Environ Sci Pollut Res (2016) 23:22467–22476
DOI 10.1007/s11356-016-7265-1

RESEARCH ARTICLE

Assessment of arsenic in colostrum and cord serum and risk exposure to neonates from an island population in China

Chenye Xu[1] · Mengling Tang[1] · Siyu Zhu[1] · Hua Naranmandura[2] · Weiping Liu[1]

Received: 4 June 2015 / Accepted: 14 July 2016 / Published online: 23 August 2016

Abstract Arsenic (As) has been proven to be highly toxic to humans, but limited attention has focused on exposure levels and potential risks to mother-neonate pairs of coastal populations. This study was conducted by examining the As concentration in colostrum and umbilical cord serum collected from 106 mother-neonate pairs living on Shengsi Island, facing the Yangtze River estuary and Hangzhou Bay in China. Average concentrations of total As in colostrum and cord serum were 18.51 ± 7.00 and 19.83 ± 10.50 μg L^{-1}. One-way ANOVA analysis showed delivered ages and source of drinking water played significant roles in influencing the maternal exposure patterns. Correlation analysis indicated a significantly positive association between As concentrations in colostrum and cord serum. Multivariable linear regression models adjusted for other confounders clarified the dose-response relationship with a coefficient value of 0.23 and a 95 % confidence interval of (0.006, 0.492); $p < 0.05$. The calculated daily intake of total As for neonates through breastfeeding was in the range from 0.413 to 3.65 μg kg^{-1} body weight, and colostrum As, especially the most toxic species, inorganic arsenic (iAs), would pose a risk to neonates.

Responsible Editor: Philippe Garrigues

Electronic supplementary material The online version of this article (doi:10.1007/s11356-016-7265-1) contains supplementary material, which is available to authorized users.

✉ Weiping Liu
wliu@zju.edu.cn

[1] MOE Key Laboratory of Environmental Remediation and Ecosystem Health, College of Environmental and Resource Sciences, Zhejiang University, Hangzhou 310058, China

[2] Department of Toxicology, School of Medicine and Public Health, Zhejiang University, Hangzhou 310058, China

Keywords Arsenic · Colostrum · Umbilical cord serum · Correlation analysis · Exposure assessment · Inorganic arsenic speciation

Introduction

Arsenic (As), well known for its high toxicity, was recognized as as a group 1 carcinogen by International Agency for Research on Cancer (IARC 2004) and ranked at the top of the Priority List of Hazardous Substances announced by the Agency for Toxic Substances and Disease Registry in 2011 and 2013 (ATSDR 2013). As a ubiquitous natural element, arsenic can seriously pollute the land, air, water, and other compartments of the environment, which eventually threaten the human beings. Due to As-related health problems, it has become one of World Health Organization's top 10 chemicals of major public health concern (WHO 2012). Since the late 1960s, evidence has indicated that high levels of As can induce skin lesions and increase the risk of skin cancer (Kazi et al. 2009; Kolachi et al. 2011). Many previous in vitro and human epidemiological studies have indicated that chronic exposure to arsenic is associated with an increased risk of serious cardiovascular abnormality, neural injury (Bryant et al. 2011), developmental malformation, and reproductive toxicity (Mandal and Suzuki 2002). In mother-neonate populations, high levels of prenatal As exposure may affect the intellectual function at incipient stages of children's life (Hsieh et al. 2014; Liu et al. 2010; Rahbar et al. 2012).

However, until recently, most studies investigating As have put emphasis on environment medium like soils, ground water, and food chains (Bundschuh et al. 2012; Kalbitz and Wennrich 1998; Matschullat 2000; Rahbar et al. 2012). For understanding the potential risks, information about individuals' exposure level was still limited. As the largest river in

China and the most important region for agricultural and industrial development, arsenic pollution in the Yangtze River has been investigated, especially the prosperous Yangtze River Delta. Shengsi Island faces the Yangtze River estuary and Hangzhou Bay, the unique situation that makes it susceptible to industrial pollution discharged into the Yangtze River. A regional survey, which determined As concentration in the middle and lower reaches of Yangtze River from below the Three Gorges Dam to the mouth at Shanghai, showed that the average concentration of dissolved and suspended particles of As was close to the maximum concentrations recommended for ricers by the European Community (EC) (Muller et al. 2008). Arsenic exposure in drinking water was recognized as an important environmental hazard to human beings (Asante et al. 2007). The source of tap water, the islanders' main route for drinking water, comes from the reverse osmosis demineralization of seawater, which does not remove most As pollutants, thus leading to an elevated body burden of As in humans. Moreover, as this area is at the center of the East China Sea Fisheries, arsenic is abundantly present in fish and other seafood. Due to its bioaccumulation and biomagnification through the food chain, As can be finally stored in human organs and tissues (Mandal and Suzuki 2002). For these islanders are major consumers, there exist potentially elevated exposure and risks among the coastal and island populations. When the daily intake concentration surpasses the recommended safety level, As is known to produce toxic effects from a human health perspective. A previous study quantified the total As content in 200 samples of 22 species from Shandong, China and confirmed that the margin of exposure estimated that there existed a health risk for the consumers (Wu et al. 2014).

Pregnant women and their neonates are regarded as the groups most sensitive to chemical exposure. In the late gestational period, the placenta acts as a selective maternal-fetal barrier (Menai et al. 2012), allowing oxygen and nutrients to pass to the fetus while preventing detrimental compounds from crossing (Carter 2009); however, some As can still readily cross the placental barrier (Chen et al. 2003). Therefore, umbilical cord blood, one of the most easily available and noninvasive diagnostic biological fluids (Al-Saleh et al. 2011), is considered an excellent bioindicator for assessing the prenatal exposure level to As. During the lactation period, As in the human body can be released into the breast milk, which can be used as an indicator of maternal As exposure. However, unlike the transitional or mature milk, colostrum, which secreted during the earliest periods (0–5 days) after neonatal birth, usually has higher level of protein and other growth factors (Palkovicova et al. 2007). To neonates, colostrum is believed to be a unique dietary source, providing nutrition as well as chemical elements to infants. Therefore, chemicals may be more easily transferred through colostrums to neonates (Turan et al. 2001). Causing the exposure of breastfed infants to As, it seems to be the most feasible biological matrix to assess neonatal exposure risk to As poisoning (Park et al. 2011). Most recent studies have focused on total As in human milk, but inorganic As (iAs) is actually recognized as the most toxic speciation. The identification of iAs, both arsenite (iAs^{3+}) and arsenate (iAs^{5+}), seems to be essential but thus far remains unequivocal in conclusion (Lynch et al. 2014).

