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Relationships between trace element concentrations in chorionic tissue of placenta and umbilical cord tissue: Potential use as indicators for prenatal exposure

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ABSTRACT

The role of the placenta was assessed by comparing the profiles of methylmercury (MeHg), inorganic mercury (I-Hg), lead (Pb), cadmium (Cd), selenium (Se), zinc (Zn), and copper (Cu) in freeze-dried chorionic tissue of the placenta and umbilical cord tissue. The significance of the placenta and cord tissue as predictors of prenatal exposure to these trace elements in pregnant women and newborns was also examined by comparing the element profiles among placenta and cord tissue, and maternal and cord blood red blood cells (RBCs). The samples were collected from 48 mother–child pairs at birth in the general population of Japanese. The concentrations of all elements, except for MeHg, were significantly higher in placenta than in cord tissue. In particular, the Cd showed the highest placenta vs. cord tissue ratio (59:1), followed by I-Hg (2.4:1), indicating that the placental barrier works most strongly against Cd among the examined toxic elements. Contrary to the other elements, the MeHg concentration in cord tissue was significantly higher (1.6 times) than that in placenta, indicating its exceptionally high placental transfer. The MeHg in placenta showed significant correlations with total mercury (T-Hg) in maternal and cord RBCs ($r_s = 0.80$ and 0.91, respectively). The MeHg in cord tissue also showed significant correlations with T-Hg in maternal and cord RBCs ($r_s = 0.75$ and 0.85, respectively). Therefore, both placenta and cord tissue are useful for predicting maternal and fetal exposure to MeHg. The Se concentration in placenta showed significant but moderate correlations with that in maternal and cord RBCs ($r_s = 0.38$ and 0.57, respectively). The Pb, Zn, and Cu concentrations in placenta and cord tissue showed no significant correlations with those in maternal and cord RBCs. As an exception, the Cd concentration in placenta showed a moderate but significant correlation ($r_s = 0.41$) with that in maternal RBCs, suggesting that the placenta is useful for predicting maternal exposure to Cd during gestation.

1. Introduction

Fetuses depend on their mothers for nutrition, including essential elements such as selenium (Se), zinc (Zn), and copper (Cu). However, they are also exposed through their mothers to toxic elements such as methylmercury (MeHg), inorganic mercury (I-Hg), lead (Pb), and cadmium (Cd). The transfers of these toxic metals from mother to fetus have mainly been studied by comparing the concentrations of the elements in maternal and cord blood or red blood cells (RBCs) (Butler Walker et al., 2006; Miklavcic et al., 2013; Sakamoto et al., 2012; Truska et al., 1989). To date, however, simultaneous comparisons of trace elements among placenta, cord tissue, maternal blood/RBCs, and cord blood/RBCs have not been well investigated. To examine the role of the placenta in this study, we compared the concentrations of the above-mentioned toxic and essential elements between chorionic tissue of the placenta and umbilical cord tissue in 48 mother–child pairs in the general Japanese population. In addition, we assessed the usefulness of the placenta and cord tissue as predictors of maternal and fetal exposure to these trace elements.

Among the analyzed toxic elements, mercury (Hg), especially MeHg, has attracted much attention because several man-made pollution incidences and animal studies have indicated that the developing brain during the prenatal stage is vulnerable to MeHg exposure (Choi, 1989; NRC, 2000; WHO, 1990). In the severe MeHg pollution incident in Minamata, Japan, more than 20 infants exposed to MeHg through

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their mothers showed a severe cerebral palsy like-syndrome, while their mothers had mild or no manifestations of poisoning (Harada, 1978; Takeuchi et al., 1962). Although the results of the Seychelles child development study and the Faroese birth cohort study did not reach the same conclusion (NRC, 2000), the global adverse effects of MeHg exposure on pregnant women, especially those consuming large amounts of fish and seafood, remain to be elucidated. The total mercury (T-Hg) concentration in blood/RBCs is known to be a good biomarker of MeHg exposure in humans (Svensson et al., 1995; WHO, 1990). The T-Hg concentration in umbilical cord blood has been used as an effective biomarker of fetal MeHg exposure (Grandjean et al., 1999). Umbilical cord tissue has also been used to determine fetal MeHg exposure in some studies (Akagi et al., 1998; Grandjean et al., 2005; Nishigaki and Harada, 1975; Sakamoto et al., 2010).

