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Mercury levels in maternal and cord blood and attained weight through the 24 months of life

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ABSTRACT

Birth weight is a strong determinant of attained weight at early ages. Until now, many studies have reported that low birth weight corresponds with high mercury levels. However, the relationship between mercury exposure and attained weight of infant has not been well studied. Therefore, the aim of the present study was to assess the degree of prenatal exposure to mercury by measuring the total mercury levels in maternal and cord blood, and examine the relationship between the mercury level during pregnancy and the attained weight of infant during the first 24 months of life. The prospective cohort study of Mothers and Children's Environmental Health (MOCEH) was built up in 2006, and 921 mother–infant pairs were recruited. Information on the socio-demographic characteristics, health behavior and environmental exposure were collected from an interview with trained nurses. After delivery, infants and mothers were followed up at 6, 12 and 24 months and the weights of the infants were measured. The mercury concentrations in the late maternal blood ($\beta = -0.19$, $p = 0.05$) and cord blood ($\beta = -0.36$, $p = 0.01$) were negatively associated with the infants' attained weight over the first 24 months of age. The infants' attained weight in the small for their gestational age (SGA) group was lower than the normal birth weight group at the highest quartile of the mercury level. Therefore, efforts should be made to reduce the mercury level in the maternal blood at late pregnancy and cord blood. Further research on the possible harmful effects of prenatal mercury exposure on postnatal growth is recommended.

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1. Introduction

Mercury (Hg) naturally exists in the body as inorganic mercury (mostly Hg²⁺), metallic mercury (elemental, Hg⁰), and organic mercury (mostly methylmercury; MeHg). Common inorganic sources include air and water pollution, some skin creams, and herbal medicines. Metallic mercury typically comes from dental amalgam and industrial exposure. Other possible metallic mercury sources included fluorescent light bulbs (Adsit et al., 2002), cathode ray tubes, such as those used for computer screens, and industrial switches and relays (U.S. EPA, 2002). Moreover, Hg emissions have been increasing each year due to rapid

industrialization. The increasing Hg emissions in China might affect nearby areas by yellow dust transport (Xinmin et al., 2006).

Fish consumption is a main source of exposure to organic Hg (Clarkson and Magos, 2006) and a major contributor of MeHg. Because of the frequent fish consumption in Korea, there are concerns about the effects of mercury on birth outcome. Several studies have shown a correlation between blood mercury levels and MeHg exposure through fish consumption (Grandjean et al., 1992; Svensson et al., 1992; Oskarsson et al., 1996).

Hg exposure has been associated with delayed neurodevelopment (Heintze et al., 1983; Bjornberg et al., 2003; Leistevuo et al., 2001) and low birth weight (Ericson and Ka'le'n, 1989; Seidler et al., 1999; Sikorski et al., 1986). Moreover, the fetus is very susceptible to mercury exposure during organogenesis, because mercury can pass through the blood–brain-barrier and the placenta. Several

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reports claim that fetal contact with mercury can result in irreversible damage after birth ranging from defective cerebral nerve development to retarded growth while causing no visible symptoms in the mother (Weil et al., 2005; Schober et al., 2003; Jedrychowski et al., 2006; Lederman et al., 2008; Bjerregaard and Hansen, 2000).

Recently, there has been considerable research on the effects of Hg exposure on fetuses and infant weight (Grandjean et al., 2003; Ramón et al., 2009). Several studies examining Hg exposure in relation to birth weight have produced mixed results. Some studies have reported an inverse association between the birth weight and the MeHg concentration in blood (Foldspang and Hansen, 1990) and total Hg levels in hair (Sikorski et al., 1986; Xue et al., 2007) of the maternal and newborn, whereas others did not find any influence on birth weight (Grandjean et al., 2001; Lederman et al., 2008; Lucas et al., 2004; Marques et al., 2008). A recent article on the effects of the World Trade Center disaster on pregnant women, with median cord blood concentrations of total mercury of 4.3 µg/L found no significant association with birth size (Lederman et al., 2008).

Moreover, the relationship between mercury exposure and the birth outcome and postnatal growth has not been well studied. In a birth cohort study doubling of the Hg concentration in cord blood was associated with a decrease in weight at 0.19 kg at 18 months (95% confidence interval (CI) = 0.03, 0.35 kg) (Grandjean et al., 2003). Because of these issues, the mercury poisoning of pregnant women has become a subject of interest.

Also, in general, the cohort studies are normally designed to analyze the longitudinal development of a certain characteristic over time. The observations of one individual over time are not independent of each other. Therefore, the application of suitable statistical techniques is necessary.

Therefore, the aim of the present study is to assess the degree of prenatal exposure to mercury by measuring the total Hg levels in maternal and cord blood of a prospective mother–infant cohort in Korea, and examine the relationship between the Hg level during pregnancy and the attained weight of infant during the first 24 months of life using a linear mixed model that considers the repeated measured data.

