Heavy metals in maternal and cord blood in Beijing and their efficiency of placental transfer

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ABSTRACT

This study aimed to determine the effect of exposure to heavy metals in pregnant women in Beijing, China. We also evaluated the association of these heavy metals with birth weight and length of newborns. We measured the levels of 10 heavy metals, including lead (Pb), titanium (Ti), manganese (Mn), nickel (Ni), cadmium (Cd), chromium (Cr), antimony (Sb), stannum (Sn), vanadium (V), and arsenic (As), in 156 maternal and cord blood pairs. An inductively coupled plasma mass spectrometry method was used for measurement. Pb, As, Ti, Mn, and Sb showed high detection rates (>50%) in both maternal and cord blood. Fourteen (9%) mothers had blood Pb levels greater than the United States Center for Disease Control allowable threshold limit for children (50 μg/L).

In prenatal exposure to these heavy metals, there was no significant association between any heavy metal and birth weight/length. Moreover, we estimated the placental transfer efficiency of each heavy metal, and the median placental transfer efficiency ranged from 49.6% (Ni) to 194% (Mn) (except for Cd and Sn). The level and detection rate of Cd in maternal blood were much higher than that in cord blood, which suggested that Cd had difficulty in passing the placental barrier. Prospective research should focus on the source and risk of heavy metals in non-occupationally exposed pregnant women in Beijing.

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Introduction

Heavy metals are ubiquitous environmental pollutants, which results from industrial pollution, human activities, and natural combustion (Al-Saleh et al., 2011; Amaya et al., 2013). Dietary intake is the most common source of heavy metals for the general population (Amaya et al., 2013). Itai-Itai disease, which occurs in Japan, first brought global public attention to the problem of cadmium (Cd)-contaminated rice (Nogawa and Kido, 1993). In the US, several million people are suffering in arsenic (As) exposure of drinking water (Ayotte et al., 2011). The As concentration in these drinking water is above the US...
Environmental Protection Agency standard for As in drinking water systems (10 μg/L). Recently, low As exposure levels were reported to be associated with the risk of hyperuricemia in men and with the prevalence of gout in women (Kuo et al., 2015). However, for some heavy metals, such as vanadium (V) and stibium (Sb), their safe and adequate limit of intake is not known for humans (Imtiaz et al., 2015). To date, the adverse effect of heavy metals on human is gradually acknowledged because of their known and potential toxic properties.

Epidemiological evidence has demonstrated that some heavy metals exposure can dramatically affect adult fertility (Al-Saleh et al., 2008; Amaya et al., 2013; Kuo et al., 2015; Jin et al., 2016). Maternal blood lead (Pb) levels of approximately 100 μg/L would increase the risks of pregnancy hypertension and spontaneous abortion in pregnant women, and reduce neurobehavioral development in offspring (Bellinger, 2005). A recent study reported that Cd concentration in maternal blood was inversely associated with the birth weight of offspring in Bangladesh (Menai et al., 2012). Jin et al. (2014) conducted that high Pb level in pregnant women’ blood would increase the risk of neural tube defects in newborns.

The placenta is an important selective barrier to toxic compounds during pregnancy (Al-Saleh et al., 2011), however, some heavy metals can interfere with placental transport systems (Zhang et al., 2004) and then cross through the placenta (Osman et al., 2000). Because of differences between the fetus and adult in many biochemical pathways, the fetus is highly sensitive to chemicals or drugs, even at a very low exposure concentration (Wells et al., 2010). Therefore, there is a growing concern about the adverse effect on the fertility or fetal development even that the exposure level of heavy metals was much lower than international guidelines (Greet et al., 2006; Holmes et al. 2009; Al-Saleh et al., 2011). Furthermore, Mattison (2010) suggested that there were no thresholds for the effects of environmental exposure in utero or during early childhood.

To evaluate of the exposure of heavy metals exposure during pregnancy, maternal and/or cord samples was mainly used (Butler Walker et al., 2006; Amaya et al., 2013; Jin et al., 2014, 2016). Cord blood mercury levels are usually higher than that of maternal blood (Gundacker et al., 2010). Cord blood Pb levels are equal to or lower than maternal blood Pb levels (Ask et al., 2002; Al-Saleh et al., 2011), while cord blood Cd levels are always much lower than maternal blood Cd levels (Kantola et al., 2000; Al-Saleh et al., 2011). Currently, little is known about the features and mechanisms involved in heavy metal toxicokinetics through the placenta.