In addition to MeHg, mercury vapor (Hg^0), a neurotoxic agent, easily crosses the blood–brain barrier and causes damage to the brain (WHO, 1991). Furthermore, Hg^0 can transfer from mother to fetus through the placenta (Yoshida, 2002). In contrast to MeHg or Hg^0, the intestinal absorption, brain uptake, and placental transfer of divalent mercury (Hg^{2+}) are known to be limited (WHO, 1991). A comparison of I-Hg concentrations in the placenta and cord tissue may explain the limited Hg^{2+} transfer through the placenta.

With respect to other trace elements, the neurobehavioral effects of Pb, especially in children, are well documented (Liu et al., 2013; Wright et al., 2008). The Cd is also an important toxic element whose main target organ is the kidney. However, a cross-sectional epidemiological study revealed neurological effects resulting from occupational exposure to Cd (Viaene et al., 2000). A study of American children showed a negative association between Cd levels and neurodevelopmental outcomes (Ciesielski et al., 2012). Meanwhile, another cross-sectional study failed to find any neuropsychological effects of Cd (Wright et al., 2006). Consequently, investigations of the placental transfer of the above-mentioned toxic elements are of considerable interest.

The Se, an essential nutrient, plays an important role in antioxidant enzymes such as glutathione peroxidase and thioredoxin reductase (Tapiero et al., 2003). It is also well established that Se can counteract the toxicity of various elements in animals, especially that of Hg^{2+} and MeHg (Beyrouty and Chan, 2006; El-Begearmi et al., 1982; Fredriksson et al., 1993; Ganther et al., 1972; Satoh et al., 1985). Moreover, Se is known to coexist with Hg in fish and sea mammals (Burger and Gochfeld, 2007; Burger et al., 2007; Cabanero et al., 2005), and may play a role in protecting against MeHg toxicity. We recently demonstrated that selenomethionine, a food-derived Se, directly protected against neuronal degeneration caused by MeHg in the developing rat cerebrum (Sakamoto et al., 2013).

The main objectives of the present study were: 1) to investigate the role of the placenta in the transfer of various trace elements from mother to fetus during gestation, by comparing the element concentrations in chorionic tissue of placenta and cord tissue; and 2) to assess the potential use of trace element concentrations in placenta and cord tissue for predicting their body burden in mothers and newborns during gestation, by studying the relationships of the element concentrations among chorionic tissue of placenta and cord tissue as well as maternal and cord RBCs.

2. Material and methods

2.1. Subjects

Approximately 1 week before parturition, a total of 48 healthy Japanese pregnant women without any known exposure to heavy metals provided written informed consent to participate in the study. The women were aged between 21 and 41 years (mean age: 29.3 ± 4.2 years), and resided in Munakata City, Fukuoka, Japan. The babies were born healthy after full-term pregnancies (37–41 months), and comprised 25 males and 23 females. The study was approved by the Ethics Committee of the National Institute for Minamata Disease (NIMD).

2.2. Sampling

Placenta, umbilical cord tissue for 5 cm on the fetus side, and venous umbilical cord blood (13 mL) were collected from the 48 pairs of mothers and infants at parturition between May and December 2002. Venous maternal blood (10 mL) was collected before breakfast on the first day after parturition. The blood samples were obtained by venipuncture and collected in heparin-containing vacutainer tubes. RBCs were obtained by centrifugation at 3000 rpm for 10 min. All samples were stored at −80 °C until analysis.

Chorionic tissue of the placenta was separated from the placenta using scissors. The chorionic tissue of the placenta and cord tissue were rinsed five times with 0.9% saline and pressed using paper towels each time to remove the blood, and then freeze-dried. The reason for using freeze-dried cord tissue was that 48 paires of T-Hg in cord RBCs showed a better correlation coefficient with T-Hg in freeze-dried cord tissue ($r_s = 0.85$) than with T-Hg in wet cord tissue ($r_s = 0.82$) in a preliminary experiment. Grandjean et al. (2005) also previously recommended the use of freeze-dried cord tissue rather than wet cord tissue as a biomarker of fetal exposure to MeHg.

