Available online at www.sciencedirect.com

ScienceDirect

Journal of the Chinese Medical Association 80 (2017) 442−451

www.jcma-online.com

Original Article

Maternal and umbilical cord blood levels of mercury, manganese, iron, and copper in southern Taiwan: A cross-sectional study

Shih-Hui Huang [a,b], Ken-Pen Weng [c,d,e], Ching-Chiang Lin [f,g], Chung-Cheng Wang [h], Charles Tzu-Chi Lee [a], Luo-Ping Ger [i], Ming-Tsang Wu [a,j,k,*]

[a] Department of Public Health, College of Health Science, Kaohsiung Medical University, Kaohsiung, Taiwan, ROC
[b] Department of Nursing, Fooyin University, Kaohsiung, Taiwan, ROC
[c] Department of Pediatrics, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, ROC
[d] National Yang-Ming University, School of Medicine, Taipei, Taiwan, ROC
[e] Shu-Zen College of Medicine and Management, Kaohsiung, Taiwan, ROC
[f] Department of Medical Laboratory Sciences and Biotechnology, Fooyin University, Kaohsiung, Taiwan, ROC
[g] Planning Department, Fooyin University Hospital, Kaohsiung, Taiwan, ROC
[h] Department of Gynecology and Obstetrics, Fooyin University Hospital, Pingtung, Taiwan, ROC
[i] Department of Medical Education and Research, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, ROC
[j] Department of Family Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, ROC
[k] Research Center for Environmental Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, ROC

Received March 21, 2016; accepted June 30, 2016

Abstract

Background: The effect of maternal exposure to essential minerals and heavy metals on fetus is an important issue, which affects women around the world. Few data are available on the concentration of both essential minerals and heavy metals in maternal/fetal medicine. The aims of this study were to (1) assess the correlation of mercury (Hg), manganese (Mn), iron (Fe), and copper (Cu) in paired maternal/fetal blood samples, and (2) study potential confounding factors during pregnancy.

Methods: Our study recruited 145 healthy pregnant women with a mean age of 28.06 years, gathering information by collecting interviewer-administered questionnaires. Paired maternal/fetal blood samples were collected by delivery.

Results: There was a positive correlation of Hg ($r = 0.78$, $p < 0.001$), Mn ($r = 0.31$, $p < 0.001$), Fe ($r = 0.17$, $p = 0.038$), and Cu ($r = 0.21$, $p = 0.010$) in paired maternal/fetal samples. Prenatal vitamin use (>3 times/wk) was significantly associated with lower maternal Hg (adjusted odds ratio 0.272, $p = 0.005$) and lower maternal Cu (adjusted odds ratio 0.267, $p = 0.004$) levels. Median fetal Hg, Mn, and Fe levels were higher than corresponding maternal levels, while median fetal Cu level was lower than maternal Cu level.

Conclusion: There was a positive correlation of Hg, Fe, Cu, and Mn in paired maternal/fetal samples in this series. Our findings have raised the possibility of reducing maternal Hg and Cu by way of prenatal vitamin supplementation.

Keywords: copper; iron; manganese; mercury; pregnant woman; vitamin use

Conflicts of interest: The authors declare that they have conflicts of interest related to the subject matter or materials discussed in this article.

* Corresponding author. Dr. Ming-Tsang Wu, Department of Family Medicine, Kaohsiung Medical University Hospital, 100, Shih-Chuan 1st Road, Kaohsiung 807, Taiwan, ROC.

E-mail address: e_encourage@yahoo.com (M.-T. Wu).

http://dx.doi.org/10.1016/j.jcma.2016.06.007
1726-4901/

1. Introduction

The presence of multiple heavy metal contaminants is of grave concern and has received considerable attention in Taiwan.[1] Heavy metals such as mercury (Hg) are toxic contaminants, which can cross the placenta and affect fetal growth.[2,3] Essential minerals such as iron (Fe), copper (Cu), and manganese (Mn) are both nutrients and potential toxicants, depending on the amount of exposure.[4] These essential minerals are metabolized similarly to the heavy metals,[5] and they are also important metallic cofactors in catalyzing redox reactions.[4] The developing brain is highly sensitive to oxidative damage, so the concentrations of essential minerals play a crucial role in fetal brain development.[6] Few data are available on the concentrations of both essential minerals and heavy metals in maternal/fetal medicine.[7–10] Butler Walker et al[7] reported levels of total Hg and methyl Hg were significantly higher in cord blood than in maternal blood ($p < 0.0001$), whereas maternal Cu levels were significantly higher than those in cord blood ($p < 0.0001$). The confounding factors were not analyzed except for ethnicity and smoking habits; furthermore, they did not evaluate the association of these metals with birth outcome. Rudge et al[8] showed that Hg levels in cord blood were almost twice those of the mothers ($n = 62$), suggesting that the fetus may act as a filter for maternal Hg levels during pregnancy. Mn and Cu levels did not show statistically significant correlations between the two compartments. However, they also did not evaluate the confounding factors or association of these metals with birth outcome. A Taiwanese study ($n = 308$) by Lin et al[9] demonstrated that cord blood lead was lower where the mother had a higher blood concentration of Mn ($p = 0.02$). Kopp et al[10] studied the association of multiple heavy metals and trace elements between maternal and cord blood ($n = 50$). Hg accumulated in the fetus resulting in more than a three-fold increase in fetal exposure compared with maternal exposure. Their results also showed no association between internal exposure to any metals and maternal use of nutritional supplement during pregnancy.[10]

These studies[7–10] demonstrated that the levels of essential minerals in healthy pregnant women were significantly different from those of the general population. There is a need to evaluate more pregnant women, especially from different races, for the purpose of establishing specific normative levels of essential minerals. Although Taiwan is a high-fish-consuming island country, data on the accumulation of Hg in pregnant woman remain limited.[3] Furthermore, there is no Taiwanese information regarding Hg and essential minerals in both mother and fetus. The purposes of this study in south Taiwan were to (1) assess the correlation of the Hg, Mn, Fe, and Cu levels in paired maternal/fetal blood samples, and (2) study potential confounding factors such as socioeconomic factors, smoking, vitamin intake, and seafood consumption during pregnancy.