2. Materials and methods

2.1. Study population

The MOCEH study was a prospective hospital- and community-based cohort study designed to examine the effects of pre- and postnatal environmental exposures on growth, development and health from early fetal life to young adulthood (Kim et al., 2009).

The MOCEH study has been carried out since 2006 to determine the effects of maternal environmental exposure on fetal and postnatal growth or development. All pregnant women living in the targeted study site (i.e., Seoul, Cheonan, and Ulsan), who are in the first trimester of pregnancy at the time of screening, were eligible. The study protocol was approved by the institutional review boards at Ewha Womans University (Seoul), Dankook University Hospital (Cheonan), and Ulsan University Hospital (Ulsan, South Korea). At the initial prenatal visit, written informed consent was obtained from each woman.

From 2006 to 2010, 921 women were eligible. Of these, 124 women were excluded: 58 with multiple births, one with a stillbirth, 22 with preterm births, one with congenital anomaly, six with pre-eclampsia or gestational diabetes mellitus and 36 with missing values in the major confounders. The study subjects were restricted to those for whom the maternal and cord blood Hg levels were assessed. Finally, 797 pregnant women were included for acquisition of the initial data. The infant cohort included infants with data at 6 ($n = 495$), 12 ($n = 314$) or 24 ($n = 164$) months after birth as the subjects of the

analyses. Babies were born after 2008, and so who had not reach 24 months of age by the end of study, were excluded.

2.2. Data collection

Data collection consisted of an interviewed questionnaire, nutritional survey, and biological samples (blood and urine). Information on the socio-demographic characteristics, prior medical history, maternal stress index, health behavior, history of amalgam treatment, and environmental exposure was collected from an interview conducted by trained nurses. The body mass index (BMI) was calculated as the body weight divided by the height squared according to the WHO standards. The pregnant women were then classified into three groups: underweight ($BMI < 18.5 \text{ kg/m}^2$), normal weight ($BMI 18.5\text{--}22.9 \text{ kg/m}^2$), and overweight ($BMI > 23.0 \text{ kg/m}^2$) (WHO, 2000). The gestational age was estimated based on the onset of the last menstrual period. The first ultrasonographic estimation of the gestational age was used if the last menstrual period was unreliable or if there was significant discordance in dating between the ultrasonographic and last menstrual period (> 10 days). Trained nurses in the delivery room routinely measured the birth weight using a digital scale at birth and recorded it on the patient's medical charts. A well-trained dietary interviewer used semiquantitative FFQ (food frequency questionnaire) to record participants' usual dietary intake over a 1-year period prior to the interview. The FFQ method has been previously validated (Oh et al., 2007). The food and dietary intake, including the amount of fish consumption, was assessed using a computerized nutrient-intake assessment software program (CAN-Pro 3.0; Korean Nutrition Society, Seoul, Korea).

Information on the birth outcome, such as birth weight, gestational age, parity and infant's gender, was collected from the medical records at delivery. Newborns with a birth weight and length below the 10th percentile according to Korean population reference growth charts for gender and gestational age were classified as being small for their gestational age (SGA) for weight or length (The Korean pediatric society, 2007). The infants' weights, heights and head circumference at 6, 12, and 24 months of age were measured as variables to evaluate growth. The weights at six and twelve months of age were taken by laying the infant on the center of the scale to a decimal place (0.1 kg). At 24 months of age, the infants stood on the scale with both feet on the center of the scale and the weights were taken.

Information regarding the variables that can affect the infants' growth after birth (Colostrum feeding, employment state of the mother, nutritional supplements) was collected by a survey during the hospital visits. All variables were dichotomous – the answer choices were either yes or no. In addition, the survey encompassed variables, such as the mother's level of education, family income, exposure to passive smoking at home (none, inside the house, outside the house), the parents' physical condition, and family history of diseases.

2.3. Hg analysis

The maternal blood samples were obtained during early pregnancy (12–20 gestational weeks) and late pregnancy (28–42 gestational weeks). The cord blood samples were collected at birth. The blood samples were stored at -70°C until analysis. Hg analysis was performed by flow injection cold-vapor atomic absorption spectrometry (AAS) (DMA-80; Milestone, Bergamo, Italy). The sample was initially dried in an oxygen stream passed through a quartz tube located inside a controlled heating coil. The combustion gasses were decomposed further on a catalytic column at 750°C . The Hg vapor was collected on a gold amalgamation trap and then desorbed for quantification. The Hg content was determined by AAS. The laboratory analyses were carried out using standardized quality-control procedures. An internal control was used for each series of analyses. The precision

and accuracy of the Hg level measurement were verified by periodically participating in an external quality control program (interlaboratory calibration exercises). The limit of detection (LOD) was 0.158 µg/L and no sample had an Hg level below the LOD. The coefficient of variation of the overall mercury levels between the subjects and each individual was 3.0% and 2.5% respectively.