In this study, we conducted a pilot study of 156 pairs of maternal and cord blood samples that collected in Beijing, China. We aimed to characterize the occurrence, distribution, and placental transport of 10 heavy metals, including Pb, Cd, As, titanium (Ti), V, chrome (Cr), manganese (Mn), nickel (Ni), stannum (Sn), and Sb. Moreover, the association between each heavy metal and birth weight/length of newborns was investigated.

1. Materials and methods

1.1. Subjects

All maternal and cord blood that was analyzed in this study was collected by staff at Beijing Obstetrics and Gynecology Hospital, Capital Medical University, China. These samples were obtained from 987 female volunteers who were hospitalized between November 2015 and December 2016 for parturition. The experimental protocol was approved by the Research Ethics Committee at all participating institutions, and informed consent of all participating subjects was obtained. General criteria for inclusion of the pregnant women in the study were: (1) a resident in the study area for longer than 1 year; and (2) no history of possible occupational exposure to heavy metals, such as work in mining. Based on these criteria, a total of 156 pairs of blood samples were selected for analysis.

1.2. Chemicals and reagents

Germanium (GSB04-1728-2004), indium (GSB04-1731-2004), and rhenium (GSB04-1745-2004) standard solutions, and a multi-element standard solution (GSB04-1767-2004) were purchased from Guobiao Testing & Certification Co., Ltd. (Beijing, China). HNO3 and H2O2 were purchased from Merck (Darmstadt, Germany). All chemical reagents that were used were analytical reagent grade. Deionized water (18.2 MΩ; Milli-Q, Bedford, MA, USA) was used in the whole experimental process.

1.3. Blood collection and analysis

Maternal and cord blood (10 mL) was collected at delivery in Beijing Obstetrics and Gynecology Hospital. All of the blood samples were immediately stored at −80°C before analyzed. A 0.5 mL of whole blood is mixed with 0.5 mL HNO3 and 0.2 mL H2O2, and then digested on an electric hot plate for 3 hr at 95°C. After digestion, the solution is diluted to a final volume of 10 mL with deionized water. Ten heavy metals in maternal and cord blood are then measured by inductively coupled plasma-tandem mass spectrometry (ICP-MS, Agilent8800; CA, USA). Multiple-element standard solution is used for calibration and validation of the standard curves. Germanium, indium, and rhenium are used as internal references to calibrate the ICP-MS system. Each sample is measured in duplicate. A quality control blood sample and a blank solution are incorporated in each batch of 15 samples. It is recorded as zero when the concentration of an element was lower than the limit of detection. Method validation parameters for determination of each heavy metal are shown in Table 1.

1.4. Statistical analysis

IBM SPSS Statistics 20 (IBM Corporation, NY, USA) was used to analyze the data. The mean, skewness, and percentiles are used to describe the distribution of heavy metals. The Mann–Whitney U test is used to compare heavy metal levels between maternal and umbilical cord blood. Spearman’s test was used
to describe the correlations of metals between maternal and cord blood. Statistical significance was set as a two-tailed \( p \) value of <0.05.

2. Results and discussion

2.1. Participants’ characteristics

General characteristics of the 156 pairs of mothers and newborns are shown in Table 2. The age of the mothers ranged from 22 to 45 years, and 31 (20%) were older than 35 years. Of the 156 mothers, 122 (78%) had their first pregnancy. Of the 156 newborns, 17 (11%) were small for gestational age infants (gestational weeks, ≤37), while the remaining 139 (89%) newborns were born following a normal number of weeks of pregnancy (37–41 weeks). Seventy-seven (49%) newborns were boys and 79 (51%) were girls. The birth weight of 4 (3%) newborns was <2500 g and that of 16 (10%) newborns was >4000 g. The birth length of four (3%) newborns was <47 cm and that of three (2%) newborns was >53 cm.

2.2. Heavy metals in maternal and cord blood

The detection rates, levels, and descriptive statistics for each metal in maternal and cord blood are shown in Table 3. The detection rates of five metals, including Pb, Ti, Mn, As, and Sb, were higher than 50% in both maternal and cord blood. Mn, Sb, and Pb had similar detection rates in maternal and cord blood. The detection rates of Ti, V, Cr, and As in maternal blood were slightly lower than those in cord blood. However, the detection rate of Cd (53.8%) in maternal blood was much higher than that in cord blood (4.5%). Sn, which had a detection rate lower than 10% in maternal and cord blood, is not further discussed in this study.