2. Methods

2.1. Studying individuals and sampling

This study was a prospective cross-sectional study. Women were considered eligible if they were 20–45 years old and pregnant with a term singleton fetus. Women with chronic medical conditions or infectious diseases, or those who reported illicit drug use were excluded. A total of 150 women consented to participate and initially met eligibility requirements. Two women withdrew because of twin fetuses, one withdrew because of stillbirth, and two others withdrew consent prior to being discharged from the hospital.

A total of 145 healthy pregnant women with a mean age of 28.06 years were recruited at the Department of Obstetrics and Gynecology of Fooyin University Hospital in Tong Gang, Taiwan, from September 30, 2010 to May 25, 2011. The city of Tong Gang is a major seaside fishing area in southern Taiwan. The participants received a detailed explanation of the study procedures before consenting to participate. The research protocol was approved by the Institutional Review Board of Fooyin University (FYH-IRB-099-04-02-A), and written informed consent was obtained from all participants. Information on the gestational age, prenatal examination, and characteristics of the birth and newborn, were obtained from the medical records. We used interviewer-administered questionnaires to collect information on demographic characteristics, smoking habits, alcohol drinking habits, betel nut chewing habits, use of Chinese medicine, seafood consumption, nutritional supplement (vitamin), and degree of education. The degree of seafood consumption was defined as the sum scores of seafood consumption items in the questionnaire. A total of nine items were about the amount of fresh fish and seafood consumption of each participant during pregnancy. High sum scores revealed more seafood consumption. The cutoff score of high and low seafood consumption was defined as the median value of the sum scores in the questionnaire. The participants were asked to record their nutritional supplement of vitamin consumption during pregnancy in the questionnaire. Anthropometric measurement of newborns was made by delivery room staff, using standard anthropometric procedures.

2.2. Blood sampling and sample analysis

Umbilical cord blood and maternal venous whole blood samples were collected into 9 mL standard laboratory issued EDTA tubes, separately. All samples were processed within 2 hours of delivery and stored at −80°C. Samples were sent to the Department of Biomedical Engineering and Environmental Sciences, Ultra Trace Micro-Analysis Laboratory at National Tsing Hua University, and were analyzed by a inductively coupled plasma-mass spectrometer (7500ce; Agilent, Tokyo, Japan). The limit of detection was 0.353 μg/L (ppb) for Hg, 0.125 μg/L (ppb) for Mn, 0.061 μg/mL (ppm) for Fe, and 0.00066 μg/mL (ppm) for Cu.[11]

2.3. Statistical analysis

We used Pearson's correlation coefficient to reveal the association between pairs of the following variables: heavy metal concentrations (Hg, Mn, Fe, and Cu) in maternal blood, heavy metal concentrations (Hg, Mn, Fe, and Cu) in cord blood, vitamin, and seafood consumption. Log-transformed data of heavy metals were used to reveal the association between maternal and fetal pairs.

Table 1
Maternal and neonatal characteristics ($n = 145$pairs).

Characteristics	Mean ± SD or N (%) (range)
Maternal	
Mean age	28.1 ± 5.2
Race/ethnicity	
Taiwan	123 (84.8)
Foreign	22 (15.2)
Education	
Elementary	9 (6.2)
Junior high school	23 (15.9)
High school	71 (49.0)
College degree	33 (22.8)
Missing	9 (6.2)
Height	158.5 ± 5.1 (145.0−171.0)
Prepregnant weight	55.3 ± 8.6 (38.0−81.0)
Perinatal weight	69.9 ± 10.5 (44.5−97.0)
Increment of BMI	5.9 ± 2.3 (1.0−16.0)
Smoked while pregnant	13 (9.0)
Drank alcohol while pregnant	11 (7.6)
Areca chewing while pregnant	10 (6.9)
Chinese medicine	
Yes	14 (9.7)
No	125 (86.2)
Missing	6 (4.1)
Vitamin supplement	
>3 times/wk	40 (27.6)
≤3 times/wk	105 (73.4)
Seafood (missing = 19)	
High seafood	67 (53.2)
Low seafood	59 (46.8)
Neonatal	
Male sex	74 (51.0)
Birth weight	3081.6 ± 387.3 (1700.0−4040.0)
Birth length	49.6 ± 2.5 (41.5−55.0)
Birth head circumference	34.3 ± 1.4 (30.5−37.0)
Chest circumference	32.6 ± 1.6 (27.0−36.5)
Gestational age at birth	
Term (37−40 wk)	108 (74.5)
Post-term (>40 wk)	29 (20.0)
Preterm(<37 wk)	8 (5.5)
Low birth weight (<2500 g)	
Yes	10 (6.9)
No	135 (93.1)

Increment of BMI = (perinatal BMI) − (prepregnant BMI).
BMI = body mass index; N = number; SD = standard deviation.

Multivariate logistic regression was used to reveal the association of heavy metal (Hg, Mn, Fe, and Cu) concentrations in maternal and cord blood by controlling maternal age, race, smoking, vitamin use, and seafood consumption. Unadjusted odds ratios and fully adjusted odds ratios were reported. The significance of p value was set at 0.05. All analyses were performed using SPSS software (version 20; SPSS Institute Inc., Chicago, IL, USA).

3. Results

A total of 150 women consented to participate and initially met eligibility requirements. Two women withdrew because of twin fetuses, one withdrew because of stillbirth, and two others withdrew consent prior to being discharged from the hospital. A total of 145 healthy pregnant women with a mean age of 28.06 years were recruited at the Department of Obstetrics and Gynecology of Fooyin University Hospital in Tong Gang, Taiwan, from September 30, 2010 to May 25, 2011.