2.3. Metal analysis

The T-Hg concentrations were determined by cold vapor atomic absorption spectrophotometry using a mercury analyzer Model Hg-201 (Sanso Seisakusho Co. Ltd., Tokyo, Japan) according to the method of Akagi et al. (2000), which involved sample digestion with HNO_3, $HClO_4$, and H_2SO_4, followed by reduction to Hg^0 by $SnCl_2$. The method detection limit was 0.01 ng/g. A blood reference material, Level 2, MR9067 (Nycomed Co., Oslo, Norway) was used to check the accuracy of the results. The average Hg concentration measured in the reference material was 7.5 μg/L (recommended range: 6.8–8.5 μg/L). For selective quantification of I-Hg, MeHg in the acidified sample homogenate was removed by toluene as much as possible (5 times) using a previously reported procedure (Yasutake and Hirayama, 1990), and the Hg concentrations were determined using an oxygen combustion-gold amalgamation method and an atomic absorption mercury detector (MD-A; Nippon Instruments Co. Ltd., Tokyo, Japan). The method detection limit was 0.01 ng/g. The MeHg was calculated as T-Hg minus I-Hg.

Analyses of the remaining trace elements in RBCs, placenta, and cord tissue were carried out by IDEA Consultants Inc. (Shizuoka, Japan). The RBC samples (about 200 mg) were precisely weighed. Freeze-dried placenta and cord tissue (about 20 mg) were precisely weighed. Samples were diluted to 2 mL with a matrix solution containing 0.05 mL of concentrated ammonia, 1 mL of 0.01 M disodium ethylenediaminetetraacetate, 0.7 mL of Triton X-100, and 20 mL of butanol per liter. The diluted samples were analyzed by a standard addition analysis technique using a 7500c ICP-MS system (Agilent Technologies, Santa Clara, CA). Accuracy was checked by measuring a reference blood material, Level 1, MR4206 (Nycomed Co.). The average values measured in the reference blood and the recommended values were as follows: 27.3 and 27.6 ± 1.4 ng/mL for Pb; 0.74 and 0.74 ± 0.06 ng/mL for Cd; 72.3 and 79.8 ± 5.4 ng/L for Se; 5330 and 5550 ± 300 ng/mL for Zn; and 552 and 564 ± 33 ng/mL for Cu. The detection limits were 0.4 ng/mL for Pb, 0.08 ng/mL for Cd, 2 ng/mL for Se, 4 ng/mL for Zn, and 1 ng/mL for Cu.

2.4. Statistical analysis

Differences in trace element concentrations between placenta and cord tissue were analyzed by a paired *t*-test. Associations among elements in the samples were tested using Spearman rank correlation coefficient. Values of $P < 0.05$ were considered to indicate statistical significance.

Table 1
Concentrations (median values and interquartile ranges in ng/g) of MeHg, I-Hg, T-Hg, Pb, Cd, Se, Zn, and Cu in 48 pairs of placenta and cord tissue (dry weight basis).

	MeHg	I-Hg	(T-Hg)	Pb	Cd	Se	Zn	Cu
Placenta	43.1 (34.7–48.1)	7.3 (6.1–8.2)	51.2 (41.3–55.7)	56.6 (41.4–75.0)	68.6 (54.4–91.7)	1040 (975–1200)	48,100 (43,700–50,400)	3910 (3390–4300)
Cord tissue	67.2** (51.0–84.3)	3.1** (2.3–3.7)	71.7** (54.0–87.5)	39.9* (33.8–50.1)	1.16** (0.87–1.68)	454** (384–528)	35,700** (32,000–41,900)	2960** (2600–3330)

The percentage of I-Hg vs. T-Hg in placenta (14.3%) was significantly ($P < 0.001$) higher than that in cord tissue (4.3%).
* $p < 0.01$.
** $p < 0.001$.