Mn had the highest median levels in maternal and cord blood samples, with median values of 19.4 and 47.8 \( \mu \)g/L, respectively. Median levels of Pb (17.6 vs 12.5 \( \mu \)g/L), Sb (4.97 vs 4.00 \( \mu \)g/L), As (2.17 vs 1.53 \( \mu \)g/L), and V (0.53 vs 0.37 \( \mu \)g/L) were slightly higher in maternal samples than in cord blood samples. Ti levels were slightly lower in maternal samples than in cord blood samples (14.6 vs 16.0 \( \mu \)g/L). The median Ni level was significantly higher in maternal blood than in cord blood samples (12.8 vs 4.47 \( \mu \)g/L). However, the median Cr level was significantly lower in maternal blood than in cord blood samples (3.42 vs 7.44 \( \mu \)g/L). The median Cd level was 0.52 \( \mu \)g/L in maternal blood, but most cord blood Cd samples were below the detection limit.

2.3. Correlations between heavy metals

Relationships between different heavy metal levels in blood samples were studied using Spearman rank correlation coefficients. Here only heavy metals with more than 30 data pairs (concentrations in both maternal and cord blood more than the limit of quantitation) were analyzed. Therefore, eight metals (except for Ni and Sn) were considered for maternal blood, and seven metals (except for Ni, Sn, and Cd) for cord blood. Mn-Mn, Ti-Pb, and Mn-Pb showed significant positive correlations (all \( p < 0.01 \)), and Ti-Sb was significantly positively correlated (\( p < 0.05 \)) in maternal blood (Table 4). V-As showed a negative significant correlation (\( p < 0.05 \)). In cord blood, Ti-Mn (\( p < 0.05 \)), Ti-Pb (\( p < 0.05 \)), and Mn-Pb (\( p < 0.01 \)) were significantly positively correlated, while V-Mn (\( p < 0.01 \)) showed a negative significant correlation. These moderate correlations usually suggest a possible common source or sources shared by these metallic elements. Moreover, the differences in correlations between heavy metals in maternal and cord blood suggest differential passage through the placenta.

2.4. Placental transfer efficiency of heavy metals

The occurrence of heavy metals in cord blood suggested that these chemicals can access through the placenta. Relationships between cord and maternal blood were further studied for eight metals (except for Sn and Cd). Linear regression curves of these metals are shown in Fig. 1, with exclusion of
any point with at least one value below the limit of quantitation. There was no significant correlation between maternal and cord blood for Cr, dual biomarker. Ratios between cord and maternal levels were used to compare metal-specific trans-placental transfer rates. We arranged the placental transfer efficiency (PTE) of each metal from low to high (Fig. 2). The median values of PTE for Mn and Cr were 97.3%, 94.8%, 80.1%, 70.0%, 66.5%, and 49.6%, respectively.

### 2.5. Relationships among birth outcomes and heavy metals

The associations between birth weight/length and each heavy metal level (with a detection rate > 50%) in maternal and cord blood were measured. To the best of our knowledge, this study is the first to evaluate the extent of heavy metals exposure in a mother–child cohort in Beijing and to predict the potential risks of birth.

The observed blood Pb levels in pregnant women in our study are lower than those reported in pregnant women in Shanxi (24.5 μg/L, China) (Jiang et al., 2011), Chengdu (68.8 μg/L, China) (Jiang et al., 2011), Japan (78 μg/L) (Tsuchiya et al., 1984), Iran (48.2 μg/L) (Vigeh et al., 2006), and Peru (272 μg/L) (Jorge 2013). Our observed Pb levels are similar to those observed in pregnant women in France (17 μg/L) (Menai et al., 2012), but higher than those observed in pregnant Flemish women (11.1 μg/L) (Baeyens et al., 2014) and in Canada (4.3–8.1 μg/L) (Thomas et al., 2015). Maternal blood Pb levels in our study are much lower than those reported in Beijing in 2003 (43.4 μg/L) (Yao and Huang 2003). This difference between findings might be contributed to that Beijing has banned the use of leaded gasoline and paid attention to environmental pollution control in recent years. The CDC recommends follow-up activity and interventions beginning at blood Pb levels ≥50 μg/L in pregnant women to prevent possible adverse effects for either the mother or fetus (CDC, 2010). However, despite this ban, in the present analysis, 14 maternal blood samples showed blood Pb levels >50 μg/L, and three cord blood samples had blood Pb levels >40 μg/L.

