umbilical cord blood; **MB:** maternal blood (MB); **TotalHg**: Total mercury; **MeHg**: methylmercury.

this. Special characteristics of the amino acid transporters may facilitate the transference of xenobiotics to the placental bed (the amino acid transporters located on the apical side of the syncytiotrophoblast control the uptake of MeHg) [33]. In other hypotheses, the participation of metallothioneins in the fetal tissue beginning in the third trimester and the placental transfer area are factors that might contribute to the higher or lower concentration of the metal in the venous blood of the umbilical cord to the fetus [21]. Mechanisms of transformation/detoxification may occur in the placental itself when the MB reaches the intervillous space, where the exchanges occur, exerting an influence on the greater or lesser transference of the toxicants to the fetal circulation [20]. Recently, it was demonstrated that the use of a vitamin supplement during pregnancy can exert an influence on total Hg concentrations in the maternal and fetal blood [13].

Mercury concentration in umbilical cord tissue (UCT), dry weight and wet weight, umbilical cord blood, maternal blood, correlation between mercury concentration in UCT versus UCB, and correlation between mercury concentration in UCT with maternal blood are shown in Table 2.

Dalgard et al. (1994), using 12 preserved umbilical cord samples of children with Congenital Minamata Disease had estimated values for a linear correlation with total Hg concentrations in UCB, whose results were highly significant (r: 0.85 p<0.001). The authors also found that total Hg in UCB had correlation with the frequency of whale intake during pregnancy and that total Hg in UCT was correlated with concentrations in UCB and the mother's hair.

Seven studies were found involving a correlation between total Hg and/or MeHg concentrations in umbilical cord tissue/blood and/or maternal blood. Most analyzed total Hg in umbilical cord tissue in dry weight. The correlation with total Hg concentration in blood cord was observed in four of these studies, which showed a strong correlation between these two biomarkers, suggesting that both matrices are useful as biomarkers of prenatal exposure to mercury [10,18,19,34]. Three other studies based on total Hg in wet weight cord tissue and maternal blood were analyzed by Grandjean et al, 2005; Kozikowska et al, 2013; Sakamoto et al, 2016. In all studies a significant correlation between these two biomarkers have been demonstrated.

In the Minamata disease, the median concentration of methylmercury in umbilical cord tissue (UCT), several years after the tragedy in Japan was 1.63µg/g, ranging from 0.15 to 53µg/g. From this measure, the concentration of methylmercury in the cord blood (UCB), was estimated using a factor of 132.38 based on a previous correlation study whose results were 216 µg/L and variation from 20 to 699µg/L (2).

On the other hand, Grandjean et al. (2005), evaluating the usefulness of UCT as an exposure biomarker, demonstrated that UCB is the best biomarker of exposure to MeHg. The UCT is an appropriate alternative, especially when total Hg concentrations are measured in lyophilized tissue, however there is an imprecision which is less than the concentrations measured in wet weight and in hair samples, which needs to be considered.

In a study comparing total Hg concentrations in UCT using dry weight and wet weight samples, higher concentrations were found in the dry weight ones. In this study involving 447

Table 2: Correlations between umbilical cord tissue (UCT), umbilical cord (UCB) and maternal blood (MB).

Authors	UCT (dry weight)	UCT (wet weight)	UCB	MB	UCT vs. UCB	UCT vs. MB
Dalgard *et al,* (1994)	TotalHg median: 4.95nmol/g	ND	TotalHg median: 668 nmol/L	TotalHg median: 114 nmol/g	ND	ND
Akagi *et al,* (1998)	MeHg median: (interquartile range): 1.63 µg/g(0.81-2.34)	ND	MeHg median: (interquartile range): 216µg/L (107-310)	ND	ND	ND
Grandjean *et al.* (2005)	TotalHg geometric mean (interquartile range): 0.210 ng/g (0.132-0.360) ng/g	TotalHg geometric mean (interquartile range): 0.0249 ng/g (0.0149-0.0440) ng/g	TotalHg geometric mean (interquartile range): 22.35 µg/L (13.1-40.4) µg/L	ND	r:0.94	ND
Needhan *et al.* (2011)	TotalHg median: 0.085 µg/g	ND	TotalHg median: 12.1 µg/L	ND	r = 0.97	ND
Kozikowska *et al.* (2012)	ND	TotalHg median (range): 0.008µg/g(0.003-0.064)	TotalHg median(range): 8 µg/L((3-16)	ND	r = 0.4687	ND
Sakamoto *et al,* 2013	TotalHg median: 3.1ng/g Interquartile: 2.3-3.7	ND	TotalHg median : 14.0 ng/g Interquartile: 10.3-18.0	TotalHg median: 9.1ng/g Interquartile:10.3-18.0	r 0.85 p<0.001	r: 0.74 p< 0.001
Sakamoto *et al.* (2016)	TotalHg median (range): 62.2ng/g(7.60-164) MeHg median(range): 56.7ng/g(7.50-145)	TotalHg median (range): 5.55 ng/g(0.65-14.5) MeHg median(range) :5.34 ng/g(0.66-12.8)	TotalHg median(range): 7.26ng/g(1.48-14.4) -	TotalHg median(range): 3.79 ng/g(1.03-9.59)	r = 0.912 p < 0.01 r = 0.797 p < 0.01	ND