3. Results

3.1. Trace element concentrations in placenta and cord tissue

The medians and interquartile ranges of the MeHg, I-Hg, T-Hg, Pb, Cd, Se, Zn, and Cu concentrations in placenta and cord tissue on a dry weight basis are shown in Table 1. All element levels, except for MeHg, were significantly ($P < 0.01$ for Pb; $P < 0.001$ for others) higher in placenta than those in cord tissue. The Cd showed the highest ratio of the median values in placenta vs. cord tissue (59:1), followed by I-Hg (2.4:1), Se (2.3:1), Pb (1.4:1), Zn (1.3:1), and Cu (1.3:1). Among the examined elements, only the level of MeHg in cord tissue was significantly ($P < 0.001$) higher (1.6 times) than that in placenta. However, the level of I-Hg level in placenta was significantly ($P < 0.001$) higher (2.4 times) than that in cord tissue. Consequently, the percentage of I-Hg vs. T-Hg in placenta (14.3%) was significantly ($P < 0.001$) and 3.3 times higher than that in cord tissue (4.3%).

The correlations between the placenta and cord tissue concentrations of MeHg, I-Hg, Pb, and Cd are depicted in Fig. 1. In all cases, the MeHg concentrations in cord tissue were higher than those in placenta, while the I-Hg and Cd concentrations in placenta were higher than those in cord tissues. In many cases, the Pb concentrations in placenta were higher than those of cord tissues.

The correlations between the placenta and cord tissue concentrations of Se, Zn, and Cu are depicted in Fig. 2. In all cases, the Se concentrations in placenta were higher than those in cord tissue. In many cases, the Zn and Cu concentrations in placenta were higher than those in cord tissue.

3.2. Trace element concentrations in maternal and cord RBCs

The medians and interquartile ranges of the T-Hg, Pb, Cd, Se, Zn, and Cu concentrations in maternal and cord RBCs are shown in Table 2. Among the toxic elements, only the T-Hg level in cord RBCs was significantly ($P < 0.001$) higher (1.5 times) than that in maternal RBCs. The Pb and Cd levels in cord RBCs were significantly ($P < 0.001$) lower than those in maternal RBCs. The Se, Zn, and Cu levels in cord RBCs were significantly ($P < 0.001$ for Se and Zn; $P < 0.01$ for Cu) higher than those in maternal RBCs.

3.3. Correlations of MeHg in placenta and cord tissue vs. T-Hg in maternal and cord RBCs

Table 3 shows the Spearman rank correlation coefficients of MeHg in placenta and cord tissue vs. T-Hg in maternal and cord RBCs. The MeHg in placenta showed significant ($P < 0.001$) correlations with T-Hg in

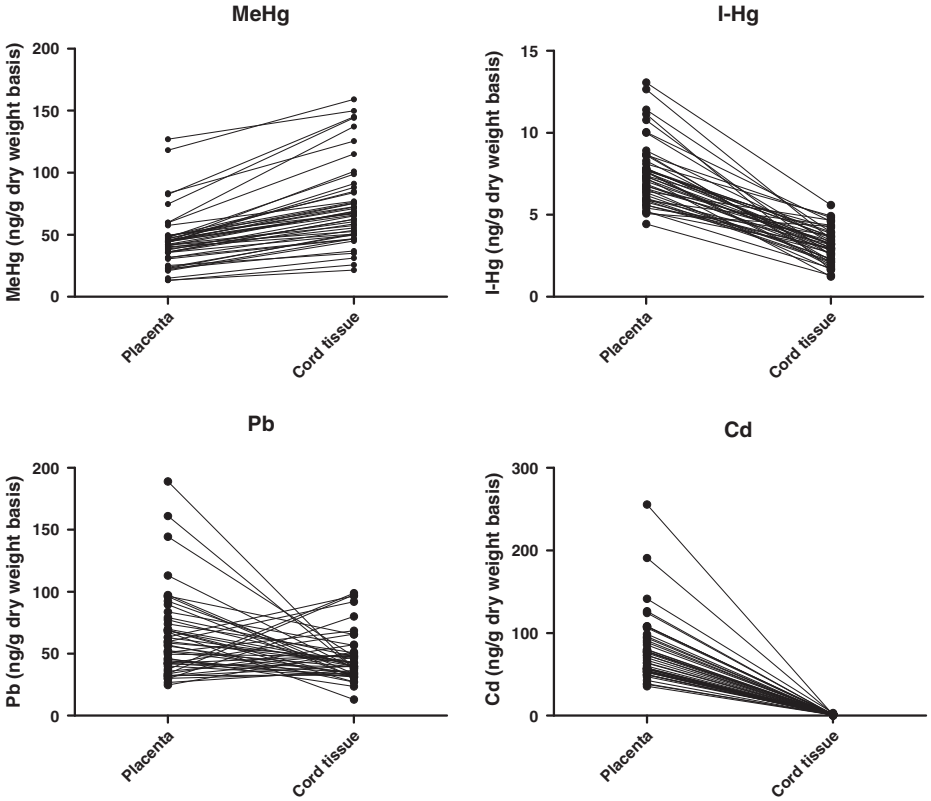

Fig. 1. Correlations between 48 pairs of placenta and cord tissue concentrations (dry weight basis) of MeHg, I-Hg, Pb, and Cd.