2.4. Statistical analysis

Descriptive analyses were used to examine the characteristics of the study subjects at birth, 6 months, 12 months and 24 months. After descriptive analyses, the Hg concentrations were the natural log-transformed logarithmically because of their skewed distribution. The geometric means (GMs) and percentiles of the Hg concentrations were calculated. The Spearman correlation coefficient test was used to identify the relationship between the mercury levels in the maternal and cord blood. The relationship between the Hg concentration and risk factors was examined using a Wilcoxon rank-sum test or Kruskal–Wallis rank sum test. Because the parts of participants have missing data for some variable, these observations were excluded from multivariate analyses.

A linear mixed regression model was used to assess the effect of prenatal Hg exposure on weight of infants between birth and 2 years. This approach can consider the dependence of the within-subject repeated measurements taken at irregular time intervals

(Brown and Prescott, 2006; Singer, 1998). Also, the best option for analysis is the general linear mixed model, which can be used even with longitudinal data series.

Firstly, univariate analysis was performed to assess the association between Hg concentration, maternal and infant factors, and infant weight. The variable was considered to be a potential confounder if the variables were related to the infants' weight and Hg level at $p < 0.20$ according to univariate analysis.

Secondly, multivariate analysis was performed to examine the effects of prenatal Hg exposure on growth when controlling for confounding factors. The maternal and infant factors included the following: infant's gender, maternal age (<30, ≥30 years), pre-pregnancy body mass index (BMI; <18.5, 18.5 to <23, ≥23 kg/m²), maternal educational level (<12, ≥12 years), parity (0, 1, ≥2), family income (<200, 200–300, ≥300, 10,000 won/month), mother's state of employment (full-time job with work hours of 8 h per day during pregnancy, unemployment) during pregnancy, Colostrum feeding (yes, no), and continuous variables for the mothers' weight prior to pregnancy (kilograms), and gestational age (weeks). In addition, information on amalgam fillings was collected but there was no correlation between the presence of amalgam fillings and the Hg levels. Therefore, amalgam fillings were not included in the further analysis.

Thirdly, after including the confounding variable in the model, its covariance structure was tested by likelihood ratio test. Because the

Table 1
Characteristics of study population^a.

Characteristic	N (%), mean ± SD			
	Baseline data, at birth (N = 797)	At 6 month (n = 495)	At 12 month (n = 314)	At 24 month (n = 164)
<i>Mother</i>				
Age (years)				
<30 years	355 (44.5)	220 (44.4)	149 (47.5)	82 (50.0)
≥30 years	442 (55.5)	275 (55.6)	165 (52.5)	82 (50.0)
Job				
No	450 (63.3)	305 (67.3)	199 (69.1)	104 (66.7)
Yes	261 (36.7)	148 (32.7)	89 (30.9)	52 (33.3)
Weight at prepregnancy (kg)	59.5 ± 9.1	59.7 ± 9.1	59.5 ± 8.8	60.0 ± 9.6
Height at prepregnancy (cm)	161.1 ± 4.8	161.2 ± 4.7	161.2 ± 4.7	160.9 ± 4.5
BMI at prepregnancy (kg/m ²)				
<18.5	32 (4.4)	20 (4.3)	11 (3.7)	8 (5.1)
18.5 to 23.0	377 (52.0)	244 (52.8)	163 (55.3)	80 (51.0)
≥23.0	316 (43.6)	198 (42.9)	121 (41.0)	69 (44.0)
Education status				
<12 years	240 (30.1)	145 (29.2)	98 (21.2)	53 (32.3)
≥12 years	557 (69.9)	350 (70.7)	216 (68.8)	111 (67.7)
Family's income (10,000 won/month)				
<200	101 (12.9)	46 (9.3)	28 (8.9)	15 (9.2)
200 to 300	554 (69.5)	366 (73.9)	242 (77.1)	125 (76.2)
≥300	142 (17.8)	83 (16.8)	44 (14.0)	24 (14.6)
Tobacco smoking during pregnancy				
No	792 (99.4)	490 (99.0)	311 (99.0)	163 (99.4)
Yes	5 (0.6)	4 (1.0)	3 (1.0)	1 (0.6)
Amalgam restoration during pregnancy				
No	436 (65.3)	272 (64.3)	186 (65.7)	101 (67.3)
Yes	232 (34.7)	151 (35.7)	97 (34.3)	49 (32.4)
<i>Infants</i>				
Gender				
Male	412 (51.7)	264 (53.3)	164 (52.2)	87 (53.1)
Female	385 (48.3)	231 (46.7)	150 (47.8)	77 (46.9)
Parity				
0	290 (54.3)	248 (53.7)	151 (51.0)	78 (49.4)
1	194 (38.4)	179 (38.7)	118 (39.9)	68 (42.0)
≥2	46 (7.3)	35 (7.6)	27 (9.1)	12 (7.6)
GA (weeks) ^b	39.5 ± 1.1	39.5 ± 1.0	39.5 ± 1.0	39.4 ± 1.0
Weight	3.3 ± 0.4	8.5 ± 1.0	10.2 ± 1.1	12.5 ± 1.4
LBW ^b	6 (0.8)	2 (0.4)	2 (0.7)	1 (0.6)
SGA ^b	63 (8.2)	40 (8.4)	24 (8.4)	13 (8.4)
Colostrum feeding (yes vs no)	–	391 (92.4)	248 (93.6)	–

^a Numbers of subgroups varies slightly because of missing value for each variable.