The median As value in maternal blood in this study is higher than that observed in pregnant women in other areas, including Shanxi (0.52 μg/L, China) (Jin et al., 2014), Flemish

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### Table 3 – Heavy metal levels in maternal and cord blood (n = 156, μg/L).

<table>
<thead>
<tr>
<th>Metals</th>
<th>Maternal blood</th>
<th>Cord blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Ti</td>
<td>126 (80.8)</td>
<td>17.7 ± 11.8</td>
</tr>
<tr>
<td>V</td>
<td>49 (31.4)</td>
<td>1.75 ± 1.94</td>
</tr>
<tr>
<td>Cr</td>
<td>40 (25.6)</td>
<td>6.36 ± 8.08</td>
</tr>
<tr>
<td>Mn</td>
<td>153 (98.1)</td>
<td>24.3 ± 19.5</td>
</tr>
<tr>
<td>Ni</td>
<td>49 (31.4)</td>
<td>14.5 ± 11.5</td>
</tr>
<tr>
<td>As</td>
<td>105 (67.3)</td>
<td>2.90 ± 2.13</td>
</tr>
<tr>
<td>Cd</td>
<td>84 (53.8)</td>
<td>0.72 ± 0.51</td>
</tr>
<tr>
<td>Sn</td>
<td>4 (2.56)</td>
<td>33.2 ± 42.5</td>
</tr>
<tr>
<td>Sb</td>
<td>149 (95.5)</td>
<td>6.38 ± 5.49</td>
</tr>
<tr>
<td>Pb</td>
<td>156 (100)</td>
<td>23.1 ± 21.2</td>
</tr>
</tbody>
</table>

<sup>a</sup> Number and percentage of samples with heavy metal levels higher than the limit of quantitation.
(0.64 μg/L, Belgium) (Baeyens et al., 2014), and Canada in 2008–2011 (0.69 μg/L) (Ettinger et al., 2017). Our median As level is lower than that in pregnant women in Bolivia (3.81 μg/L) (Barbieri et al., 2016) and Iran (74.7 μg/L) (Vigeh et al., 2015). Cd levels in maternal blood in our study are similar to those in Shanxi (0.47 μg/L, China) (Jin et al., 2014), France (0.8 μg/L) (Menai et al., 2012), Iran (0.54 μg/L) (Vigeh et al., 2006), Saudi Arabia (0.986 μg/L) (Al-Saleh et al., 2014), and Flemish (0.312 μg/L, Belgium) (Baeyens et al., 2014), but lower than those in Peru (88 μg/L) (Jorge 2013) and Japan (7 μg/L) (Tsuchiya et al., 1984). Observed Mn levels in maternal blood in our study are similar to those observed in Costa Rica

Fig. 1 – Concentrations of each heavy metal in cord blood versus concentrations in maternal blood. Regression curves calculated from values above LOQ in maternal-cord blood pairs.

Fig. 2 – Placental transfer efficiency (PTE) of heavy metals based on the ratio between heavy metal levels in cord and maternal blood.
(24.5 μg/L) (Mora et al., 2015), Taipei, China (22.8 μg/L) (Lin et al., 2010), and Iran (17.1 μg/L) (Vigeh et al., 2006), but lower than those in Japan (31 μg/L) (Tsuchiya et al., 1984).

In our study, the median values of other heavy metals, including V, Cr, Ni, and Sb, were much lower than those of Pb and Mn in maternal blood. However, the relatively high detection rate (>25%) of these heavy metals in maternal and cord blood strongly suggests an potential adverse health effect of these heavy metals in chronic exposure. Exposure to inorganic V is associated with numerous adverse health outcomes, such as carcinogenicity, immunotoxicity and neurotoxicity, and may lead to V-related inflammation (Zwolak, 2014). The level of maternal urinary V may be associated with low birth weight (Jiang et al., 2016). Studies have also reported that V and Ni in particulate matter are related to low birth weight (Basu et al., 2014; Bell et al., 2010; Pedersen et al., 2016). An increased mortality rate of lung cancer and respiratory heart diseases may be associated with exposure of workers to Sb (Schnorr Teresa et al., 1995). Another study suggested that chronic Sb exposure results in reproductive disorders and chromosomal damage (Winship 1987). Environmental exposure to Sb can lead to an increased risk of preeclampsia in women (Vigeh et al., 2006).