Specific characteristics of the paired pregnant women and their neonates are shown in Table 1. The mean age of pregnant women in this study was 28.06 ± 5.18 years. Of the study participants, 72.41% were Taiwanese and approximately 48.97% were high school graduates. Prepregnant and perinatal body mass indexes were 22.04 ± 3.33% and 27.82 ± 3.86%, respectively. The percentages of smoking, alcohol drinking, and areca nut chewing during pregnancy were 8.97%, 7.59%, and 6.9%, respectively. A minority of the participants (9.66%) used Chinese medicine prenatally. Forty pregnant women (27.6%) used prenatal vitamin >3 times/wk. There were 71 female and 74 male neonates. Mean birth weight, length, and head circumference were 3081.59 ± 387.31 g, 49.61 ± 2.49 cm, and 34.3 ± 1.4 cm respectively. A large majority of the neonates (74.48%) were full term, and only 10 neonates (6.9%) had a low birth weight (<2500 g).

Table 2 shows data on metals in paired maternal and umbilical cord blood. Median maternal and fetal Hg levels were 2.24 μg/L and 2.3 μg/L, respectively. There was a significant association between maternal and fetal Hg (Fig. 1A, $r = 0.78$, $p < 0.001$). Median maternal and fetal Mn levels were

Table 2
Data on metal concentrations in maternal blood and umbilical blood.

Parameter	Median	IQR[a]	Range	5%[b]	95%[b]	% (N)[c]
Mercury (μg/L)						
Maternal Hg	2.24	(0.98−4.97)	0.10−24.65	0.42	12.48	100 (145)
Fetal Hg	2.30	(1.12−5.05)	(0.04−53.17)	0.47	16.74	100 (145)
Manganese (μg/L)						
Maternal Mn	44.96	(34.44−59.20)	(12.20−483.10)	23.05	98.08	100 (145)
Fetal Mn	61.68	(46.24−81.09)	(1.90−291.70)	25.74	118.5	100 (145)
Iron (mg/L)						
Maternal Fe (mFe)	292.30	(217.00−362.10)	(65.66−572.90)	133.33	492.20	100 (145)
Fetal Fe (fFe)	414.40	(305.25−503.00)	(11.68−651.40)	116.91	608.12	100 (145)
Copper (mg/L)						
Maternal Cu	1.47	(1.33−1.71)	(0.56−2.71)	1.07	2.15	100 (145)
Fetal Cu	0.73	(0.53−0.99)	(0.34−2.55)	0.40	1.78	100 (145)

Cu = copper; Fe = iron; Hg = mercury; IQR = interquartile range; Mn = manganese.
[a] IQR, 25th−75th percentile.
[b] 5% and 95%, fifth and 95th percentiles.
[c] Prevalence in % (number of samples above limit of quantitation).

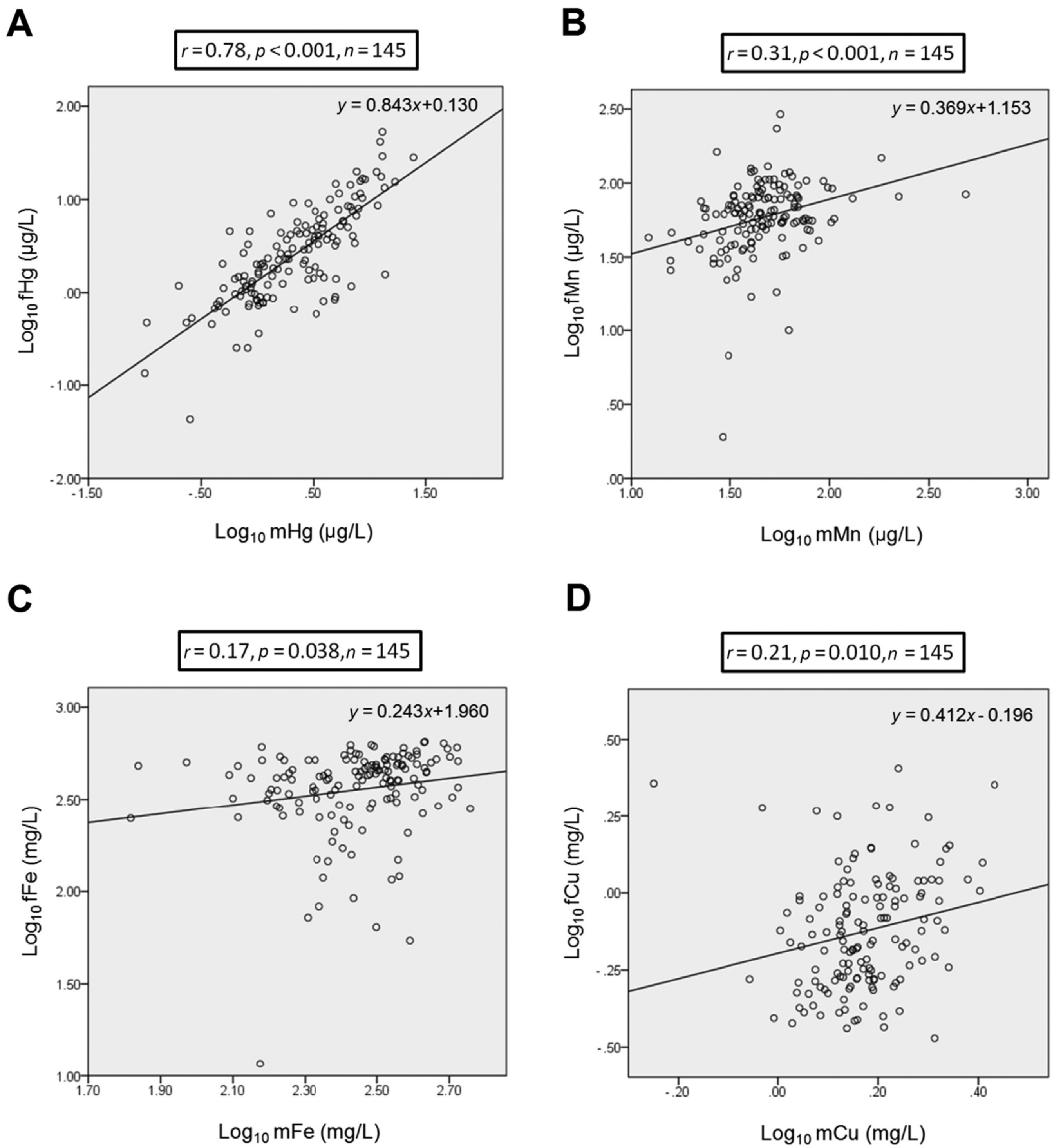

Fig. 1. (A) Association between mHg and fHg. (B) Association between mMn and fMn. (C) Association between mFe and fFe. (D) Association between mCu and fCu. fCu = copper in cord blood; fFe = iron in cord blood; fHg = mercury in cord blood; fMn = manganese in cord blood; mCu = copper in maternal blood; mFe = iron in maternal blood; mHg = mercury in maternal blood; mMn = manganese in maternal blood.