Legend: **UCT**: umbilical cord tissue; **UCB**: umbilical cord blood; **MB**: maternal blood ; **UCT vs UCB**: umbilical cord tissue versus umbilical cord blood; **UCT vs MB**: umbilical cord tissue versus maternal blood; **TotalHg** : total mercury; **MeHg**: methylmercury; **ND**: not detected.

newborns on the Faroe Islands, a significant positive correlation was found between total Hg concentrations in UCT and UCB. The concentration in UCT was 0.210µg/g in dry weight and 0.024µg/g in wet weight. The authors recommend the use of the umbilical cord in dry weight as a measure of prenatal exposure, but when wet weight is used, a 30% imprecision factor should be taken into consideration in relation to UCB and mother's hair [18]. It was observed that two other studies analyzing Total Hg in lyophilized UCT found a significant correlation with total Hg concentrations in UCB [10,19].

Sakamoto et al, (2013), analyzing MeHg, HgI and others metals concentrations in placental tissue and UCT in freeze-dried samples from 48 pairs of mothers and full-term newborns, found correlation between total Hg concentrations in UCT with those of MB (rs = 0.74) and UCB (rs = 0.85). The median totalHg concentration was 14µg/L in UCB and 9.1µg/L in MB (range: 6.9 to 10.8µg/L). The authors also found higher concentrations of total Hg and inorganic mercury in the placenta than in the UCT, whereas MeHg was higher in UCT than the placenta ($p < 0.001$).

In another study Sakamoto et al. (2016), investigated preserved umbilical cord for total mercury and methylmercury to determine correlations between total Hg concentrations in UCT and those in MB and mother's hair as useful biomarkers for predicting fetal exposure to MeHg in 54 pairs of mothers and newborns. The authors found a strong correlation between total Hg concentrations in UCT and UCB, suggesting UCT as a useful biomarker of prenatal exposure, mainly reflecting the mercury load in the third trimester.

Table 3: Umbilical cord matrices as biomarkers of prenatal exposure to mercury associated with birth outcomes.

Authors	**Umbilical cord blood (UCB)** µg/L Mean ±SD geometric mean (interquartile range)	**Maternal blood (MB)** µg/L Mean ±SD geometric mean (interquartile range)	**Outcomes**
Kuntz *et al*. (1982)	TotalHg:1.15 µg/L ± 0.18	ND	It was found to have significant association between previous stillbirths and malformed infants and mercury levels in both maternal and cord blood.
García-Esquinas *et al*. (2013)	TotalHg: 6.72 µg/L (5.74 -7.87, 95%CI)	TotalHg: 3.90 µg/L (3.38-4.50,95%CI)	TotalHg were higher in newborns than in their mothers. No associations were observed between TotalHg levels and newborn's weight or length.
Rahbar *et al*. (2015)	TotalHg:4.4 µg/L ± 2.4	TotalHg: 3.9 µg/L (ND)	No associations for TotalHg concentrations with birth outcomes (birth weight, crown-length, head circumference, apgar, gestational age) were found.
Wells *et al,*(2016)	MeHg:0.94µg/L (0.84-1.07, 95% CI)	ND	The association between MeHg in cord blood and birth weight was affected by n-3 HUFAs, selenium and IHg. Infants with higher levels of MeHg and n-3 HUFAs have lower height and head circumference at birth.
Agbonlahor, Emokpae and Evbuomwan (2018)	TotalHg in low weight: 0.025±0.005 µg/L TotalHg in normal weight: 0.022±0.002 µg/L *p<0.010*	TotalHg in low weight: 0.07±0.014 µg/L TotalHg in normal weight: 0.06±0.017 µg/L *p<0.022*	TotalHg concentrations in MB and UCB were higher in low weight than normal newborn.
Ballester *et al.* (2018)	TotalHg:8.2µg/L (7.9-8.5,95% IC)	ND	TotalHg concentration was associated with small reduction of biparietal diameter early in pregnancy, but no significant changes were observed in other fetal anthropometric parameters by ultrasounds.
Viget *et al*. (2018)	TotalHg:10.15 ± 7.74 µg/L	TotalHg:4.97 ± 3.25 µg/L	There was a negative correlation between TotalHg in UCB in the early stages of gestation and newborn birth weight. The mean levels of mercury in the first trimester and in umbilical cord blood were higher than the safe dose recommended by the US EPA (5.8 g/L), potentially increasing the risk of adverse effects on pregnancy outcomes.