To better understand the concentration and distribution of As exposure in the most susceptible population, we used colostrum and umbilical cord serum samples to investigate maternal-neonatal pairs living on this specific island. The purposes of this study are as follows. (1) Measure the As concentration in the two biological samples to determine the initial exposure level of pregnant women and neonates by comparison to certain international standards and other studies. (2) Investigate the maternal characteristics influencing the exposure patterns. (3) Explore the relationship between the colostrum and umbilical cord serum As levels to speculate on the possible distribution and transfer of As during lactation. (4) Assess the exposure risk of total As to neonates via breastfeeding. (5) Give a preliminary description of speciated iAs (iAs^{3+} and iAs^{5+}) for further understanding of the potential risk. This study involves As exposure and its health effects and provides information for future studies and advice on establishing the safety of breastfeeding in an As-contaminated area.

Materials and methods

Study design and population

The subjects of this study were all living on Shengsi Island. This island is located in southeastern China, facing the Yangtze River estuary and Hangzhou Bay, which boasts a significant geographic importance on the national scale (Fig.1). Pollutants from the waters can easily influence the local system and the island's residents. Furthermore, due to its special location, all types of seafood are part of the main diet of the islanders.

From July 2011 to May 2012, 120 pregnant women recruited in a single hospital agreed to join in the research. Shengsi Island only has one hospital with an obstetrics and gynecology unit, and approximately 50 % of all pregnant women deliver there. Each participant provided a sample of umbilical cord serum and a sample of colostrum and completed a questionnaire about their general characteristics including age, prepregnancy BMI, pregnancy weight gain, education level, and other factors. We excluded women with multiple gestations or history of chronic diseases including diabetes, hypertension, or renal pathologies. And those with hepatic disease

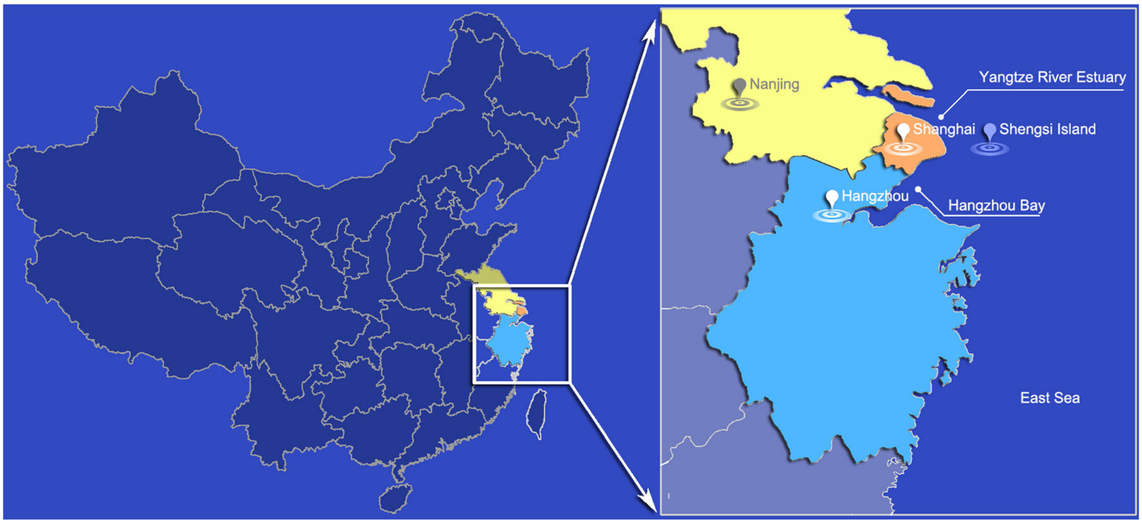

Fig. 1 Geographic location of the study island

or nephropathy and/or endocrine disease were also excluded, whereas any maternal history of illness, history of drug usage ($n = 5$), singleton births with congenital diseases ($n = 2$), and couples without quantitative samples including umbilical cord serum or colostrum ($n = 4$) samples was defaulted ($n = 3$). A total of 106 mother-infant pairs were included in the statistical analysis. All mothers were informed about the content of this investigation and signed informed consent forms; ethics approval was obtained from all participants.

Arsenic in colostrum and umbilical cord serum

Colostrum samples were collected manually during the first 5 days after birth. Umbilical cord serum was collected by a common aseptic procedure on delivery. Both colostrum and cord serum were stored at −20 °C until analysis in the laboratory. The total As was analyzed according to a low-contamination digestion bomb method using a Teflon double vessel for biological materials published in 1984 (Okamoto and Fuwa 1984) with slight modification. Briefly, 0.5 mL of each sample was placed in Teflon crucibles and then digested with 2 mL HNO_3 and 1 mL H_2O_2. The cap of the polytetrafluoroethylene (PTFE) vessel was closed, and the vessel was placed on a thermostat heating plate. The temperature was raised to 120 °C and held for 3.5 h until the samples were clear and transparent (approximately 0.5 mL, near dryness).

The digested mixture was cooled to room temperature, and deionized water was added to wash it. Finally, the whole mixture was transferred into a 10-mL glass flask. A portion of the digested sample was analyzed by inductively coupled plasma-mass spectrometry (ICP-MS, Agilent 7500a, Agilent, Santa Clara, CA, USA) at the Institute of Environmental Science of Zhejiang University, Hangzhou, China to quantify the target metals (Kosanovic et al. 2008).