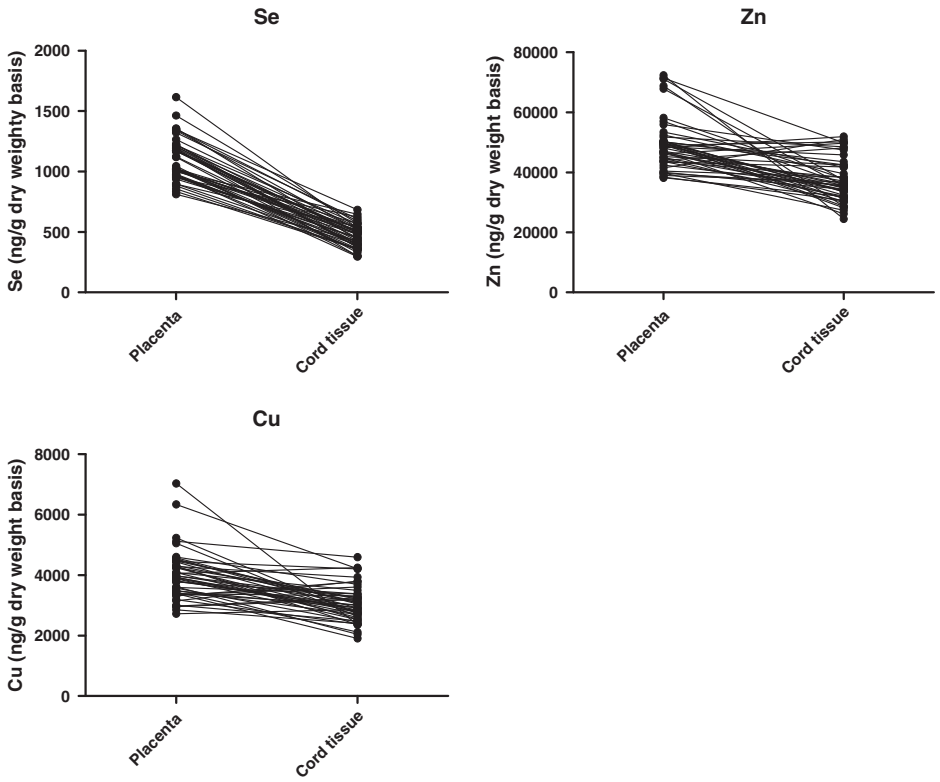

Fig. 2. Correlations between 48 pairs of placenta and cord tissue concentrations (dry weight basis) of Se, Zn, and Cu.

maternal and cord RBCs ($r_s = 0.80$ and 0.91, respectively). The MeHg in cord tissue also showed significant ($P < 0.001$) correlations with T-Hg in maternal and cord RBCs ($r_s = 0.75$ and 0.85, respectively).

3.4. Correlations of trace elements among placenta, cord tissue, maternal RBCs, and cord RBCs

Table 4 shows the Spearman rank correlation coefficients of T-Hg, Pb, Cd, Se, Zn, and Cu among placenta, cord tissue, maternal RBCs, and cord RBCs. The T-Hg in placenta showed significant ($P < 0.001$) and strong correlations with T-Hg in maternal and cord RBCs ($r_s = 0.81$ and 0.90, respectively). The T-Hg in cord tissue showed significant ($P < 0.001$) and strong correlations with T-Hg in maternal and cord RBCs ($r_s = 0.74$ and 0.85, respectively). In addition, the T-Hg showed significant ($P < 0.001$) and strong correlations among all the tissues examined. The Se in placenta showed significant but moderate correlations with the Se in maternal RBCs ($r_s = 0.38$; $P < 0.01$) and cord RBCs ($r_s = 0.57$; $P < 0.001$). The Se in cord tissue showed significant ($P < 0.01$) but moderate correlation with the Se in maternal RBCs ($r_s = 0.36$). However, the Pb, Zn, and Cu in placenta and cord tissue showed no significant correlations with those in cord and maternal RBCs, respectively. The Cd in cord tissue showed no significant correlations with Cd in maternal and cord RBCs. However, the Cd in placenta showed a significant ($P < 0.001$) but moderate correlation with that in maternal RBCs ($r_s = 0.41$).