^b GA: gestational age. LBW: low birth weight. SGA: small for gestational age.

repeated observations within one subject are not independent of each other, a correction must be made for these within-subject correlations (Twisk, 2003). The choice for the working correlation structure in a final model is an exchangeable covariance structure (compound symmetry). In this the correlations between subsequent measurements are assumed to be the same, irrespective of the length of the time interval. Selection of the appropriate variance–covariance structure was performed based on the Akaike's Information Criteria to obtain the best fit. All potential confounding factors were treated as fixed variables. Sensitivity analysis was also performed to estimate the effect of Hg exposure on the infants' weight, considering the birth size of infants (SGA vs normal group). All statistical analyses were carried out using SAS statistical software (version 8.2; SAS Institute Inc., Cary, NC, USA) based on two-tailed tests; $p \leq 0.05$ indicated statistical significance.

3. Results

The general characteristics of the pregnant women and infants are shown in Table 1. The pregnant women were older than 30 years and had completed >12 years of education. The women were unlikely to have smoked cigarettes before becoming pregnant. Approximately 30% of the pregnant women had amalgam restorations during pregnancy. The proportions of male and female infants were similar. The mean of birth weight was 3.3 kg, and the gestational age was 39.5 weeks. The incidence of a low birth weight and small for gestational age (SGA) were 0.08% and 8.2%, respectively. The general characteristics remained consistent during monitoring at 6, 12, and 24 months after delivery. The average weights of the infants at 6, 12, and 24 months of age were 8.6 kg, 10.2 kg and 12.6 kg, respectively.

Table 2 shows the distribution of the Hg concentrations during pregnancy. The GM of the maternal blood Hg concentration was 3.4 $\mu\text{g/L}$ during early pregnancy and 3.1 $\mu\text{g/L}$ during late pregnancy. The Hg concentrations were higher in the cord blood than the maternal blood. 39.1% of cord blood had concentrations greater than >5.8 $\mu\text{g/L}$ the current reference dose used by the US EPA (Mahaffey, 2005). The Hg levels in the cord blood correlated with those in the maternal blood during late pregnancy (Spearman Pearson $r = 0.72$, $p < 0.0001$).

Table 3 lists the distribution of the maternal and cord blood Hg concentration ($\mu\text{g/L}$) according to the maternal and infants characteristics. The maternal and cord blood mercury level increased significantly with increasing BMI at pre-pregnancy. Women who worked during pregnancy had significantly higher mercury levels in the maternal blood at late pregnancy and the cord blood than women who did not ($p = 0.01$). The maternal and cord blood mercury level was increased significantly by the total fish consumption. A larger number

Table 2

Geometric means and percentiles of total mercury concentration in maternal and cord blood.

	Maternal blood		Cord blood
	Early pregnancy ^a	Late pregnancy ^a	
Geometric mean	3.4	3.1	5.2
Geometric standard deviation	1.6	1.7	1.6
<i>Percentile</i>			
10th	1.8	1.7	3.0
25th	2.5	2.2	3.9
50th	3.5	3.1	5.2
75th	4.7	4.1	7.0
90th	7.3	5.7	9.0
>5.8 $\mu\text{g/L}$ *, N (%)	105 (13.2)	76 (9.5)	312 (39.1)

^a Early pregnancy (12–20 gestational weeks), late pregnancy (28–42 gestational weeks).

of parity had a lower mercury level but this was not statistically significant.

Table 4 shows the relationship between the mercury level and attained weight from birth to 24 months of age using a linear mixed model. We found an inverse relationship between infants' attained weight and maternal and cord blood Hg levels. After adjusting for potential confounding factors, infants' attained weight from birth to 24 months of age were decreased 0.19% when mercury exposure was doubled in maternal blood at pregnancy, and decreased 0.36% in cord blood. However, we found no significant inverse relationship between Hg level and infants' attained weight from birth to 12 months of age.

Fig. 1 presents the results from the use of mixed models testing the effects of the 75th percentiles of mercury exposure on the SGA and normal weight group. Regarding the effect of the Hg concentration in maternal blood at late pregnancy and cord blood, the infants' attained weight from birth to 24 months in the SGA group was lower compared to the normal weight group at the 75th percentile of the mercury level adjusted for potential confounders, such as infant's gender, maternal age, pre-pregnancy body mass index, maternal educational level, parity, family income, mother's state of employment during pregnancy, Colostrum feeding, the mother's weight prior to pregnancy and gestational age. But this association was only marginally significant and there was no linear relation when we used maternal blood Hg levels at early pregnancy ($p = 0.06$).