Inorganic arsenic speciation analysis

iAs was determined by the hydride generation atomic fluorescence spectrometry (HG-AFS) (Beijing Kechuang Haiguang Instrument Company, China), and it was coupled with a hollow double cathode As lamp with the carrier gas of Argon (99.96 %). A mixture solution of 2 % KBH4 and 0.5 % NaOH was used as a reducing reagent to convert As into AsH_3. The extraction with hydrochloric acid was applied in this paper according to the State Standard of the People's Republic of China GB/T 5009.11-2003 determination of total As and abio-As in food, with slight modification (Yang 2003). Samples of 5 mL colostrum were placed into 25-mL volume centrifuge tubes, extracted with 12.5 mL hydrochloric acid (1 + 1), and subjected to a water bath for 4 h at 70 °C. The samples were thoroughly extracted, cooled to room temperature, and filtered through absorbent cotton. Then iAs^{5+} was restored to iAs^{3+} by the thiourea-ascorbic acid system (a mixture solution of 5 % ascorbic acid and 5 % thiourea), and iAs^{3+} was determined by HG-AFS with potassium borohydride. The concentration of iAs^{5+} was obtained by subtracting the concentration of iAs^{3+} from the total iAs. External calibration was conducted for all quantitative analyses of these samples.

Quality assurance and quality control

All the glassware and Teflon crucibles used in measurement were soaked in 10 % HNO_3 overnight. Procedural blank samples were analyzed with every 10 samples to check the cleanness of reagents and containers for quality control. Validity of the analytical data was also established by several quality parameters including precision, detection limits, linearity, and spike recovery value. Precision was obtained as percent coefficient of variation (CV%) from the relative standard deviation of 10 repeated determinations of one sample. The limit of detection (LOD) and limits of quantification (LOQ) were calculated as 3:1 and 10:1 signal versus noise value (S/N) for As of this method. Matrix controls spiked with known concentration standards were analyzed using the same methods. Linearity that was measured by the external calibration procedures that were applied was calculated from the calibration curves of As species and the value in the nonweighted least squares linear regression model. Detailed parameter values were shown in Table S1 in supporting information.

Statistical analyses

Univariate distributions were examined for all variables. All values lower than the LOD were estimated as LOD/$\sqrt{2}$ according to the Fourth National Report on Human Exposure to Environmental Chemicals published by the US Centers for Disease Control and Prevention (CDC). Extreme outliers were excluded, defined as values more than three standard deviations (SD) from the mean (Ettinger et al. 2014): subjects with cord serum As levels >51.33 μg L^{-1} (n = 2) and colostrum As levels >39.51 μg L^{-1} (n = 0). The result data was transformed to normalize the distribution of As concentrations for further statistical analysis. One-way analysis of variance (ANOVA) was used in finding out the effects of related confounders such as maternal age, pre-pregnancy BMI, pregnancy weight gain, education level, and drinking water. In the ANOVA analysis, REGWQ test and Tukey's test were conducted in the groups with homogeneity of variance; Dunnett T3 test was applied to analyze the groups with heteroscedasticity. Pearson correlation analysis was performed to observe the relationship between the colostrum and the cord serum in terms of As exposure. Associations were considered statistically significant at the level of $p < 0.05$ with the two-sided test in the models. Multivariable linear regression models with standardized regression coefficients (β) and 95 % confidence intervals (CIs) were fitted using ordinary least squares methods to explore the influence of other covariates on As level, as well as the relationship between As levels in colostrum and neonate cord serum. In all the multivariable linear regression models, we chose to investigate covariates including maternal age (Tian et al. 2009), pre-pregnancy BMI (Janssen et al. 2008), education level (Tofail et al. 2009), pregnancy weight gain, and newborn gender (Parajuli et al. 2013) based on a priori knowledge of biological significance and scientific researches (Ettinger et al. 2014). All these variables were forced into the model for adjustment. The education level (illiteracy, primary, junior high, senior high, college, and above) and newborn gender (boy and girl) were treated as categorical, while the rest were taken as continuous variables. All the statistical analyses were performed using the SPSS 16.0 software (SPSS, Chicago, IL), and figures in this paper were drawn by Origin software (OriginLab Corp, Northampton, MA, USA).

Birth exposure risk assessment

To assess the possible exposure risk to neonatal infants in Shengsi Island from the consumption of As-contaminated colostrum, we use the index of average daily intake dose (ADID). The ADID of As through colostrum was calculated using the following equations:

$$\mathrm{ADID} = \mathrm{C} \times \left(\mathrm{IR}/\mathrm{BW}\right)$$

where ADID is the daily intake of the chemical (μg kg^{-1} bw day^{-1}), BW (or bw) is body weight (kg), C is the concentration of the target chemical in colostrum (μg L^{-1}), and IR is the intake rate of the environmental medium (e.g., kg day^{-1} for food or soil, L day^{-1} for water, m^3 day^{-1} for air). We used mean milk consumption (300.2 mL day^{-1}) during the 5 days after birth reported in the Exposure Factors Handbook of EPA (US EPA 2011).

Results

Sociodemographic characteristics of study population

The sociodemographic characteristics of the Shengsi study population are listed in Table 1. In this study, the mean delivered age of the mothers was 27.16 years (SD = 2.84). The average pre-pregnancy BMI of the participating women was 20.60 kg m^{-2} (SD = 4.98). During the pregnancy, the weight gain of the mothers was 17.35 kg (SD = 10.15). Most of the study subjects had received good education: for instance, only 2.90 % had not passed junior high school and 38.1 % had received a college degree or higher. Of all infants with known gender (five missing), 58.4 % are boys and 41.6 % are girls. The mean birth weight was 3.42 kg (SD = 0.43).

Arsenic concentration level in colostrum and cord serum

All colostrum samples for As had detectable levels, and the average concentration was 18.51 μg L^{-1} (SD = 7.00; range = 4.34–45.02). All cord serum samples for As also had detectable levels, and two outliers were excluded. The mean concentration was 19.83 μg L^{-1} (SD = 10.50; range = 5.16–58.83).

Results in this study showed that characteristics of studied mother might have effects on the As in maternal colostrum (Table 2). In the one-way ANOVA analysis, we found that

Table 1 Individual characteristics of the mothers and newborn infants who participated in the study

Characteristics	Number	% or mean ± SD
Maternal characteristics		
Maternal age (years)	105	27.16 ± 2.84
Pre-pregnancy BMI (kg/m^2)	101	20.60 ± 4.98
Pregnancy weight gain (kg)	96	17.35 ± 10.15
Parity		
0	49	46.67 %
≥1	56	53.33 %
Abortion		
0	41	39.05 %
1	38	36.19 %
2	22	20.95 %
3	4	3.81 %
Education		
Illiteracy	1	0.95 %
Primary school	2	1.90 %
Junior high school	27	25.71 %
Senior high school	35	33.33 %
College school	40	38.10 %
Child characteristics		
Gender		
Girl	42	41.58 %
Boy	59	58.42 %
Birth weight (kg)	101	3.42 ± 0.43

puerperas with highest delivered age group (>30 years) had mean As value of 22.8 ± 3.26 μg L^{-1}, which was significantly higher than those with two lower groups. In addition, among all the factors, the source of drinking water played an important role, which cannot be neglected. The As level in mothers who drank rap water was 20.2 ± 6.08 μg L^{-1}, which was significantly higher than other sources of water including the well water and bottled water for the p value was at 0.000 level. However, there was no statistically significant association between neonatal As exposure and these confounders in this study.