Legend: **(UCB)µg/L**: (umbilical cord blood)micrograms /liter; **(MB)µg/L**, (maternal blood)micrograms/liter; **Total Hg**: total mercury ; **MeHg**: methylmercury; **ND**: not detected **US EPA**: Environmental Protection Agency – United States; *median

Kozikowska et al. (2013), and Sakamoto et al. (2016), determined the total Hg concentrations using the UCT in wet weight and verified median concentration in UCT lower than found in UCB. In both studies, there was a significant correlation between total Hg concentrations in the two matrices.

Kozikowska et al. (2013), determined concentrations of total Hg in the placenta, UCT and amniotic fluid and found correlations between UCT and UCB (r = 0.4687), as well as between UCB and placenta (r = 0.4309). Median total Hg concentrations were higher in the placental tissue than UCT, but concentrations in UCB were much higher (8μg/L) than those in UCT (0.008μg/g) and placenta (0.010μg/g). In this study, total Hg concentrations in UCT were only measured in wet weight, which limits comparisons to the results of other studies that also analyzed freeze-dried material [6,10,18,19].

The procedures for preparing the cord samples to analyze total Hg concentrations were varied. There was a study that used cord tissue in wet weight preserving blood cells [6,18]. Another study analyzed totalHg concentrations in umbilical cord tissue removing the blood content of the cord vessels [19]. These different techniques make it difficult to compare the results of studies that used the umbilical cord tissue matrix to measure mercury exposure.

The Table 3 presents mercury concentration in UCB and MB, and association with birth outcomes. Seven studies that used total Hg concentration in the umbilical cord blood matrix as biomarker of prenatal exposure and associated with birth outcomes (stillbirth and anthropometric measurements), were found.

Of these, two did not find association with growth alteration [26,35]. In those, the collection site of cord blood has not been identified. The other studies found an association with changes in birth outcomes [1,17,22,31,36]. However, only one made it clear the origin of the collection of cord blood [31].

A population-based study conducted to investigate levels of metals, including total Hg, found a geometric mean of 6.72μg/L in UCB, which was higher than that found in MB (3.90μg/g). The correlation coefficient was 0.57 ($p < 0.001$), and no association was found between total Hg in UCB and birth outcomes [26]. Rahbar et al. (2015), found a mean total Hg concentration in UCB of 4.4 ± 2.4μg/L in 100 newborns and also found no association with birth outcomes.

Agbonlahor, Emokpae and Evbuomwan (2018), found association between total Hg and birth weight, despite the MB and UCB ratio of 2.52. Ballester et al. (2018), investigating prenatal exposure through total Hg concentrations in UCB, selected pregnant women and their newborns from a population-based cohort study conducted in four regions of Spain for the analysis of biparietal diameter, femur size, abdominal circulation and fetal growth through ultrasound at 12, 20 and 34 weeks of gestation. The authors concluded that exposure to mercury during pregnancy was associated with a reduction in the biparietal diameter, but had no significant effect on the other variables analyzed.