44.96 μg/L and 61.68 μg/L, respectively, and there was a significant association between maternal and fetal Mn (Fig. 1B, $r = 0.31$, $p < 0.001$). Median maternal and fetal Fe levels were 288.2 mg/L and 449.4 mg/L, respectively; there was a significant association between maternal and fetal Fe (Fig. 1C, $r = 0.17$, $p = 0.038$). Median maternal and fetal Cu levels were 1.47 mg/L and 0.72 mg/L, respectively, and there was a significant association between maternal and fetal Cu (Fig. 1D, $r = 0.21$, $p = 0.01$).

However, metal levels observed in this series differed from those observed in previous studies of mother–infant cohorts (Table 3).[3,7–10,12–17]

Tables 4–7 show multiple logistic analysis of metals with the potential confounding factors. Maternal and fetal metal

Table 3
Data on mercury, manganese, Iron, and copper in maternal blood samples of pregnant reported in this and previously published studies.

Study	Year	Country	N[a]	Mercury (μg/L)	Manganese (μg/L)	Iron (mg/L)	Copper (mg/L)
Current study	2014	Taiwan	145	2.2(0.1–24.7)	45.0 (12.2–483.1	292.3 (65.7–572.9)	1.5 (0.6–2.7)
Previous studies							
Kopp et al[10]	2012	Germany	50	0.4 (—)	17.0 (6.4–38.4)	530.5 (205.6–628.0)	1.1 (0.7–1.8)
Gundacker et al[12]	2010	Austria	52	0.7 (0.1–5.2)	—	—	—
Lin et al[9]	2010	Taiwan	308	—	22.8[b] (—)	—	—
Rudge et al[8]	2009	South Africa	62		16.8 (8.7–63.5)		1.73 (1.20–2.42)
Zota et al[13]	2009	USA	470	—	22.0 (—)	—	—
Wang et al[14]	2008	China	130	—	54.4 (—)		
Vigeh et al[15]	2008	Iran	231	—	19.1 (—)	—	—
Hsu et al[3]	2006	Taiwan	65	8.3 (—)	—	—	—
Butler Walker et al[7]	2006	Canada	385	1.7[c] (Nd–33.9)	—	—	—
Takser et al[16]	2004	Canada	101	—	16.3[b] (9.2–37.1)	—	—
Takser et al[17]	2003	France	222	—	20.4[c] (6.3–151.2)	—	—

The median concentrations (and the corresponding ranges) are presented.
[a] N: number of pregnant women.
[b] Mean.
[c] Geometric mean.

Table 4
Multivariate logistic regression analysis in terms of median levels of mercury (μg/L) in maternal and cord blood ($n = 145$).

Explanatory variable	Maternal blood		OR (95% CI)	p	AOR (95% CI)	p
	mHg ≤ 2.24	mHg > 2.24				
	N (%)	N (%)				
Maternal age	72 (49.66)	73 (50.34)				
Mean ± SD	28.10 ± 4.96	28.04 ± 5.43	0.998 (0.937–1.063)	0.948	0.999 (0.933–1.069)	0.972
Race						
Foreign	9 (40.90)	13 (59.09)	1		1	
Taiwan	63 (51.22)	60 (48.78)	0.659 (0.263–1.655)	0.375	0.785 (0.302–2.040)	0.619
Smoking (missing = 4)						
No	65 (50.78)	63 (49.22)	1		1	
Yes	5 (38.46)	8 (61.54)	1.651 (0.512–5.318)	0.401	1.749 (0.515–5.944)	0.370
Vitamin						
≤3 times/wk	44 (41.90)	61 (58.10)	1		1	
>3 times/wk	28 (70.00)	12 (30.00)	0.309 (0.142–0.674)	0.003	0.300 (0.133–0.676)	0.004
Seafood (score) (missing = 19)						
Low seafood	32 (54.24)	27 (45.76)	1		1.00	
High seafood	33 (49.25)	34 (50.75)	1.221 (0.606–2.462)	0.577	1.468 (0.692–3.114)	0.317

Explanatory variable	Cord blood		OR (95% CI)	p	AOR (95% CI)	p
	fHg ≤ 2.30	fHg > 2.30				
	N (%)	N (%)				
Maternal age	71 (49.00)	74 (51.03)				
Mean ± SD	27.72 ± 5.02	28.41 ± 5.35	1.026 (0.963–1.093)	0.424	1.039 (0.956–1.128)	0.370
Race						
Foreign	9 (40.91)	13 (59.09)	1		1	
Taiwan	62 (50.41)	61 (49.59)	0.681 (0.271–1.710)	0.414	0.754 (0.237–2.402)	0.633
Smoking (missing = 4)						
No	63 (49.22)	65 (50.78)	1		1	
Yes	6 (46.15)	7 (53.85)	1.131 (0.360–3.550)	0.833	0.770 (0.155–3.827)	0.749
Vitamin						
≤3 times/wk	46 (43.81)	59 (56.19)	1		1	
>3 times/wk	25 (62.50)	15 (37.50)	0.468 (0.222–0.988)	0.046	1.026 (0.409–2.576)	0.957
Seafood (score) (missing = 19)						
Low seafood	29 (49.15)	30 (50.85)	1		1	
High seafood	32 (47.76)	35 (52.24)	1.057 (0.525–2.130)	0.876	0.741 (0.297–1.847)	0.520
Maternal blood Hg						
Mean ± SD	1.64 ± 2.00	5.43 ± 4.28	1.808 (1.443–2.265)	<0.001	1.833 (1.450–2.316)	<0.001

AOR = adjusted odds ratio; CI = confidence interval; fHg = mercury concentration in cord blood (μg/L); Hg = mercury; mHg = mercury concentration in maternal blood (μg/L); OR = odds ratio; SD = standard deviation.