Correlation between exposure levels in colostrum and cord serum

In present study, correlation analysis was conducted using Pearson's coefficient, and the results are shown in Fig. 2. We found that the As level in colostrum is significantly associated with the level in cord serum ($r = 0.202$, $p = 0.045$). A multivariable linear regression model with the coefficient and the 95 % CI was further used to quantitatively describe the association (Table 3). When adjusted for other variables, including maternal age, BMI, education level, pregnancy weight gain, and newborn gender, As in colostrum is significantly and positively correlated with As in umbilical cord serum, $r = 0.23$ (95 % CI: 0.006, 0.492) ($p < 0.05$).

Intake of As from colostrum

The value of ADID of the total As in neonates from colostrum consumption was used to assess the essentiality and toxicity of As for the newborns, which are outlined in Table 4 and Fig.3 shows the results according to the maternal ages. With a range from 0.413 to 3.65 μg kg^{-1} bw day^{-1}, the median value of ADID for each child was 1.78 μg kg^{-1} bw day^{-1}.

Moreover, we also analyzed the inorganic As species and their contribution to neonatal daily intake level into consideration. As shown in Table S2, the results indicated that the average daily intake of iAs is approximately 1.159 μg kg^{-1} bw day^{-1}. The percentage of iAs^{3+} in these samples accounts for approximately 20.8 % of total As, while iAs^{5+} accounts for 33.7 %. The average daily intake of iAs^{3+} and iAs^{5+} is approximately 0.462 and 0.697 μg kg^{-1} bw day^{-1}. Some studies indicated that As excretion via breast milk was low and mostly of the trivalent form of iAs, although there is still a scarcity of adequate data (Fangstrom et al. 2008; Gurbay et al. 2012).

Discussion

To our knowledge, there is no or little standard about elements in breast milk or umbilical cord serum that have been established by international organizations, therefore, we choose to compare the present results with studies in other regions of China and abroad (μg L^{-1}). As summarized in Table S3, the reported As values in breast milk vary in a large range depending on environmental exposure. However, on the whole, our study still found a higher level than in other regions in China (Zhang 2009). Compared with a multinational study initiated by WHO on breast feeding from nine countries (Chile, Ethiopia, Guatemala, Hungary, India, Nigeria, Philippines, Sweden, and Zaire) in 1973 (Park et al. 1991), the As concentration value in this study surpasses the values in other countries except for specimens from the Philippines (median = 18.89; range = 1.13–95.57 μg L^{-1}). We explain the higher levels in this study by the characteristics of studied area, drinking water, and dietary habits. First, Shengsi Island has a special geographic location of the intersection of the marine outfall of Yangtze and Qiantang River; discharged waste from the industrial and economical activities made it a susceptible area for As pollution. In 1998, Chen et al. reported As concentrations in the Shanghai coastal zone of the Yangtze River estuary reaching up to 60 μg L^{-1}, which substantially exceeds the current WHO guideline of 10 μg L^{-1} (Uneyama et al. 2007). In addition, it should be mentioned that the source of tap water, the main islanders' drinking water, comes from the reverse osmosis demineralization of seawater, which does

Table 2 Levels of arsenic (μg L^{-1}) in colostrum for selected maternal characteristics

Characteristic	Number	Mean ± SD	Percentile		
			25th	50th	75th
Colostrum					
Maternal age					
≤25	39	16.8 ± 6.34	10.2	18.4	22.0
25–30	52	18.6 ± 7.78	11.9	19.2	23.8
>30	14	22.8 ± 3.26	21.2	22.5	24.7
p value	0.024*				
Pre-pregnancy BMI (kg/m^2)[a]					
≤18.5	22	18.3 ± 7.36	10.4	19.9	22.8
18.5–24.5	62	18.6 ± 7.01	13.5	19.8	22.5
>24.5	17	17.8 ± 7.22	9.51	18.6	24.0
p value	0.991				
Pregnancy weight gain (kg)					
≤10	12	22.9 ± 8.76	17.6	22.7	27.2
10–15	30	16.2 ± 6.65	9.40	18.7	20.9
>15	54	19.1 ± 6.39	16.8	20.1	23.9
p value	0.129				
Education					
≤9	30	18.5 ± 6.28	12.7	19.2	22.5
9–12	35	18.8 ± 7.89	13.2	20.1	23.8
>12	40	18.4 ± 6.86	15.1	20.1	22.5
p value	0.974				
Drinking water					
Tap water	56	20.2 ± 6.08	18.4	21.0	24.1
Well water	15	12.1 ± 5.89	7.27	10.4	16.1
Bottle water	20	17.9 ± 5.81	12.2	19.1	22.2
p value	0.000**				

The categories of BMI were estimated by WHO

*$p < 0.05$; **$p < 0.01$

[a] Body mass index (BMI) was calculated by dividing body weight (kg) by body height (m^2)

not remove all the As pollutants, thus leading to an elevated body burden of As in humans. Residents living on the island can easily be affected by contaminated waters from the Yangtze River. Previous studies have also confirmed concentration of As in breast milk of lactating mothers related to the exposure to As through drinking water (Asante et al. 2007; Concha et al. 1998a). Furthermore, as indicated in many previous studies, besides the occupation exposure or drinking water, food is the primary contributor for human As intake (Molin et al. 2015; WHO 2012). These islanders are all fish consumers; fish and seafood are main contributors of As in the diet. There is a positive correlation between the frequency of total fish consumption and the As level in breast milk (Miklavcic et al. 2013). The high level of As in seafood (Borak and Hosgood 2007; Molin et al. 2015), which was preferential to intake by the studied population, could lead to the higher level in this study.