Effects on growth were also observed by Wells et al. (2016), who found an association between MeHg concentrations in umbilical cord blood with length and head circumference that was influenced by fatty acids n-3 HUFAs, selenium and inorganic mercury (IHg). Kuntz et al. (1982), analyzed Total Hg in MB and in the mixture of UCB in the prepartum, partum and postpartum periods and found that concentrations in MB in the postpartum period were higher than concentrations in UCB. The study showed significant association between previous stillbirths and mercury levels in both maternal and cord blood. Previous malformed infants significantly correlated with prenatal background mercury level.

On the other hand Vigeh et al. (2018), investigated the association between mercury prenatal exposure using UCB, MB and anthropometric measures of the newborn and found that the mean concentration was two folds higher in UCB than MB; moreover, a negative correlation was found between total Hg concentrations and birth outcomes ($r = -0.134$ and -0.119, $p < 0.03$). In the adjusted analysis, a correlation was found between total Hg concentrations in UCB and birth weight.

Discordances in the correlations between the concentrations of total Hg in the UCB and the growth parameters of the newborns can be explained by the different methods of mercury analysis in the cord blood. While some used the mixture of blood from the umbilical arteries and veins, others used the blood of the cord vein or even the concentration of mercury separately in the vein and umbilical arteries.

The Table 4 shows total mercury concentration in umbilical cord matrices as biomarkers of prenatal exposure to mercury associated with child neurodevelopment alterations.

Six studies analyzed the association between total Hg concentrations in umbilical cord blood (UCB), [3,8,9,18,23,37], and two associated umbilical cord tissue with neurodevelopmental outcomes [18,37]. The majority showed association of neurodevelopmental outcomes with total Hg in blood and tissue from umbilical cord.

The safety limit in umbilical cord blood recommended by the US EPA is 5,8μg/L, a level beyond which it potentially increases the risk of adverse effects on pregnancy outcomes. Among the studies that assessed neurodevelopment in association with total Hg concentration in cord blood above the safety limit, all found association with cognitive and or psychomotor changes, as shown in Table 4 [3,18,23,37]. However, a study shows changes in child neurodevelopment even at low concentrations of mercury [8,38]. Jedrychowski et al. (2006), assessed cognitive and psychomotor status of 1-year-old infants whose mothers were exposed to low, but varying amounts of mercury during pregnancy. These studies showed that the children with mercury concentrations higher than 0.80μg/L in cord blood or higher than 0.50μg/L in maternal blood showed a significantly greater probability of delayed psychomotor or mental performance.

Jedrychowski et al. (2007), assessed the status cognitive and psychomotor of children and estimated the amount of mercury absorbed by mothers and newborns as a result of fish consumption during pregnancy and tested associations between total Hg in UCB and cognitive and psychomotor deficits in a cohort of 374 children using two development scales (BSID II and PDI). The authors found a non-significant deficit at 12 months of age and no developmental problems at 24 and 36 months.

Table 4: Total mercury concentration in umbilical cord matrices as biomarkers of prenatal exposure to mercury associated with child neurodevelopmental outcomes.

Authors	Umbilical cord blood (UCB) Mean ±SD geometric mean (interquatile range)	Umbilical cord tissue (UCT) Mean ±SD geometric mean (interquartile range)	Outcomes
Grandjean *et al.* (1999)	TotalHg:22.9µg/g	ND	TotalHg in UCB associated with language, attention and memory deficits
Grandjean *et al.* (2005)	TotalHg: 22,350.0249 µg/L (13.1-40.4) µg/L	TotalHg(dw): 0.210 µg/g (0.132-0.36) µg/g TotalHg(ww): 0.0249 µg/g (0.0149-0.044) µg/g	The imprecision of the TotalHg dry-weight concentration was lower than of the wet-weight, and it was intermediate between those of the cord blood and the hair biomarkers. Regression analyses showed that the dry-weight cord mercury concentration showed as good a predictor of methylmercury-associated neuropsychological deficits at 7 years of age as was the cord-blood mercury concentration.
Grandjean *et al.* (2007)	TotalHg(dw): 22.35 µg/g	TotalHg(dw): 0.210 µg/g TotalHg(ww): 0.024 µg/g	Relation between exposure and outcomes too limited to determine the most precise biomarker.
Jedrychowski *et al.* (2006)	TotalHg: 0.85 µg/L (normal): TotalHg: 1.05 µ/L (abnormal): TotalHg: 0.88 µg/L	ND	Mercury in UCB is associated with psychomotor and cognitive deficits; risk for delayed development when TotalHg in MB > 0.50 µg/L. r = 0.62, p < 0.000
Jedrychowski *et al.* (2007)	TotalHg:1.09µg/g	ND	TotalHg in UCB>0,9µg/L was associated with neurocognitive and psychomotor retardation of children at 12 months. This effect was less visible at 24 and 36 months of age.
Tatsuta *et al*,2017	GirlsTotalHg:15.8 µg/L Boys TotalHg: 16.5 µg/L	ND	Association between TotalHg in UCB and behavioral problems in boys, but not girls.