4. Discussion

These results give some strong support for the hypothesis of a negative effect of intrauterine exposure to mercury on the children's growth up to 12 months and 24 months of age, respectively. These results showed that the weight of the infants decreased significantly with increasing mercury level in the cord blood and maternal blood at late pregnancy according to the mixed linear regression model. The total mercury level in the cord blood can serve as an important indicator for examining the effect of mercury exposure on the fetus. Also, perhaps also the maternal blood mercury concentration close to the time of parturition might be useful as a risk indicator.

The average total mercury level in the cord blood was lower than that of Japan (9.8 $\mu\text{g/L}$), Faroe Islands (20.4 $\mu\text{g/L}$), or Spain (9.9 $\mu\text{g/L}$), but was considerably higher than that of Canada, Hawaii, and Sweden (Ramón et al., 2009; Sato et al., 2006; Bjornberg et al., 2003; Butler et al., 2006; Sakamoto et al., 2007). Thirty nine percent of the total subject population exceeded the permitted levels set by the Environment Protection Agency (EPA), thereby exhibiting a higher distribution rate than in Canada (25%) or Hawaii (28.3%) (Butler et al., 2006; Sato et al., 2006). Moreover, the total mercury levels in the cord blood were significantly higher than in the maternal blood, which is in agreement with the findings in Spain, Poland, Greenland and Japan, where it was also reported that the mercury concentration was higher in the cord blood than maternal blood (Ramón et al., 2008; Jedrychowski et al., 2006; Sakamoto et al., 2007). This phenomenon can be explained by the accumulation of mercury in the body due to its prolonged half-life: mercury remains bound to hemoglobin and glutathione in the red blood cells while they are pumped to different parts of the body. Naturally, fetuses have higher hemoglobin levels than their mothers and are more liable to mercury accumulation (Sakamoto et al., 2007; Vahter et al., 2000).

We found that increasing BMI at prepregnancy was associated with increased maternal blood Hg concentrations, but was not associated with cord blood Hg concentrations. The concentration of total Hg in cord blood was not significantly increased with level of BMI at prepregnancy in both the INMA cohort study and case–control study of Taiwan (Ramón et al., 2008; Hsu et al., 2007). It is possible that the association between blood Hg concentrations and weight may at least be partly explained by differences in fat distribution.

Table 3
Distribution of maternal and cord blood mercury concentration by mothers' and infants' characteristics.