Compared with other regions in China, the umbilical cord serum As concentration here is higher than in other eastern cities (Jin 2010; Wang et al. 2008; Zheng et al. 2014) but similar to the level reported for populations living in certain polluted areas of developing countries such as Matlab, Bangladesh (15.7 ± 8.7 μg L^{-1}) (Hall et al. 2007) and San Antonio de los Cores, Argentina (median = 9.0 μg L^{-1}) (Concha et al. 1998a). The variations in As levels may also be attributed to the specific geographic background and dietary customs.

When considered the influence of maternal factors on the exposure pattern, our results found that As level in colostrum were higher in mothers who were at higher delivered ages. This can be attributed to the fish and seafood consumptions as potential sources of As exposure, people at older ages tend to have consumed more fishes, and the increased level of As in women of increased age may reflect its long-term exposure.

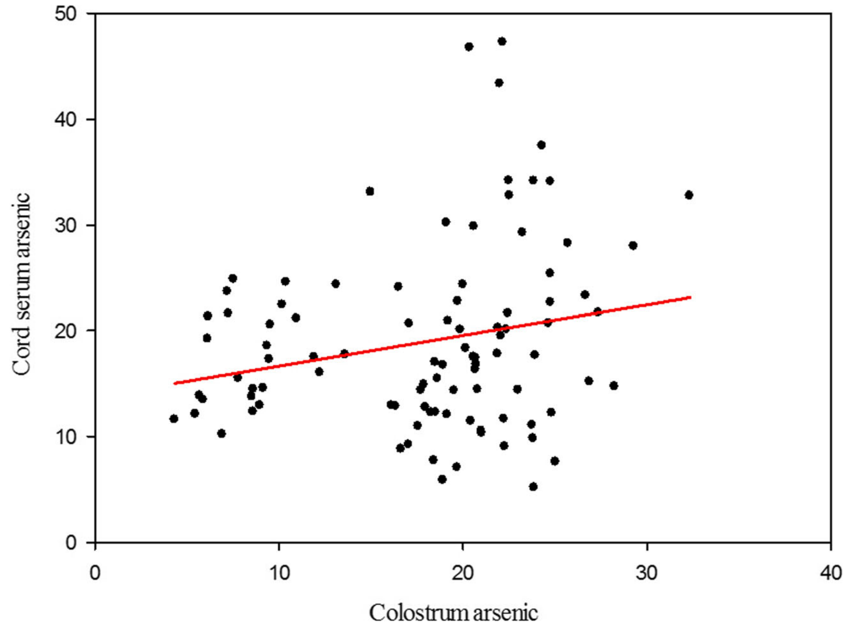

Fig. 2 Correlation between As concentrations in colostrum and cord serum (μg L^{-1})

Apart from that, it is worth mentioning, ANOVA analysis revealed that As concentrations were considerably higher in women who drank the tap water than the other two ways. Although tap water, oriented from seawater desalination through reverse osmosis methods, is believed to be the fine work to filter mineral substances, combined with bottled water, As in mothers who usually drank tap water remains higher in this study. Numerous studies have proved that concentrations of As in human urine (Asante et al. 2007), hair, nails, breast milk (Samanta et al. 2007), and blood (Kazi et al. 2009) increased significantly with those in water, which implied that the source of As in humans could be from the water origin.

Previous studies have reported a strong association of As concentration between different biological fluids, such as maternal and cord blood (Hall et al. 2007), blood and urine (Concha et al. 1998b), or breast milk and As in urine of breastfed children (Islam et al. 2014), but few have examined whether there is also any correlation between breast milk and umbilical cord blood. Because breast milk is the matrix from which As is ultimately transferred to the breastfeeding infant, it represents the exposure level of the mothers, while the umbilical cord blood, collected at birth via a noninvasive method (Islam et al. 2014), has been frequently tested to assess prenatal exposure to a variety of metals (Al-Saleh et al. 2014). The significant correlation results in this study may indicate the trans-generational transfer of As from mothers to neonates. Laboratory experiments have proven that As, especially iAs, is able to undergo trans-placental transfer, crossing the selective maternal-fetal barrier to enter the fetal circulation (Jin

Table 3 Multivariable linear regression analyses of the association between arsenic concentrations in colostrums and cord serum

	Unadjusted	Basic adjusted[a]	Further adjusted[b]
B	0.204	0.189	0.249
95 % CI	0.004, 0.404	0.027, 0.404	0.006, 0.492
Beta	0.202	0.183	0.230
P value	0.045*	0.085	0.045*

*$p < 0.05$

[a] Adjusted by maternal age, pregnancy BMI, and education

[b] Adjusted by maternal age, pregnancy BMI, education, weight gain, and newborn gender

Table 4 Daily intake of As to neonates through breastfeeding (μg kg^{-1} bw day^{-1})

Characteristic	Mean ± SD	Percentile		
		25th	50th	75th
Total As	1.65 ± 0.65	1.20	1.78	2.05
Maternal age				
≤25	1.53 ± 0.81	0.98	1.75	2.01
25–29	1.61 ± 0.71	1.14	1.78	2.03
>30	1.66 ± 0.69	1.23	1.79	2.06
Pregnancy BMI (kg m^{-2})[a]				
<18.5	1.66 ± 0.70	1.25	1.80	2.05
18.5–24.5	1.63 ± 0.70	1.15	1.77	2.03
≥24.5	1.66 ± 0.71	1.24	1.78	2.05
Infants gender				
Male	1.64 ± 0.71	1.21	1.78	2.05
Female	1.67 ± 0.70	1.15	1.77	2.06

The categories of BMI and birth weight were estimated and formulated by WHO, respectively

[a] Body mass index (BMI) was calculated by dividing body weight (kg) by body height (m^2)