Legend: **(UCB)**: (umbilical cord blood); **(UCT):** umbilical cord tissue; **(MB)**, (maternal blood); **TotalHg**: total mercury ; **MeHg** : methylmercury; **ND**: not detected

The analysis of methylmercury exposure from 447 umbilical cord tissue was verified that when expressed in relation to the dry weight to the tissue the cord mercury concentration correlated very well with that in cord blood. While using the structural equation model analysis, it has been shown that these two biomarkers have the average of the total imprecision about 30% also, and the imprecision of the dry-weight –based concentration was lower than that of the wet-weight-based parameter. The study even showed that the dry-weight cord mercury concentration was almost as good a predictor of methylmercury associated neuropsychological deficits at seven years of age as was the cord-blood mercury concentration [18].

Posteriorly, Grandjean et al. (2007), admitted that the relationship between mercury exposure measured through dry weight and wet weight umbilical cord tissue and umbilical cord blood with neurodevelopmental outcomes was limited to indicate the most accurate biomarker.

Despite the different techniques of blood collection and processing of umbilical cord tissue, the results of the studies showed that these matrices could be used as potential biomarkers of prenatal exposure to mercury in association with child neurodevelopment.

In most studies, concentrations of total Hg and MeHg have been analyzed in a mixture of umbilical venous and arterial blood. Umbilical venous blood was the fetal matrice analyzed in few studies and very few studies analyzed total Hg in the venous or arterial blood of the umbilical cord separately, such as a way to enable a better interpretation of these results based on fetal-placental circulation. Blood vessels form an extensive arterial-capillary-venous system within the chorionic villi, maintaining the fetal blood very close to the maternal blood. This system offers a large contact area for the exchange of substances and gases between the maternal blood currents, normally with no mixture of maternal and fetal blood [20].

In the majority of studies analyzed in the present review, total mercury concentrations in the umbilical cord tissue were correlated with the concentrations in both the umbilical cord blood and maternal blood, regardless of the method employed, although the processing of tissue samples seems to be one of the methodological factors that can influence the results. The total Hg concentrations were higher in the umbilical cord samples processed in dry weight compared to wet weight. The umbilical cord and placenta are not particularly lipophilic and therefore the concentrations of total Hg or MeHg in these tissues should

reveal the concentrations contained in the vascular compartment of these organs [14,39].

Few studies used umbilical cord tissue to test the association with child neurodevelopment. Due to the ease to obtain this tissue, the availability of the material for processing and the executability of the total Hg and MeHg analysis method, the use of umbilical cord matrices were recommended as biomarkers of prenatal exposure. Previous studies indicated the use of the umbilical cord in dry weight as a biomarker of prenatal exposure. However, wet weight analyses can be considered provided that a correction factor is applied.

Inherent factors to the placenta as well as the different methods used to collect the umbilical cord blood and to process the tissue umbilical cord, the diversity in the analysis methods among the studies may explain the uncertainties regarding the definition of the best biomarker of exposure to mercury.

In Conclusion, the studies analyzed in the present review showed that mercury concentrations in umbilical cord tissue were lowly studied as bioindicators of prenatal exposure to methylmercury. Total Hg and MeHg concentrations were generally higher in the umbilical cord blood than the maternal blood and the concentrations in the umbilical cord tissue were better correlated with the concentrations in the umbilical cord blood than the maternal blood.

Different methods were used to collect the umbilical cord blood and to process the tissue samples. In the majority of the studies that used the umbilical cord matrices as biomarkers of prenatal exposure, some showed associations between total Hg concentrations in the umbilical cord blood/tissue with anthropometric or neurodevelopmental abnormalities. Inherent factors to the placenta as well as the diversity in the collection and analysis methods among the studies may explain the uncertainties regarding the definition of the best biomarker of exposure to mercury.

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