Characteristic	Maternal blood				Cord blood	
	Early pregnancy ^a		Late pregnancy ^a		GM (GSD) ^b	p ^c
	GM (GSD) ^b	p ^c	GM (GSD) ^b	p ^c		
<i>Mother</i>						
<i>Age (years)</i>						
<30 (n = 355)	3.5 (1.6)	0.68	3.1 (1.6)	0.84	5.2 (1.6)	1.00
≥30 (n = 442)	3.4 (1.7)		3.1 (1.7)		5.2 (1.6)	
<i>Job</i>						
No (n = 450)	3.4 (1.7)	0.41	3.0 (1.7)	0.01 ^d	5.1 (1.6)	0.01 ^d
Yes (n = 261)	3.5 (1.6)		3.3 (1.6)		5.4 (1.6)	
<i>Weight at prepregnancy (kg)</i>						
<58 (<50th) (n = 343)	3.4 (1.6)	0.25	2.9 (1.7)	0.05 ^d	5.0 (1.6)	0.03 ^d
≥58 (≥50th) (n = 401)	3.5 (1.6)		3.2 (1.6)		5.4 (1.6)	
<i>Height at prepregnancy (cm)</i>						
<161 (<50th) (n = 261)	3.5 (1.7)	0.45	3.0 (1.8)	0.36	5.1 (1.6)	0.49
≥161 (≥50th) (n = 470)	3.4 (1.6)		3.2 (1.6)		5.3 (1.6)	
<i>BMI at prepregnancy (kg/m²)</i>						
<18.5 (n = 32)	3.0 (1.8)	0.20	2.3 (2.3)	0.03 ^d	4.4 (1.8)	0.19
18.5 to 23.0 (n = 377)	3.4 (1.6)		3.1 (1.6)		5.2 (1.6)	
≥23.0 (n = 316)	3.5 (1.6)		3.3 (1.6)		5.4 (1.6)	
<i>Education status</i>						
<12 years (n = 240)	3.5 (1.7)	0.32	3.1 (1.6)	0.84	5.0 (1.6)	0.21
≥12 years (n = 557)	3.4 (1.6)		3.1 (1.7)		5.3 (1.6)	
<i>Family's income (10,000 won/month)</i>						
<200 (n = 101)	3.7 (1.6)	0.43	3.0 (1.6)	0.26	5.0 (1.6)	0.06
200 to 300 (n = 554)	3.4 (1.6)		3.1 (1.6)		5.2 (1.6)	
≥300 (n = 142)	3.4 (1.7)		3.1 (1.8)		5.4 (1.6)	
<i>Smoked during pregnancy</i>						
No (n = 660)	3.4 (1.6)	0.43	3.1 (1.7)	0.30	5.2 (1.6)	0.10
Yes (n = 85)	3.6 (1.6)		3.4 (1.6)		5.5 (1.7)	
<i>Amalgam restoration</i>						
Yes (n = 436)	3.5 (1.7)	0.28	3.1 (1.7)	1.00	5.2 (1.6)	0.81
No (n = 232)	3.4 (1.6)		3.1 (1.6)		5.2 (1.6)	
<i>Total fish intake</i>						
Rarely/never (n = 223)	3.3 (1.6)	0.01	3.0 (1.6)	0.002 ^d	4.7 (1.7)	0.0001 ^c
1–2 servings (n = 191)	3.2 (1.7)		2.9 (1.6)		5.0 (1.6)	
≥3 servings (n = 383)	3.6 (1.6)		3.2 (1.7)		5.6 (1.6)	
<i>Infants</i>						
<i>Gender</i>						
Male	3.5 (1.7)	0.25	3.0 (1.6)	0.37	5.2 (1.6)	0.82
Female	3.7 (1.6)		3.1 (1.7)		5.2 (1.6)	
<i>Parity</i>						
0 (n = 408)	3.5 (1.6)	0.52	3.2 (1.6)	0.19	5.3 (1.6)	0.28
1 (n = 288)	3.4 (1.7)		3.0 (1.7)		5.2 (1.6)	
≥2 (n = 55)	3.4 (1.7)		2.9 (1.9)		4.7 (1.9)	
<i>Birth weight (g)</i>						
Birth weight (g) <2500 (n = 6)	2.5 (2.0)	0.15	2.8 (2.4)	0.59	5.2 (1.6)	0.95
Birth weight (g) ≥2500 (n = 791)	3.4 (1.6)		3.1 (1.6)		4.1 (2.4)	
<i>SGA</i>						
Yes (n = 63)	3.5 (1.6)	0.71	3.1 (1.7)	0.35	5.5 (1.7)	0.09
No (n = 703)	3.4 (1.6)		3.1 (1.7)		5.2 (1.6)	
<i>GA (weeks)</i>						
<42 (n = 250)	3.4 (1.7)	0.26	3.1 (1.7)	0.99	5.1 (1.7)	0.36
≥42 (n = 547)	3.5 (1.6)		3.1 (1.6)		5.2 (1.6)	

^a Early pregnancy (12–20 gestational weeks), Late pregnancy (28–42 gestational weeks).

^b GM: geometric mean, GSD: geometric standard deviation.

^c p-value calculated by the Wilcoxon rank sum test or Kruskal–Wallis rank sum test because of the skewness of the mercury data.

^d p < 0.05.

The present study could not identify an increased risk for infants' weight among those women receiving mercury-containing dental fillings. Although 34% of mothers had amalgam restoration during pregnancy, there was no correlation between amalgam restoration and mercury level. In addition, several studies have reported little or no relationship between total Hg and exposure to amalgams (Berglund et al., 2005; Bjornberg et al., 2003; Hansen et al., 2004; Pesch et al., 2002). These findings suggest that any contribution of dental amalgam to the total mercury burden is not significant.

It is well known that fish consumption is likely to be associated with mercury levels. This study found association between fish consumption and the total Hg level in the maternal and cord blood.

Until now, many studies have reported that high fish intake corresponds with high mercury levels (Olsen et al., 1993; Olsen et al., 1990; Grandjean et al., 2001; Jedrychowski et al., 2007; Hightower and Moore, 2003; Myers et al., 2003). However, we excluded the fish consumption in the model because the fish intake is the major source of MeHg. We thought that inclusion of fish intake in this modeling could result in over-adjustments.

A few studies have shown that Hg concentrations are associated with dietary intake such as breast or bottle feeding and with occupational exposure to Hg (Seidler et al., 1999; Dórea, 2009). Infants may have received MeHg from their mother during pregnancy, MeHg and inorganic mercury from breast feeding and foods on which they are

Table 4
The relationship between mercury level and weight of infants by linear mixed regression analysis.^{a, b, c}

Exposure period of total Hg	Weight of infants (kg)					
	Until 12 months of age			Until 24 months of age		
	Coefficients	95% confidence interval	P	Coefficients	95% confidence interval	P
Maternal blood						
Early pregnancy ^d	−0.032	−0.091 to −0.028	0.30	−0.030	−0.289 to 0.222	0.80
Late pregnancy ^d	−0.041	−0.095 to 0.013	0.14	−0.186	−0.369 to 0.002	0.05 ^e
Cord blood	−0.047	−0.113 to 0.020	0.17	−0.359	−0.622 to −0.096	0.01 ^e