4. Discussion

In this study, the roles of the placenta in the transfer of some toxic elements from mother to fetus during gestation were well demonstrated by comparing the profiles of the elements between chorionic tissue of the placenta and cord tissue. All of the element levels, except for MeHg, were significantly higher in placenta than those in cord tissue. The placental barrier worked most strongly against Cd, followed by I-Hg. Our study also indicated that the MeHg or T-Hg concentrations in both placenta and cord tissue were useful biomarkers for prenatal MeHg exposure in newborns. In turn, the Cd concentration in placenta can be useful for predicting maternal Cd exposure during mid-to-late gestation.

Among the elements examined, only MeHg level was significantly higher (1.6 times) in cord tissue than in placenta. The T-Hg level in cord RBCs was also significantly higher (1.5 times) than that in maternal RBCs, in agreement with previous studies (Sakamoto et al., 2004; Stern and Smith, 2003). These phenomena may be explained by active MeHg transfer from mother to fetus across the placenta via neutral amino acid carriers (Aschner and Clarkson, 1988; Kajiwara et al., 1996). It is known that the developing brain during the prenatal stage is highly susceptible to MeHg toxicity. In addition, the higher MeHg accumulation in fetuses than in mothers at late gestation is an important public health issue, especially for the Japanese and other populations whose diets largely consist of fish and seafood.

Table 2
Concentrations (median values and interquartile ranges in ng/g) of T-Hg, Pb, Cd, Se, Zn, and Cu in 48 pairs of maternal and cord RBCs.

	T-Hg	Pb	Cd	Se	Zn	Cu
Maternal RBCs	9.1 (6.9–10.8)	23.4 (19.6–30.7)	1.9 (1.5–2.2)	197 (182–212)	1190 (1150–1260)	558 (524–599)
Cord RBCs	14.0** (10.3–18.0)	12.5** (10.5–15.7)	0.20** (0.14–0.27)	221** (204–248)	2260** (1870–2610)	618* (580–650)

* $p < 0.01$.
** $p < 0.001$.

Table 3
Spearman rank correlation coefficients (r_s) of 48 pairs of MeHg in placenta and cord tissue vs. T-Hg in maternal RBCs and cord RBCs.

MeHg in placenta vs. T-Hg in maternal RBCs	0.80*
MeHg in placenta vs. T-Hg in cord RBCs	0.91*
MeHg in cord tissue vs. T-Hg in maternal RBCs	0.75*
MeHg in cord tissue vs. T-Hg in cord RBCs	0.85*

* $p < 0.001$.

The I-Hg level in placenta was significantly higher (2.4 times) than that in cord tissue. The MeHg level in placenta was significantly lower (64%) than that in cord tissue as mentioned earlier. Consequently, the percentage of I-Hg vs. T-Hg in placenta was significantly and 3.3 times higher than that in cord tissue. These results indicated that, different from MeHg, the inorganic divalent Hg in maternal blood was efficiently trapped within the placenta.

The Pb concentration in placenta was significantly higher (1.4 times) than that in cord tissue, and the Pb level in cord RBCs was about 50% of that in maternal RBCs. These results indicated that the placental barrier protected the fetus from Pb exposure to a limited degree.

Among the toxic elements, the Cd level in placenta was significantly and extraordinarily higher (59 times) than that in cord tissue, which implies that maternal blood Cd was most strongly trapped within the placenta. Consequently, the Cd concentration in cord RBCs was approximately 10% of that in maternal RBCs. Lower Cd concentrations in cord blood/RBCs compared with those in maternal blood/RBCs have previously been reported by a number of investigators (Baranowska, 1995; Breen et al., 1994; Sakamoto et al., 2012). Metallothionein in the placenta may play an important role in trapping Cd within the placenta (Breen et al., 1994; Goyer et al., 1992).