Table 5
Multivariate logistic regression analysis in terms of median levels of manganese (μg/L) in maternal and cord blood (n = 145).

Explanatory variable	Maternal blood		OR (95% CI)	p	AOR (95% CI)	p
	mMn ≤ 44.96	mMn > 44.96				
	N (%)	N (%)				
Maternal age	73 (50.34)	72 (49.66)				
Mean ± SD	27.25 ± 5.37	28.90 ± 4.89	1.066 (0.998−1.137)	0.056	1.067 (0.996−1.143)	0.067
Race						
Foreign	11 (50.00)	11 (50.00)	1		1	
Taiwan	62 (50.41)	61 (49.59)	0.984 (0.397−2.438)	0.972	0.906 (0.346−2.376)	0.841
Smoking (missing = 4)						
No	63 (49.22)	65 (50.78)	1		1	
Yes	8 (61.54)	5 (38.46)	0.606 (0.188−1.952)	0.401	0.444 (0.123−1.602)	0.215
Vitamin						
≤3 times/wk	57 (54.29)	48 (45.71)	1		1	
>3 times/wk	16 (40.00)	24 (60.00)	1.781 (0.850−3.733)	0.126	1.919 (0.878−4.193)	0.102
Seafood (score) (missing = 19)						
Low seafood	33 (55.93)	26 (44.07)	1		1.00	
High seafood	34 (50.75)	33 (49.25)	1.232 (0.610−2.487)	0.561	0.993 (0.474−2.081)	0.985
Explanatory variable	Cord blood		OR (95% CI)	p	AOR (95% CI)	p
	fMn ≤ 61.68	fMn > 61.68				
	N (%)	N (%)				
Maternal age	73 (50.34)	72 (49.66)				
Mean ± SD	27.86 ± 5.82	28.28 ± 4.49	1.016 (0.954−1.082)	0.629	1.012 (0.945−1.083)	0.742
Race						
Foreign	9 (40.91)	13 (59.09)	1		1	
Taiwan	64 (52.03)	59 (47.97)	0.638 (0.254−1.602)	0.339	0.635 (0.244−1.655)	0.353
Smoking (missing = 4)						
No	60 (48.44)	66 (51.56)	1		1	
Yes	8 (61.54)	5 (38.46)	0.587 (0.182−1.892)	0.372	0.590 (0.173−2.006)	0.398
Vitamin						
≤3 times/wk	55 (52.38)	50 (47.62)	1		1	
>3 times/wk	18 (45.00)	22 (55.00)	1.344 (0.647−2.793)	0.428	1.292 (0.592−2.819)	0.520
Seafood (score) (missing = 19)						
Low seafood	33 (55.93)	26 (44.07)	1		1	
High seafood	31 (46.27)	36 (53.73)	1.474 (0.729−2.978)	0.280	1.372 (0.653−2.884)	0.404
Maternal blood Mn						
Mean ± SD	45.89 ± 20.52	60.71 ± 59.55	1.014 (1.000−1.029	0.058	1.014 (0.999−1.029)	0.077

AOR = adjusted odds ratio; CI = confidence interval; fMn = manganese concentration in cord blood (μg/L); mMn = manganese concentration in maternal blood (μg/L); Mn = manganese; OR = odds ratio; SD = standard deviation.

levels were not associated with maternal age except for maternal Cu level. There was a borderline significant association between maternal age and maternal Cu level [adjusted odds ratio (AOR) 0.936, p = 0.057]. Maternal and fetal metal levels were not associated with race and smoking. High seafood consumption is associated with lower maternal Fe (AOR 0.404, p = 0.017) and Cu (AOR 0.434, p = 0.034). Prenatal vitamin use (>3 times/wk) was significantly associated with lower maternal Hg (AOR 0.272, p = 0.005) and lower maternal Cu (AOR 0.267, p = 0.004) levels.

4. Discussion

In this series, we found a positive correlation of Hg, Mn, Fe, and Cu in maternal and umbilical cord blood of paired mother/child samples. These data may contribute to establishing reference levels in pregnant women, and studying the role and mode of action of environmental metals in both mother and fetus. Further analysis of confounding factors showed that prenatal vitamin use decreased the maternal levels of Hg and Cu. To the best of our knowledge, this is the first report about the effect of prenatal vitamin use on maternal metals.

The Hg concentrations found in Taiwanese studies, including our investigation, are higher than those found in foreign studies.[7,10,12] The dietary habit during pregnancy may partially account for the difference between our series and foreign studies. Fish consumption during pregnancy is generally higher in Taiwan than in other countries because of the traditional idea of eating fish to provide improved nutrition for the fetus.[3] Fish consumption can be a major source of Hg during pregnancy. A Taiwanese study by Chien et al[18] showed that 21.6−24.3% and 45.6−57.4% of the daily Hg dose estimates exceeded the reference doses for typical and high seafood consumers, respectively. Their analysis suggested that

Table 6
Multivariate logistic regression analysis in terms of median levels of iron (mg/L) in maternal and cord blood (n = 145).

