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Prenatal mercury exposure and birth weight

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ABSTRACT

Adverse effects of prenatal mercury exposure on pregnancy outcomes remain a public health concern. We assessed the relationship between prenatal mercury exposure and newborn anthropometric characteristics in 334 mother-child pairs from the early stages of pregnancy to delivery in Tokyo, Japan, between December 2010 and October 2012. We found a negative correlation between blood mercury levels during the first and second trimesters of gestation and birth weight ($r = -0.134$ and -0.119, respectively; $p < 0.05$). Multiple linear regression analysis confirmed the relationship between first-trimester maternal blood mercury levels and birth weight when adjusted for independent variables ($\beta = -0.170$, $t = -2.762$; $p = 0.006$). Mean mercury levels in umbilical cord blood were twice as high as maternal blood levels (10.15 ± 7.74 and 4.97 ± 3.25 μg/L, respectively; $r = 0.974$, $p < 0.001$). Our findings suggest that pregnant women and women of reproductive age should avoid mercury exposure, even at low levels, because of its potentially adverse effects on fetal development.

1. Introduction

Chronic and relatively lower-level exposures to heavy metals remain a serious public health concern [1], because metals can accumulate in organs and induce toxicity. Mercury, a ubiquitous environmental contaminant, is a metal without any known physiological function that can exert adverse effects in humans [2]. Thus, the internal concentration of mercury should ideally approach zero. Mercury is present in three forms: Elemental mercury, inorganic mercury, and organic mercury. Exposure to inorganic mercury most frequently occurs in industrials and occupational settings. Organic mercury compounds are formed bacterial conversion processes (methylmercury is the most biologically available and toxic form [3]), and tend to accumulate in the food chain, in particular in marine organisms such as fish and shellfish [4] [5]. The US National Institute for Occupational Safety and Health (NIOSH) has set a limit of 0.1 mg/m^3 for airborne mercury in the workplace [6], and the US Environmental Protection Agency (EPA) recommends that blood mercury levels not exceed 5.8 μg/dL in women of childbearing age [7].

Consumption of fish appears to be the major source of organic mercury [8–10]. Because of its fat solubility, methylmercury can cross the placenta and potentially affect fetus health [4,11]. Methylmercury may exert various adverse effects on neurology and mental development/behavior [12,13], and birthweight [9], and may induce preterm delivery [14]. Neurological and developmental disorders appear to be the most reported conditions [15,16]. Although several studies have reported that mercury can induce preterm delivery and/or low birth weight [14,17–19] other studies did not find an association between maternal mercury exposure low birth weight [20–22]. Thus, the data on prenatal mercury exposure and newborn anthropometric characteristics are insufficient and inconsistent.

Birth weight is an important predictor of newborn well-being and long-term health, and may be influenced by maternal nutrition and prenatal exposures [23]. Low birth weight is associated with neonatal mortality/morbidity and increased risk of non-communicable diseases [24]. In Japan, 9.6% of infants are classified

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as low birth weight, a higher rate than the average among Organization for Economic Co-operation and Development countries [25]. In addition, Japanese birth data indicate an up to 130-g decline in mean birth weight, with a concomitant increase in the prevalence of preterm or term low-birth-weight infants over the past decades [26].

The present study aimed to quantify total blood mercury concentrations via serial prenatal measurements during the first, second, and third trimesters of pregnancy, as well as in umbilical cord blood, to offer a better estimate of the body burden of mercury. We also analyzed the relationship between maternal blood mercury levels and neonatal anthropometric characteristics, including birth weight and body length.

2. Materials and methods

2.1. Subjects

The study was conducted from early gestation (week 12) at Juntendo University Hospital, Tokyo, Japan, between December 2010 and October 2012. Pregnant women (n = 525) who met the survey criteria (able to communicate, aged ≥20 years, singleton pregnancy, planned to undergo prenatal care and delivery at the research hospital, and free from chronic conditions, such as hypertension, diabetes, and cancers) and agreed to participate were included. Nineteen women were excluded for the following reasons: Spontaneous and/or induced abortion (n = 12), intra-uterine fetal death (n = 2), essential hypertension (n = 2), a heart pacemaker (n = 1), congenital biliary atresia (n = 1), and breast cancer (n = 1). A total of 506 pregnant women were followed throughout their pregnancy for blood sampling and data collection. One-hundred and seventy-two subjects were censored for missing information, incomplete blood sampling, and undetectable mercury levels or no matching with standards/blank samples. The final statistical analysis included data from 334 participants; there was no significant difference in age, lifestyle habits, and socioeconomic characteristics, between study participants and censored subjects.