Maternal blood appears to be a better predictr of heavy metal exposure than cord blood because maternal blood can be obtained at any time during pregnancy. Although it is known that some heavy metals can cross through placenta (Caserta et al., 2013), little is known about the mechanisms involved in toxicokinetics of heavy metals in the placenta. To simultaneously evaluate the risk of heavy metal exposure for both mother and fetus only using maternal blood, placental transfer of each heavy metal needs to be determined. In the current study, we attempted to compare PTE of each test heavy metal using the ratio between heavy metals in cord and maternal blood of our participants. We found that median cord blood Cr and Mn levels were higher than those in maternal blood, while Sb, Pb, As, and Ni cord blood levels were lower than those in maternal blood. The results suggested that it must be taken in consideration of different PET when using maternal blood as a predictor of heavy metal exposure to fetus. A previous study showed that Cd accumulated in placental tissue and placental Cd levels were related to maternal blood levels, but not cord blood levels (Esteban-Vasalillo et al., 2012). We also found that Cd was mostly detected in maternal blood, but not cord blood. However, Cd may affect fetal health by affecting maternal health, because Cd can affect endocrine hormone synthesis, alter trophoblast cell migration, and induce early decidualization of human endometrial stroma cells (Gundacker and Hengstschläger, 2012).

To date, heavy metals pollution is a serious problem in many places in China. Therefore, the health risks of heavy metals exposure have been raised a great public health concern. In large cities, various anthropogenic activities, such as fuel combustion, can release heavy metals. Automobile exhaust might be a main source of heavy metals (Men et al., 2018), because the number of vehicles in Beijing have exceeded 5.6 million in 2018. Additionally, heavy metals might come from other sources in or around Beijing, such as coal combustion and the manufacture (Men et al., 2018). The general population lived in Beijing may undergo daily exposure to these released heavy metals through soil, dust, atmosphere, water, and contaminated food. Considering that exposure to heavy metals at low level is associated with some diseases, such as cardiovascular disease (Mendy et al., 2012; Feng et al., 2015), and infertility (Tanikut et al., 2014), it is necessary to investigate the source and evaluate the risk of heavy metals in general population in the future.

Table 5 – Correlations between heavy metal levels in maternal and cord blood and newborn weight or length (n = 156).

<table>
<thead>
<tr>
<th>Metal</th>
<th>BW r</th>
<th>p-values</th>
<th>BL r</th>
<th>p-values</th>
<th>BW r</th>
<th>p-values</th>
<th>BL r</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ti</td>
<td>0.024</td>
<td>0.767</td>
<td>0.076</td>
<td>0.348</td>
<td>0.117</td>
<td>0.146</td>
<td>0.114</td>
<td>0.158</td>
</tr>
<tr>
<td>Mn</td>
<td>0.086</td>
<td>0.286</td>
<td>0.064</td>
<td>0.432</td>
<td>0.125</td>
<td>0.126</td>
<td>0.037</td>
<td>0.653</td>
</tr>
<tr>
<td>As</td>
<td>0.107</td>
<td>0.187</td>
<td>0.113</td>
<td>0.16</td>
<td>0.061</td>
<td>0.467</td>
<td>0.029</td>
<td>0.727</td>
</tr>
<tr>
<td>Sb</td>
<td>−0.032</td>
<td>0.696</td>
<td>−0.032</td>
<td>0.692</td>
<td>−0.108</td>
<td>0.189</td>
<td>−0.031</td>
<td>0.705</td>
</tr>
<tr>
<td>Pb</td>
<td>0.085</td>
<td>0.292</td>
<td>0</td>
<td>0.999</td>
<td>0.099</td>
<td>0.227</td>
<td>−0.014</td>
<td>0.864</td>
</tr>
</tbody>
</table>

BW: birth weight; BL: birth length.

3. Conclusions

The present study showed widespread exposure to heavy metals in pregnant women in Beijing. Our results provide informative baseline biomonitoring data of heavy metal exposure in non-occupationally exposed pregnant women in Beijing. Moreover, the PTE data that were obtained in this study can help to evaluate the fetus’s status in terms of heavy metal exposure at an earlier stage using maternal blood during pregnancy. Despite the finding that health risk assessment showed no potential concern for developmental toxicity in newborns, further studies are warranted to identify the exposure source and potential chronic adverse effects on mothers and their neonates.

Acknowledgment

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