Explanatory variable	Maternal blood		OR (95% CI)	p	AOR (95% CI)	p
	mFe ≤ 292.3	mFe > 292.3				
	N (%)	*N* (%)				
Maternal age	73 (50.34)	72 (49.66)				
Mean ± SD	28.22 ± 5.61	27.92 ± 4.75	0.989 (0.928–1.053)	0.725	0.999 (0.934–1.070)	0.985
Race						
Foreign	8 (36.36)	14 (63.64)	1		1	
Taiwan	65 (52.85)	58 (47.15)	0.510 (0.200–1.303)	0.159	0.483 (0.183–1.280)	0.143
Smoking (missing = 4)						
No	64 (50.00)	64 (50.00)	1		1	
Yes	8 (61.54)	5 (38.46)	0.625 (0.194–2.013)	0.431	0.633 (0.186–2.157)	0.465
Vitamin						
≤3 times/wk	50 (47.62)	55 (52.38)	1		1	
>3 times/wk	23 (57.50)	17 (42.50)	0.672 (0.322–1.401)	0.289	0.821 (0.378–1.784)	0.618
Seafood (score) (missing = 19)						
Low seafood	23 (38.98)	36 (61.02)	1		1.00	
High seafood	41 (61.19)	26 (38.81)	0.405 (0.198–0.830)	0.014	0.404 (0.192–0.853)	0.017
Explanatory variable	Cord blood		OR (95% CI)	p	AOR (95%CI)	p
	fFe ≤ 414.4	fFe > 414.4				
	N (%)	*N* (%)				
Maternal age	73 (50.34)	72 (49.66)				
Mean ± SD	28.33 ± 5.80	27.81 ± 4.50	0.981 (0.920–1.045)	0.542	0.988 (0.923–1.057)	0.723
Race						
Foreign	12 (54.55)	10 (45.45)	1		1	
Taiwan	61 (49.59)	62 (50.41)	1.220 (0.491–3.032)	0.669	1.442 (0.560–3.714)	0.448
Smoking (missing = 4)						
No	63 (49.22)	65 (50.78)	1		1	
Yes	7 (53.85)	6 (46.15)	0.831 (0.265–2.608)	0.751	0.959 (0.294–3.127)	0.945
Vitamin						
≤3 times/wk	54 (51.43)	51 (48.57)	1		1	
>3 times/wk	19 (47.50)	21 (52.50)	1.170 (0.564–2.426)	0.673	1.135 (0.526–2.451)	0.747
Seafood (score) (missing = 19)						
Low seafood	29 (49.15)	30 (50.85)	1		1	
High seafood	33 (49.25)	34 (50.75)	0.996 (0.495–2.005)	0.991	1.126 (0.534–2.374)	0.756
Maternal blood Fe						
Mean ± SD	276.20 ± 101.90	314.48 ± 103.18	1.004 (1.000–1.007)	0.028	1.004 (1.001–1.007)	0.022

AOR = adjusted odds ratio; CI = confidence interval; Fe = iron; fFe = iron concentration in cord blood (mg/L); mFe = iron concentration in maternal blood (mg/L); OR = odds ratio; SD = standard deviation.

the acceptable ingestion rate of fish for women during childbearing is 90.8 ± 15.7 g/d. Although there was no significant association of Hg level and birth outcome in this series, Hg has been reported to be associated with developmental delay in children whose mothers were exposed to it during pregnancy.[19,20] Pregnant woman should be educated about the risk of high Hg level associated with overingestion of specific types and quantities of fish to help protect their children's health.

There was a positive correlation between umbilical cord blood levels and maternal concentrations in terms of Fe, Cu, and Mn. High seafood consumption was associated with lower maternal Fe and Cu levels in multiple logistic regression. This relationship requires detailed ingredients of seafood to elucidate the mechanism. However, the distribution of three essential minerals between maternal and umbilical cord blood was different. Median fetal Mn level (61.68 μg/L) was 40% higher than maternal Mn level (44.96 μg/L), whereas median fetal Fe level (449.40 μg/L) was 60% higher than maternal Fe level (288.20 μg/L). In the study by Kopp et al,[10] median fetal Fe level (635.8 mg/L) was 20% higher than maternal Fe level (530.5 mg/L), but median fetal Mn level (28.8 μg/L) was 70% higher than maternal Mn level (17.0 μg/L). Median maternal Fe level was much lower, and median maternal Mn level was far higher in this series than in Kopp et al.'s[10] study. Women with low Fe stores absorbed about 5% of dietary Mn, but women with normal Fe stores absorbed only about 1% of dietary Mn.[21] The effect of Fe deficiency on Mn absorption is apparently due to the ability of the divalent metal transporter 1.[22] Therefore, Fe deficiency, particularly among women of reproductive age, is a potential risk factor for Mn toxicity when intestinal Mn exposure is high. The low Fe status may partially account for the higher maternal Mn level in this series than in other studies in America and Europe (Table 3). Overall, the interaction of Fe and Mn in fetus is somewhat complicated. The fetus requires increased amounts

Table 7
Multivariate logistic regression analysis in terms of median levels of copper (mg/L) in maternal and cord blood ($n = 145$).

Explanatory variable	Maternal blood		OR (95% CI)	*p*	AOR (95% CI)	*p*
	mCu ≤ 1.47	mCu > 1.47				
	N (%)	*N* (%)				
Maternal age	73 (50.34)	72 (49.66)				
Mean ± SD	28.15 ± 5.69	27.99 ± 4.65	0.994 (0.933–1.059)	0.848	1.029 (0.958–1.106)	0.436
Race						
Foreign	10 (45.45)	12 (54.55)	1		1	
Taiwan	63 (51.22)	60 (48.78)	0.794 (0.319–1.973)	0.619	0.974 (0.366–2.592)	0.959
Smoking (missing = 4)						
No	61 (47.65)	67 (52.34)	1		1	
Yes	9 (69.20)	4 (30.80)	0.405 (0.119–1.382)	0.149	0.375 (0.101–1.399)	0.144
Vitamin						
≤3 times/wk	44 (41.90)	61 (58.10)	1		1	
>3 times/wk	29 (72.50)	11 (27.50)	0.274 (0.124–0.606)	0.001	0.268 (0.116–0.619)	0.002
Seafood (score) (missing = 19)						
Low seafood	22 (37.29)	37 (62.71)	1		1.00	
High seafood	39 (58.21)	28 (41.79)	0.427 (0.208–0.874)	0.020	0.434 (0.201–0.939)	0.034
Explanatory variable	**Cord blood**		**OR (95% CI)**	***p***	**AOR (95% CI)**	***p***
	fCu ≤ 0.73	fCu > 0.73				
	N (%)	*N* (%)				
Maternal age	73 (50.34)	72 (49.66)				
Mean ± SD	28.15 ± 5.18	27.99 ± 5.22	0.994 (0.933–1.059)	0.848	1.027 (0.956–1.103)	0.462
Race						
Foreign	9 (40.91)	13 (59.09)	1		1	
Taiwan	64 (52.03)	59 (47.97)	0.638 (0.254–1.602)	0.339	0.770 (0.285–2.084)	0.607
Smoking (missing = 4)						
No	62 (48.44)	66(51.56)	1		1	
Yes	8 (61.54)	5 (38.46)	0.587 (0.182–1.891)	0.372	0.591 (0.167–2.094)	0.415
Vitamin						
≤3 times/wk	44 (41.90)	61 (58.10)	1		1	
>3 times/wk	29 (72.50)	11 (27.50)	0.274 (0.124–0.606)	0.001	0.370 (0.158–0.865)	0.022
Seafood (score) (missing = 19)						
Low seafood	24 (40.68)	35 (59.32)	1		1	
High seafood	40 (59.70)	27 (40.30)	0.463 (0.227–0.944)	0.034	0.508 (0.235–1.101)	0.086
Maternal blood Cu						
Mean ± SD	1.44 ± 0.26	1.61 ± 0.40	4.755 (1.639–13.798)	0.004	2.946 (0.967–8.974)	0.057