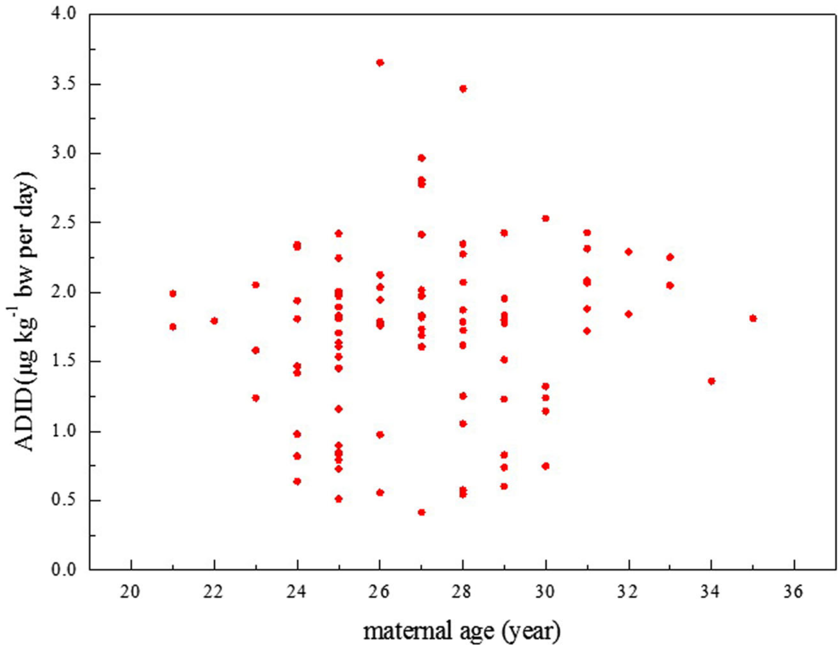

Fig. 3 Daily intake of As to neonates according to maternal age

et al. 2006). Research on the crossing of the placental barrier and lactation transfer to infants through breast milk is of crucial importance.

Since it is universally acknowledged, early life exposure to As may bring about many adverse health effects in later life, but limited information was available on the postnatal As exposure via human milk. For breast milk, this represents a unique source of As exposure to infants through breastfeeding (Ettinger et al. 2014). The oral intake level indicates the contribution of colostrum As to newborns' exposure, which has meaningful implications for maternal decisions regarding breastfeeding. For young children (0–6 years old), the EPA has established guidelines of acute and subchronic exposure to As at 0.015 and 0.005 µg kg^{-1} bw day^{-1}, respectively. The results in this study were also lower than the recommended dietary allowance of 0.005 µg kg^{-1} bw day^{-1} provided by the EPA, which means that the intake of breast milk during the earliest periods of their life will not pose an acute or subchronic threat to neonatal children, even in their most sensitive period (Tsuji et al. 2004). Several states and regions have conducted numerous studies to establish the exposure standard level, but considering that complex factors could influence the results, it is very difficult to assess or estimate dietary exposure to As. From the data submitted to Joint FAO/WHO Expert Committee on Food Additives (JECFA) at the 72nd conference, the mean daily exposure to As for infants under 12 months ranges from 0.03 to 1.63 µg kg^{-1} bw in Europe and from 0.24–1.19 µg kg^{-1} bw in the USA. In 1998, Yost et al. reported that the estimated daily dietary intake of iAs ranges from 8.3 to 14 µg day^{-1} in the USA and from 4.8 to 12.7 µg day^{-1} in Canada for various age groups, suggesting that approximately 21 to 40 % of total dietary As occurs in inorganic forms (Yost et al. 1998). Compared with these results, our study showed a higher level of total As daily intake that warrants public concern.

It should be pointed out that different As compounds in humans are different with respect to toxicity, the inorganic As may be among the most toxic forms that can lead to serious health problems; therefore, we also TOOK the inorganic As species and their contribution to neonatal daily intake level into consideration. The dietary intake of iAs (1.15 ± 0.48 µg kg^{-1} bw day^{-1}) was found to be considerably in excess of the reference dose (RfD) for chronic oral exposure of 3×10^{-4} mg kg^{-1} day^{-1} established by EPA. Generally speaking, the RfD is an estimate of a daily exposure for populations likely to be without risk of deleterious effect during their lifetime (US EPA 1998). However, we only consider the duration period for neonates of 5 days after birth. Whether colostrum As will pose a lifelong risk remains unclear. The JECFA sets a provisional tolerable weekly intake (PTWI) for iAs of 15 µg kg^{-1} bw (2.1 µg kg^{-1} bw day^{-1}) in 1998 (JECFA 1988). All the data calculated in our study were below the safety level compared with these standard guidelines. However, the PTWI for As has been withdrawn in 2011 as no longer health protective, but the benchmark dose for a 0.5 % increased incidence (BMDL0.5) of lung cancer. Because iAs can easily pass the placenta and is proven to be associated with a moderately increased risk of impaired fetal growth and fetal mortality, although the infants are partly protected by the methylation of As during pregnancy and lactation, early-life exposure may induce changes that will become apparent later in life.

Although advantages are associated with breastfeeding, nursing mothers in this population are still advised to consider the possible risk associated with long-term intake of breast milk As to establish safe breastfeeding. Moreover, because we did not continue to investigate the changes in breast milk As throughout the duration of lactation, whether a larger intake dose will lead to an elevated exposure risk remains a significant problem that requires further research. Apart from water may be polluted at the source during treatment or transport, infants' exposure to As while growing up may occur from drinking water should be put on emphasis, infant formula may replace human milk as another source of neonatal exposure. Previous studies were carried out to estimate the relative contribution of breast milk and formula to As exposure during early infancy and made the conclusion that breastfed infants have lower As exposure than formula-fed infants, and both drinking water and formula powder can be sources of exposure for infants (Carignan et al. 2015; Ljung et al. 2011), which also deserved further research.

Conclusions

This study demonstrated the As level in the colostrum and umbilical cord serum of maternal-neonate pairs in Chinese fish consumers. A positive and significant correlation between the As levels in colostrum and cord serum was observed. The intake levels of total As and As species through breastfeeding indicate the contribution of colostrum As to newborns' exposure. This result has meaningful implications for maternal decisions regarding breastfeeding. Other health impacts, if any, that arise from such exposure remain to be further explored.

Acknowledgments This work was funded in part by the National Natural Science Foundation of China (No. 21177112, 2150070146).

Conflict of interest The authors declare that they have no conflict of interest.