The concentrations of essential elements such as Se, Zn, and Cu in placenta were significantly higher than those in cord tissue. Differently from toxic elements, the placenta does not work as a barrier for essential elements. The higher concentrations of Se, Zn, and Cu in placenta than those in cord tissue can be explained by the existence of Se-, Zn-, and Cu-containing enzymes in the placenta, i.e., glutathione peroxidase and thioredoxin reductase for Se (Ejima et al., 1999; Knapen et al., 1999) and Zn, Cu-superoxide dismutase for Zn and Cu (Ali Akbar et al., 1998; Zadrozna et al., 2009).

The concentrations of MeHg in placenta showed significant and strong correlations with those of T-Hg in cord and maternal RBCs ($r_s = 0.80$ and 0.91, respectively). The concentrations of MeHg in cord tissue also showed significant and strong correlations with those of T-Hg in cord and maternal RBCs ($r_s = 0.75$ and 0.85, respectively). In addition, the T-Hg concentrations showed significant and strong correlations among all the tissues examined. These results show that, unlike the other elements, MeHg is distributed equally among the tissues, implying that either placenta or cord tissue is a useful biomarker for prenatal MeHg exposure in mothers and newborns. The Se concentrations in placenta showed significant and moderate correlations with cord RBCs ($r_s = 0.57$), suggesting that the Se concentration in placenta can predict approximately 30% of the Se body burden in newborns. On the other hand, the Cd and Pb concentrations in placenta and cord tissue showed no significant correlations with those in cord RBCs, indicating that placenta and cord tissue are not good predictors for the body burden of these elements in newborns. The Zn and Cu concentrations in placenta and cord tissue also showed no significant correlations with those in cord RBCs, suggesting that homeostatic control processes regulate these essential elements. Therefore, placenta and cord tissue will not be good predictors for the body burden of Zn and Cu in newborns. As an exception, the Cd concentration in placenta showed a significant and moderate correlation with that in maternal RBCs ($r_s = 0.41$). This may be caused by the very efficiently trapped maternal blood Cd within the placenta. Therefore, the Cd concentration in placenta can be used as a biomarker for maternal Cd exposure during mid-to-late gestation.

Table 4
Spearman rank correlation coefficients (r_s) of T-Hg, Pb, Cd, Se, Zn, and Cu among 48 pairs of placenta, cord tissue, maternal RBCs, and cord RBCs.

	T-Hg	Pb	Cd	Se	Zn	Cu
Placenta vs. maternal RBCs	0.81***	0.28	0.41**	0.38**	0.01	0.14
Placenta vs. cord RBCs	0.90***	0.19	0.25	0.57***	0.01	−0.05
Cord tissue vs. Maternal RBCs	0.74***	−0.05	0.25	0.36**	0.02	0.05
Cord tissue vs. Cord RBCs	0.85***	−0.02	−0.03	0.27	−0.11	−0.14
Placenta vs. Cord tissue	0.78***	−0.17	0.37**	0.33*	0.07	0.05
Maternal RBCs vs. Cord RBCs	0.87***	0.79***	0.33*	0.74***	0.13	0.07

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

5. Conclusions

By comparing the relationships of the toxic and essential elements analyzed here between chorionic tissue of placenta and cord tissue, the role of the placenta became clearer. The Cd, I-Hg, Pb, Se, Zn, and Cu concentrations in placenta were significantly higher than those in cord tissue. Among the examined toxic elements, the placental barrier worked most strongly against Cd, followed by I-Hg. In contrast to the other toxic elements, MeHg level in cord tissue was significantly higher (1.6 times) than that placenta, indicating exceptionally higher placental transfer of MeHg among the toxic elements examined. The MeHg and T-Hg in placenta or cord tissue can be useful biomarkers for prenatal MeHg exposure in newborns, because MeHg and T-Hg in these tissues showed significant and strong correlations with T-Hg in cord RBCs. As an exception, the Cd concentration in placenta can be useful for predicting maternal exposure to Cd during gestation, because Cd was very efficiently trapped in the placenta and the Cd level in placenta showed a moderate but significant correlation with that in maternal RBCs.

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