AOR = adjusted odds ratio; CI = confidence interval; Cu = copper; fCu = copper concentration in cord blood (mg/L); mCu = copper concentration in maternal blood (mg/L); OR = odds ratio; SD = standard deviation.

of Fe for high oxygen and energy consumption. However, Fe is also capable of generating harmful reactive oxygen species via Fenton chemistry.[23] Mn superoxide dismutase is a mitochondrial enzyme, which can selectively decrease oxidative damage without affecting Fe-mediated oxygen transport and energy production.[24] In addition, Chen et al[25] observed a dramatic decrease of reactive oxygen species as a consequence of upregulation of Mn-dependent superoxide dismutase and catalase during osteogenic differentiation of human mesenchymal stem cells. The biological roles of fetal Fe and Mn can be further elucidated by the abovementioned mechanism. The simultaneous increase of fetal Mn and Fe levels observed in this series is beneficial rather than detrimental. Further studies are required to study the potentially high Mn exposure and its relationship with Fe absorption in Taiwan.

In contrast, median Cu level (0.73 mg/L) in our study was approximately 50% lower than that in maternal blood (1.47 mg/L). Our result is consistent with several previously published studies,[8,10,26] which showed a 50–60% decrease in Cu level in the fetus. The observed decrease in fetal Cu, a major metallic cofactor in a variety of oxidoreductases, may reduce the potential of cellular oxidative damage in the developing fetus.[27] However, Cu is an essential mineral, and its deficiency can result in many nutritional and vascular disorders.[28] Maintaining an adequate amount of Cu in the human body is important, especially for the newborns who are dependent on stored Cu.

Prenatal vitamin use significantly decreased the maternal levels of Hg and Cu in this series. From animal studies, some data on the effect of vitamin E on heavy metals are available.[29–31] Al-attar's[29] study suggested that the administration of vitamin E protects against heavy metal-induced renal and testicular oxidative stress and injuries in male mice. Another Al-attar's[30] study showed that vitamin E protects against the heavy metal-induced liver injury in albino mice, and the attenuating effect of vitamin E may be due to its antioxidant activity. Abd El-Aziz et al[31] reported that vitamin E may ameliorate some aspects of methyl Hg developmental toxicity in rat fetuses. Kim et al[32] also found a negative association between serum folate and blood Hg concentrations in pregnant Korean women. Their findings suggest that folate is associated with the blood Hg level by participating in the Hg detoxification process.[32] It is still unclear by which mechanism prenatal vitamin use can reduce maternal levels of Hg and Cu. The effect of vitamin use on heavy metals in pregnant woman still requires further investigation.

Several limitations in this study need to be specified. This study was a single-center investigation of pregnant woman with a modest sample size. In addition, this is a cross-sectional study without level change of Hg and essential minerals during the entire pregnancy. Therefore, it was a limitation of the representative in terms of metal levels based on the collection time by delivery. Additionally, the data regarding potential exposure sources for heavy metals and essential minerals were not complete. The collection of maternal vitamin use is not detailed in the ingredients. In addition, assessment of seafood consumption was not precise, and Fe deficiency of the participants was not evaluated. Therefore, multicenter studies with a large sample size and precise assessment of seafood consumption are suggested for future investigations.

In conclusion, there was a positive correlation of Hg, Fe, Cu, and Mn in maternal and umbilical cord blood of paired mother/child samples in this series. However, the distribution of Hg and three essential minerals between maternal and umbilical cord blood was different. Median Hg, Mn, and Fe levels were higher in cord blood than in maternal blood, while median Cu level was lower in cord blood than in maternal blood. The low Fe status in pregnant women may partially account for the higher maternal Mn level. Our findings raise the possibility of reducing maternal Hg and Cu levels via prenatal vitamin supplementation, although the effect of vitamin use on heavy metals during pregnancy requires further study.

Acknowledgments

Part of this research was supported by the Kaohsiung Veterans General Hospital (VGHKS103-81, VGHKS103-82, VGHUST104-G7-7-3, VGHKS105-106, and VGHUST105-G3-1-3) and Kaohsiung Medical University (MOST104-2314-B-037-012-MY2, and MOST105-2632-B-037-002). We thank Huei-Han Liou in Kaohsiung Veterans General Hospital for the statistical analysis.