References

Al-Saleh I, Shinwari N, Mashhour A, Mohamed GED, Rabah A (2011) Heavy metals (lead, cadmium and mercury) in maternal, cord blood and placenta of healthy women. Int J Hyg Environ Health 214:79–101

Al-Saleh I, Shinwari N, Mashhour A, Rabah A (2014) Birth outcome measures and maternal exposure to heavy metals (lead, cadmium and mercury) in Saudi Arabian population. Int J Hyg Environ Health 217:205–218

Agency for Toxic Substance and Disease Registry (ATSDR) (2013) The Priority List of Hazardous Substances. Available: http://www.atsdr.cdc.gov/spl/

Asante KA, Agusa T, Subramanian A, Ansa-Asare OD, Biney CA, Tanabe S (2007) Contamination status of arsenic and other trace elements in drinking water and residents from Tarkwa, a historic mining township in Ghana. Chemosphere 66:1513–1522

Borak J, Hosgood HD (2007) Seafood arsenic: implications for human risk assessment. Regul Toxicol Pharmacol 47:204–212

Bundschuh J, Nath B, Bhattacharya P, Liu C, Armienta MA, Moreno Lopez MV, Lopez DL, Jean J, Cornejo L, Lauer Macedo LF, Filho AT (2012) Arsenic in the human food chain: the Latin American perspective. Sci Total Environ 429:92–106

Carignan CC, Cottingham KL, Jackson BP, Farzan SF, Gandolfi AJ, Punshon T, Folt CL, Karagas MR (2015) Estimated exposure to arsenic in breastfed and formula-fed infants in a United States cohort. Environ Health Perspect 123:500–506

Carter AM (2009) Evolution of factors affecting placental oxygen transfer. Placenta 30:S19–S25

Chen Y, Guo YL, HJ S, Hsueh Y, Smith TJ, Ryan LM, Lee M, Chao S, Lee JY, Christiani DC (2003) Arsenic methylation and skin cancer risk in southwestern Taiwan. J Occup Environ Med 45:241–248

Concha G, Vogler G, Lezcano D, Nermell B, Vahter M (1998b) Exposure to inorganic arsenic metabolites during early human development. Toxicol Sci 44:185–190

Concha G, Vogler G, Nermell B (1998a) Low-level arsenic excretion in breast milk of native Andean women exposed to high levels of arsenic in the drinking water. Int Arch Occup Environ Health 71:42–46

Ettinger AS, Roy A, Amarasiriwardena CJ, Smith DR, Lupoli N, Mercado-García A, Lamadrid-Figueroa H, Tellez-Rojo MM, Hu H, Hernández-Avila M (2014) Maternal blood, plasma, and breast milk lead: lactational transfer and contribution to infant exposure. Environ Health Perspect 122:87–92

Fangstrom B, Moore S, Nermell B, Kuenstl L, Goessler W, Grander M, Kabir I, Palm B, Arifeen SE, Vahter M (2008) Breast-feeding protects against arsenic exposure in Bangladeshi infants. Environ Health Perspect 7:963–969

Gurbay A, Charehsaz M, Eken A, Sayal A, Girgin G, Yurdakök M, Yiğit Ş, Erol DD, Şahin G, Aydın A (2012) Toxic metals in breast milk samples from Ankara, Turkey: assessment of lead, cadmium, nickel, and arsenic levels. Biol Trace Elem Res 149:117–122

Hall M, Gamble M, Slavkovich V, Liu X, Graziano J (2007) Determinants of arsenic metabolism: blood arsenic metabolites, plasma folate, cobalamin, and homocysteine concentrations in maternal-newborn pairs. Environ Health Perspect 115:1503–1509

Hsieh R, Huang Y, Shiue H, Huang S, Lin M, Mu S, Chung C, Hsueh Y (2014) Arsenic methylation capacity and developmental delay in preschool children in Taiwan. Int J Hyg Environ Health 217:678–686

International Agency For Research On Cancer IARC (2004) Overall evaluations of carcinogenicity to humans: as evaluated in IARC monographs, Volumes 1–82 (a Total of 900 Agents, Mixtures and Exposures)

Islam MR, Attia J, Alauddin M, McEvoy M, McElduff P, Milton AH (2014) Availability of arsenic in human milk in women and its correlation with arsenic in urine of breastfed children living in arsenic contaminated areas in Bangladesh. Environ Health 13:101

Janssen AJ, Nijhuis-van DSM, Akkermans RP, Oostendorp RA, Kollee LA (2008) Influence of behaviour and risk factors on motor performance in preterm infants at age 2 to 3 years. Dev Med Child Neurol 50:926–931

Joint FAO/WHO Expert Committee on Food Additives (JECFA) (1988) Arsenic. Available:http://apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=1863

Jin Y, Xi S, Li X, Lu C, Li G, Xu Y, Qu C, Niu Y, Sun G (2006) Arsenic speciation transported through the placenta from mother mice to their newborn pups. Environ Res 101:349–355

Jin ZQ (2010) Correlation studies of the As contents in normal mother's venous blood, cord blood and breast milk. Dissertation. China Medical University

Kalbitz K, Wennrich R (1998) Mobilization of heavy metals and arsenic in polluted wetland soils and its dependence on dissolved organic matter. Sci Total Environ 209:27–39

Kazi TG, Arain MB, Baig JA, Janali MK, Afridi HI, JalbanIi N, Sarfraz RA, Shah A, Niaz A (2009) The correlation of arsenic levels in drinking water with the biological samples of skin disorders. Sci Total Environ 407:1019–1026

Kolachi NF, Kazi TG, Wadhwa SK, Afridi HI, Baig JA, Khan S, Shah F (2011) Evaluation of selenium in biological sample of arsenic exposed female skin lesions and skin cancer patients with related to non-exposed skin cancer patients. Sci Total Environ 409:3092–3097

Kosanovic M, Adem A, Jokanovic M, Abdulrazzaq MY (2008) Simultaneous determination of cadmium, mercury, lead, arsenic, copper, and zinc in human breast milk by ICP-MS/microwave digestion. Anal Lett 3:406–416

Liu Y, McDermott S, Lawson A, Marjorie Aelion C (2010) The relationship between mental retardation and developmental delays in children and the levels of arsenic, mercury and lead in soil samples taken near their mother's residence during pregnancy. Int J Hyg Environ Health 213:116–123

Ljung K, Palm B, Grander M, Vahter M (2011) High concentrations of essential and toxic elements in infant formula and infant foods—a matter of concern. Food Chem 127:943–951