^a Adjusted for the infant's exact age at test administration, gestational age at birth, maternal age, maternal education, family's income, infant's sex, maternal job, BMI at prepregnancy, parity, and colostrum feeding in analysis until 12 months of age.
^b Adjusted for the infant's exact age at test administration, gestational age at birth, maternal age, maternal education, family's income, infant's sex, maternal job, BMI at prepregnancy, parity, mercury level of 24 months, and colostrum feeding in analysis until 24 months of age.
^c This subject has as many data records as there are measurements over time.
^d Early pregnancy (12–20 gestational weeks), late pregnancy (28–42 gestational weeks).
^e p<0.05 by linear mixed regression analysis.

weaned, and MeHg from thimerosal-containing vaccines (Marques et al., 2007a,b).

These results support the hypothesis of a negative effect of intra-uterine exposure to mercury in the cord blood and maternal blood at late pregnancy on the infants' attained weight up to 12 and 24 months, respectively. Most studies on the effects of mercury exposure on pregnant women dealt with the weight data acquired immediately after birth. On the other hand, the relationship between mercury exposure and postnatal growth has not been well studied and remains unclear. Until now, only one study has reported the relationship between mercury exposure during pregnancy and infant's growth after birth. That study was carried out in Denmark and revealed that the weight of eighteen-month-old infants decreased significantly by 0.63 kg with a log 1 µg/dL increase in the methyl mercury concentration in the cord blood (Grandjean et al., 2003). Meanwhile, the experimental animal studies by Vorhees (1985), and Fredriksson et al. (1993) also showed that exposure to high mercury concentrations affected the rats' weight at birth and during growth.

The mercury level in the maternal at late pregnancy and cord blood is an important indicator for examining the effect of mercury

exposure on the fetus. Some studies reported an inverse association between the birth weight and mercury concentration in cord blood (Foldspang and Hansen, 1990). In a birth cohort study in Turkey, the group with a higher mercury concentration in the cord blood weighed significantly less than the group with a lower concentration (Unuvar et al., 2007). Other studies in Greenland and Spain reported likewise (Ramón et al., 2009; Bjerregaard and Hansen, 2000). In MOCEH study from 2006 to 2008, an inverse relationship was found between the birth weight and maternal and cord blood Hg levels (Lee et al., 2010). On the other hand, Marques RC et al., reported a tendency for the birth weight to increase with increasing mercury levels (Marques et al., 2008). No correlation between the total mercury concentration in the cord blood and birth weight was discovered in the World Trade Center birth cohort study of 329 pregnant mothers (Lederman et al., 2008). Studies by Lucas et al. (2004) of Canada also reported an absence of relevance between mercury exposure and the weight at birth. Although the reason behind the contrasting results has not been determined, it is possible that the intake of beneficial and necessary nutrients concurs with the absorption of mercury (Kim et al., 2005). Another report showed that genetic