2.2. Collection and analysis of blood samples

Whole-blood samples were collected during the first, second, and third trimester of pregnancy from the cubital vein, and from the umbilical cord at delivery using vacuum tubes (Venoject VP-H070K, Terumo, Tokyo, Japan). Samples were frozen at −80 °C until analysis. Total blood mercury content was determined using direct thermal decomposition, amalgamation/atomic absorption spectrophotometry (MA-3000 Mercury Analyzer; Nippon Instruments Corporation, Tokyo, Japan). A standard mercury working solution for the calibration curve was prepared using a standard solution (1, 10, and 100 μg/L mercury) according to the manufacturer's protocol. For instrument calibration throughout the measurements, at least 10% of the analyses were external standard samples, and 5% were of a blank (pure water).

2.3. Quality control and quality assurance

We analyzed the quality control materials Seronorm Trace Elements Whole Blood control level-1, level-2, and level-3 (Sero, Billingstad, Norway) with target values of 1.77–2.17, 13.6–16.8, and 28.0–34.8 ng/mL, respectively. Our mean concentrations for these control materials (n = 10) were 2.06 ± 0.04, 14.24 ± 0.15, and 29.93 ± 0.33 ng/mL, respectively, which is in good agreement with the target values. For internal quality assurance regarding mercury levels we determined temporal variations by monitoring the intra- and inter-day variations of the mean values of in-house control samples. Satisfactory intra-day and inter-day precision was achieved with relative standard deviations smaller than 3.5%. The limit of detection was the concentration equivalent to the mercury signal, and equals to three-fold the standard deviation of 10 repeated measurements of the blank signal. The limit of quantification was the concentration equivalent to the mercury signal, and equal to 10-fold the standard deviation of 10 repeated measurements of the digestion blank signal. The limit of detection and limit of quantification values were 0.003 and 0.013 ng/mL, respectively. There was no sample with mercury levels below the limit of quantification in the study.

2.4. Questionnaire and measurements

The study participants completed a structured self-administered questionnaire that was developed for this survey. The questions focused on variables such as maternal age, socio-demographic characteristics, and lifestyle habits (tobacco and alcohol consumption). A food-frequency questionnaire (FFQg Ver. 3.0; Kenpakusya Co., Tokyo, Japan) based on 29 food groups and 10 food preparation methods was used to estimate energy and nutrient intake. Total pregnancy weight gain was calculated by subtracting maternal weight, obtained at the time of admission for labor, from the participants' weight at the first visit (before week 12 of gestation). The newborn's weight and length were measured within 5 min of delivery.

2.5. Ethical considerations

The present study was conducted after approval was received from the ethics committees of Juntendo University and of the Japanese National Institute of Occupational Safety and Health. Written informed consent was obtained from all participants after explaining the purpose and procedure of the study, privacy protection, the right to refuse to participate, and withdrawal from the study at will. Participation in the survey was strictly voluntary.

2.6. Statistical analysis

To reduce outlier values effects and to normalize the residual distribution, the common logarithm ($\log_{10}$) values of blood mercury concentrations were used in the statistical analysis. Pearson's correlation coefficient was used to analyze relationships between anthropometric characteristics and mercury levels. Spearman's rank correlation coefficient was calculated to assess associations between consumption of fish throughout gestation with newborn anthropometric characteristics and maternal blood mercury levels. Multiple linear regression analysis was used to examine the relationship between prenatal mercury levels and offspring birth weight, controlling for possible effect modifiers, such as maternal weight and height, pregnancy weight gain, gestational age, fish consumption, and newborn sex. Student's *t*-test was used to assess differences in mercury concentrations and other variables between male and female newborns. All statistical analyses were conducted using SPSS (IBM SPSS, Armonk, NY, USA), and statistical significance was determined at $p < 0.05$.

3. Results

More than 60% of mothers were primiparous and aged 21–46 years (mean 34.5 years; Table 1). Rates of alcohol and tobacco consumption during the pregnancy were very low (5% and 2%, respectively), and the percentage of participants with a university education was 58%. On average, participants consumed fish 5 times per week (Table 1). Mean maternal blood mercury levels during the first trimester of pregnancy (6.06 ± 3.81 μg/L) were statistically higher than in the second and third trimesters (4.99 ± 3.45 μg/L and