Lynch HN, Greenberg GI, Pollock MC, Lewis AS (2014) A comprehensive evaluation of inorganic arsenic in food and considerations for dietary intake analyses. Sci Total Environ 496:299–313

Mandal BK, Suzuki KT (2002) Arsenic round the world: a review. Talanta 58:201–235

Matschullat J (2000) Arsenic in the geosphere: a review. Sci Total Environ 249:213–297

Menai M, Heude B, Slama R, Forhan A, Sahuquillo J, Charles M, Yazbeck C (2012) Association between maternal blood cadmium during pregnancy and birth weight and the risk of fetal growth restriction: the EDEN mother–child cohort study. Reprod Toxicol 34:622–627

Miklavcic A, Casetta A, Snoj Tratnik J, Mazej D, Krsnik M, Mariuz M, Sofianou K, Spiric Z, Barbone F, Horvat M (2013) Mercury, arsenic and selenium exposure levels in relation to fish consumption in the Mediterranean area. Environ Res 120:7–17

Molin M, Ulven SM, Meltzer HM, Alexander J (2015) Arsenic in the human food chain, biotransformation and toxicology—review focusing on seafood arsenic. J Trace Elem Med Biol 31:249–259

Muller B, Berg M, Yao ZP, Zhang XF, Wang D, Pfluger A (2008) How polluted is the Yangtze river? Water quality downstream from the Three Gorges Dam. Sci Total Environ 402:232–247

O Bryant SE, Edwards M, Menon C, Gong G, Barber R (2011) Long-term low-level arsenic exposure is associated with poorer neuropsychological functioning: a project FRONTIER study. Int J Environ Res Public Health 8:861–874

Okamoto K, Fuwa K (1984) Low-contamination digestion bomb method using a Teflon double vessel for biological materials. Anal Chem 56:1758–1760

Palkovicova L, Drobna B, Petrik J, Kocan A (2007) Comparison of organochlorine compound concentrations in colostrum and mature milk. Chemosphere 66:1012–1018

Parajuli RP, Fujiwara T, Umezaki M, Watanabe C (2013) Association of cord blood levels of lead, arsenic, and zinc with neurodevelopmental indicators in newborns: a birth cohort study in Chitwan Valley, Nepal. Environ Res 121:45–51

Park J, She J, Holden A, Sharp M, Gephart R, Souders-Mason G, Zhang V, Chow J, Leslie B, Hooper K (2011) High postnatal exposures to polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) via breast milk in California: does BDE-209 transfer to breast milk? Environ Sci Technol 45:4579–4585

Park J, She J, Holden A, Sharp M, Gephart R, Souders-Mason G, Niinisto L, Pineda O, Vis H, Hofvander Y (1991) Minor and trace elements in human milk from Guatemala, Hungary, Nigeria, Philippines, Sweden, and Zaire—results from a WHO/IAEA Joint Project. Biol Trace Elem Res 29:51–75

Rahbar MH, Samms-Vaughan M, Ardjomand-Hessabi M, Loveland KA, Dickerson AS, Chen Z, Bressler J, Shakespeare-Pellington S, Grove ML, Bloom K, Wirth J, Pearson DA, Boerwinkle E (2012) The role of drinking water sources, consumption of vegetables and seafood in relation to blood arsenic concentrations of Jamaican children with and without autism spectrum disorders. Sci Total Environ 433:362–370

Samanta G, Das D, Mandal BK, Chowdhury TR, Chakraborti D, Pal A, Ahamed S (2007) Arsenic in the breast milk of lactating women in arsenic-affected areas of West Bengal, India and its effect on infants. J Environ Sci Health A ToxHazard Subst Environ Eng 12:1815–1825

Tian L, Zhao Y, Wang X, Gu J, Sun Z, Zhang Y, Wang J (2009) Effects of gestational cadmium exposure on pregnancy outcome and development in the offspring at age 4.5 years. Biol Trace Elem Res 132:51–59

Tofail F, Vahter M, Hamadani JD, Nermell B, Huda SN, Yunus M, Rahman M, Grantham-McGregor SM (2009) Effect of arsenic exposure during pregnancy on infant development at 7 months in rural Matlab, Bangladesh. Environ Health Perspect 117:288–293

Tsuji JS, Benson R, Schoof RA, Hook GC (2004) Health effect levels for risk assessment of childhood exposure to arsenic. Regul Toxicol Pharmacol 39:99–110

Turan S, Saygi S, Kili Z, Acar O (2001) Determination of heavy metal contents in human colostrum samples by electrothermal atomic absorption spectrophotometry. J Trop Pediatr 47:81–85

Uneyama C, Toda M, Yamamoto M, Morikawa K (2007) Arsenic in various foods: cumulative data. Food Addit Contam 24:447–534

US EPA (1998) Integrated risk Information System (IRIS) Arsenic, inorganic (CASRN7440-38-2). Availble: https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=278

US EPA (2011) Exposure Factors Handbook Chapter 15-Human Milk Intake. Available: http://www.epa.gov/ncea/efh/report.html

Wang P, Tian Y, Shi R, Zou XY (2008) Study on maternal-fetal status of Pb, As, Cd, Mn and Zn elements and the influence factors. Chin J Prev Med 42:722–726

WHO (2012) Arsenic Available: http://www.who.int/mediacentre/factsheets/fs372/en/.

Wu X, Gao M, Wang L, Luo Y, Bi R, Li L, Xie L (2014) The arsenic content in marketed seafood and associated health risks for the residents of Shandong, China. Ecotoxicol Environ Saf 102:168–173

Yang H (2003) Determination of total arsenic and abio-arsenic in food. GB/T5009.11–2003. (In Chinese)

Yost L, Schoof R, Aucoin R (1998) Intake of inorganic arsenic in the North American diet. Hum Ecol Risk Assess 4:137–152

Zhang D (2009) Investigation on heavy metals and nutrient elements of breast milk and the influent factors in eight cities of China. Dissertation. Shanghai Jiao Tong University

Zheng G, Zhong H, Guo Z, Wu Z, Zhang H, Wang C, Zhou Y, Zuo Z (2014) Levels of heavy metals and trace elements in umbilical cord blood and the risk of adverse pregnancy outcomes: a population-based study. Biol Trace Elem Res 160:437–444