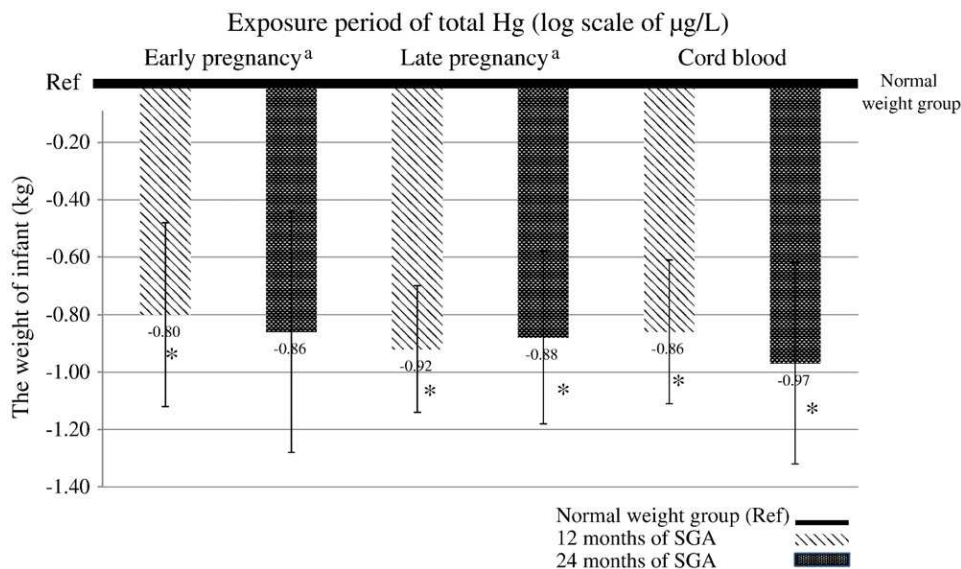


Fig. 1. Linear mixed models testing the effects of the 75th percentile groups of Hg exposure on the SGA and normal weight group. ^aAdjusted for the infant's exact age at test administration. Gestational age at birth, maternal age, maternal education, family's income, infant's sex, maternal job, BMI at pregnancy, parity, and Colostrum feeding in analysis until 12 months of age. ^bAdjusted for the infant's exact age at test administration. Gestational age at birth, maternal age, maternal education, family's income, infant's sex, maternal job, BMI at prepregnancy, parity, mercury level of 24 months, and breast-feeding in analysis until 24 months of age. ^cThis subject has many data records as there are measurements overtime. ^dMaternal blood Hg in early pregnancy has only not significantly decreased the weight of infants during 24 months, *p<0.05. ^eEarly pregnancy (12–20 gestational weeks), late pregnancy (28–42 gestational weeks).

polymorphisms caused a difference in the results (Lee et al., 2010). Therefore, it will be necessary to examine these mechanisms continuously and accurately.

This study found that infants' attained weight in SGA group was lower than the normal birth weight group when comparing the highest quartile of the mercury level. To the best of our knowledge, no study has investigated the adverse effect of mercury on postnatal growth by comparing a SGA and normal weight group. Similarly, some studies reported a negative relationship between prenatal mercury exposure and SGA and lower birth weight (Seidler et al., 1999; Koos and Longo, 1976; Borgert, 1994; Ericson and Källén, 1989). The relationship between the highest mercury exposure and weight of infants in SGA found in our study is plausible due to the known effects of mercury in animal studies and incidents of human poisonings. These studies reviewed that maternal exposure of mercury compounds can have teratogenic and embryofetotoxic effects, including reduced birth weight and growth retardation (Koos and Longo, 1976; Borgert, 1994). The results of the prospective birth cohort study of 3946 pregnant women in West Germany also suggest an association of the birth of SGA with mercury exposure (Seidler et al., 1999). In contrast, prenatal exposure to total mercury was not associated with risk of being SGA for weight in a prospective multicenter Spanish study. This inconsistency might be due to the difference in mercury levels and number of SGA in the population.

These findings suggest that infants of women exposed to high levels of mercury during pregnancy are more likely to be sensitive to the adverse effects of mercury. It is essential to develop the guidelines to improve the environmental health for susceptible groups, such as pregnant women.

How mercury affects the birth and infants' weight is unclear but mercury is believed to bond to the sulfhydryl group of a membranous protein to which it has high affinity, inducing damage to the plasma membrane. Otherwise, in the case of methyl mercury, weight reduction can occur because it impedes the action of Glutathione sulfhydryl (GSH) and catalase by binding to the thiol group (Hui et al., 2001; Yamamura et al., 1994). Moreover, weight loss might be due to the inhibition of various metabolic enzymes, suppressed genesis of macrophages and lymphocytes, decreased number of B cells in the capillary, platelet aggregation and thromboxane production. In addition, mercury may accelerate the formation of free radicals and cause the peroxidation of lipids inside the body of an organism (Houston, 2007; Charpentier et al., 1981; Ilbäck, 1991; Lawrence and McCabe, 2002).

This study had some limitations. We did not have results for exposure to other hazardous substances, such as PCBs, which have been shown to be associated with the outcome. The level of lead and cadmium may be leading potential confounder. However, we did not find any association between lead and infants' weight in our data. In this analysis, the anthropometric measure contained only the infants' weight. Formula fed infants tend to gain more weight and consume less Hg than breastfed counterparts. But, prenatal and postnatal nutrients that may confound the results could not be included in the analyses.

Nevertheless, the main strengths of this study are the prospective cohort design. The data was collected prospectively from early pregnancy through a cohort design. We were able to study prenatal exposure in relation to infants' weight. We also assessed Hg levels in maternal and cord blood which reflects the changes in recent exposure (Foldspang and Hansen, 1990; Grandjean et al., 2001; Lucas et al., 2004). The Hg concentrations assessed in the cord blood, maternal blood at early pregnancy, maternal blood at late pregnancy could reflect the exposure during early and late pregnancy because the mean half-life of Hg in the blood is approximately 45 days (range, 20–70 days) (Weil et al., 2005; Schober et al., 2003). This study has merit in that it was modeled to evaluate the multiple confounders regarding the effects of mercury exposure on the health of pregnant

mothers, fetuses and infants, and considered a range of factors regarding its effect on health.

5. Conclusion

Exposure to mercury during pregnancy is adversely associated with the infants' weight. Moreover, the effect of high mercury concentrations in the cord blood and maternal blood on the weight of infants during 24 months was apparent, particularly in SGA. Therefore, efforts should be made to reduce the mercury level in the maternal blood at late pregnancy and cord blood. Further research on the possible harmful effects of prenatal mercury exposure on postnatal growth is recommended. These results can be used to develop strategies to reduce the level of Hg exposure in high-risk groups among pregnant women in Korea.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.scitotenv.2011.08.060.

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