References

1. Lin YC, Chang-Chien GP, Chiang PC, Chen WH, Lin YC. Multivariate analysis of heavy metal contaminations in seawater and sediments from a heavily industrialized harbor in Southern Taiwan. *Mar Pollut Bull* 2013;**76**:266–75.
2. Al-Saleha I, Shinwari N, Mashhour A, Mohamed Gel D, Rabah A. Heavy metals (lead, cadmium and mercury) in maternal, cord blood and placenta of healthy women. *Int J Hyg Environ Health* 2011;**214**:79–101.
3. Hsu CS, Liu PL, Chien LC, Chou SY, Han BC. Mercury concentration and fish consumption in Taiwanese pregnant women. *BJOG* 2007;**114**:81–5.
4. Wright RO, Baccarelli A. Metals and neurotoxicology. *J Nutr* 2007;**137**:2809–13.
5. Ballatori N. Transport of toxic metals by molecular mimicry. *Environ Health Perspect* 2002;**110**(Suppl 5):689–94.
6. Ikonomidou C, Kaindl AM. Neuronal death and oxidative stress in the developing brain. *Antioxid Redox Signal* 2011;**14**:1535–50.
7. Butler Walker J, Houseman J, Seddon L, McMullen E, Tofflemire K, Millis C, et al. Maternal and umbilical cord blood levels of mercury, lead, cadmium, and essential trace elements in Arctic Canada. *Environ Res* 2006;**100**:295–318.
8. Rudge CV, Rollin HB, Nogueira CM, Thomassen Y, Rudge MC, Odland JØ. The placenta as a barrier for toxic and essential elements in paired maternal and cord blood samples of South African delivering women. *J Environ Monit* 2009;**11**:1322–30.
9. Lin CM, Wang D, Hwang YH, Chen PC. The role of essential metals in the placental transfer of lead from mother to child. *Reprod Toxicol* 2010;**29**:443–6.
10. Kopp RS, Kumbartski M, Harth V, Bruning T, Kafferlein HU. Partition of metals in the maternal/fetal unit and lead-associated decreases of fetal iron and manganese: an observational biomonitoring approach. *Arch Toxicol* 2012;**86**:1571–81.
11. Su CK, Sun YC, Tzeng SF, Yang CS, Wang CY, Yang MH. *In vivo* monitoring of the transfer kinetics of trace elements in animal brains with hyphenated inductively coupled plasma mass spectrometry techniques. *Mass Spectrom Rev* 2010;**29**:392–424.
12. Gundacker C, Frohlich S, Graf-Rohrmeister K, Eibenberger B, Jessenig V, Gicic D, et al. Perinatal lead and mercury exposure in Austria. *Sci Total Environ* 2010;**408**:5744–9.
13. Zota AR, Ettinger AS, Bouchard M, Amarasiriwardena CJ, Schwartz J, Hu H, et al. Maternal blood manganese levels and infant birth weight. *Epidemiology* 2009;**20**:367–73.
14. Wang P, Tian Y, Shi R, Zou XY, Gao Y, Wang MM, et al. Study on maternal-fetal status of Pb, As, Cd, Mn and Zn elements and the influence factors. *Zhonghua Yu Fang Yi Xue Za Zhi* 2008;**42**:722–6.
15. Vigeh M, Yokoyama K, Ramezanzadeh F, Dahaghin M, Fakhriazad E, Seyedaghamiri Z, et al. Blood manganese concentrations and intrauterine growth restriction. *Reprod Toxicol* 2008;**25**:219–23.
16. Takser L, Mergler D, de Grosbois S, Smargiassi A, Lafond J. Blood manganese content at birth and cord serum prolactin levels. *Neurotoxicol Teratol* 2004;**26**:811–5.
17. Takser L, Mergler D, Hellier G, Sahuquillo J, Huel G. Manganese, monoamine metabolite levels at birth, and child psychomotor development. *Neurotoxicology* 2003;**24**:667–74.
18. Chien LC, Yeh CY, Jiang CB, Hsu CS, Han BC. Estimation of acceptable mercury intake from fish in Taiwan. *Chemosphere* 2007;**67**:29–35.
19. Bakir F, Damluji SF, Amin-Zaki L, Murtadha M, Khalidi A, Al-Rawi NY, et al. Methylmercury poisoning in Iraq. *Science* 1973;**181**:230–41.
20. Dolbec J, Mergler D, Sousa Passos CJ, Sousa de Morais S, Lebel J. Methylmercury exposure affects motor performance of a riverine population of the Tapajos river, Brazilian Amazon. *Int Arch Occup Environ Health* 2000;**73**:195–203.
21. Finley JW. Manganese absorption and retention by young women is associated with serum ferritin concentration. *Am J Clin Nutr* 1990;**70**:37–43.
22. Fitsanakis VA, Zhang N, Garcia S, Aschner M. Manganese (Mn) and iron (Fe): interdependency of transport and regulation. *Neurotox Res* 2010;**18**:124–31.
23. Wardman P, Candeias LP. Fenton chemistry: an introduction. *Radiat Res* 1996;**145**:523–31.
24. Miao L, St Clair DK. Regulation of superoxide dismutase genes: implications in disease. *Free Radic Biol Med* 2009;**47**:344–56.
25. Chen CT, Shih YR, Kuo TK, Lee OK, Wei YH. Coordinated changes of mitochondrial biogenesis and antioxidant enzymes during osteogenic differentiation of human mesenchymal stem cells. *Stem Cells* 2008;**26**:960–8.
26. Ong CN, Chia SE, Foo SC, Ong HY, Tsakok M, Liouw P. Concentrations of heavy metals in maternal and umbilical cord blood. *Biometals* 1993;**6**:61–6.
27. Agency for Toxic Substances and Disease Registry. *Toxicological profile for copper*. US Department of Health and Human Services A, GA: ATSDR; 2004.

28. Saari JT. Copper deficiency and cardiovascular disease: role of peroxidation, glycation, and nitration. *Can J Physiol Pharmacol* 2000;**78**:848−55.
29. Al-Attar AM. Antioxidant effect of vitamin E treatment on some heavy metals-induced renal and testicular injuries in male mice. *Saudi J Biol Sci* 2011;**18**:63−72.
30. Al-Attar AM. Vitamin E attenuates liver injury induced by exposure to lead, mercury, cadmium and copper in albino mice. *Saudi J Biol Sci* 2011;**18**:395−401.
31. Abd El-Aziz GS, El-Fark MM, Saleh HA. The prenatal toxic effect of methylmercury on the development of the appendicular skeleton of rat fetuses and the protective role of vitamin E. *Anat Rec (Hoboken)* 2012;**295**:939−49.
32. Kim H, Kim KN, Hwang JY, Ha EH, Park H, Ha M, et al. Relation between serum folate status and blood mercury concentrations in pregnant women. *Nutrition* 2013;**29**:514−8.