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Sex differences in the effects of prenatal lead exposure on birth outcomes☆

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ABSTRACT

Studies on the associations between prenatal lead exposure and birth outcomes have been inconsistent, and few data are available on the sex differences in these associations. We measured the cord blood lead levels of newborns in Shanghai and determined their associations with birth outcomes, which included birth weight, birth length, head circumference, and the ponderal index, in the total sample and within sex subgroups. A total of 1009 mother-infant pairs were enrolled from 10 hospitals in Shanghai between September 2008 and October 2009. The geometric mean of the cord blood lead concentrations was 4.07 μg/dl (95% CI: 3.98–4.17 μg/dl). A significant inverse association was found between cord blood lead levels and head circumference only in the male subgroup, and increasing cord blood lead levels were related to significant decreases in the ponderal index only in females. The birth weights of the male infants were positively associated with cord blood lead levels; after adjusting for the maternal intake frequency of preserved eggs, the estimated mean differences in birth weights decreased by 11.7% for each 1-unit increase in the log10-transformed cord blood lead concentration. Our findings suggest that prenatal lead exposure may have sex-specific effects on birth outcomes and that maternal dietary intake may be a potential confounder in these relationships. Further studies on this topic are highly warranted.

1. Introduction

With the removal of lead from water pipes, paint and gasoline in recent years, environmental lead exposure levels in the general population have decreased substantially worldwide. However, due to the widespread use of lead and its ubiquitous nature, the public continues to be exposed to low levels of lead(Centers for Disease Control and Prevention [CDC], 2005). Lead can pass through the placenta from the mother's bloodstream into the fetal circulation(Agency for Toxic Substances and Disease Registry, 2007), with a fetal: maternal ratio of approximately 0.85(Goyer, 1990). Thus, the growth of the developing embryo and fetus can be affected by lead *in utero*. However, studies of the association between umbilical cord blood lead levels and anthropometric measurements of infants have shown inconsistent results. Several studies have suggested that prenatal lead exposure is a negative predictor of birth weight(Osman et al., 2000; Zentner et al., 2006), birth length(Osman et al., 2000; Xie et al., 2013; Zentner et al., 2006)and head circumference(Osman et al., 2000; Rahbar et al., 2015) among infants with average cord blood lead levels below 5 μg/dl. In contrast, other studies found no associations between cord blood lead levels and any birth outcome measures for the same levels (Al-Saleh et al., 2014; Dallaire et al., 2014; Sun et al., 2014); and a positive correlation between cord blood lead levels and crown-rump length was still reported(Obi et al., 2014). The discrepancies in the results of previous studies may be ascribed to between-study differences in lead exposure levels during the fetal period, statistical methods (such as the selection of covariates or confounders and the regression models used), and sample sizes. In summary, the extent to which fetal growth is affected by prenatal

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lead exposure is far from conclusive and warrants further study with large samples of mother-newborn pairs.

Sex-related differences in lead toxicity have been observed in previous epidemiological studies. Blood lead levels were found to be positively associated with body mass index(BMI) and obesity measurements only in women(Wang et al., 2015). The associations between the blood lead concentrations of children aged 3–5 years and an increased risk for behavioral problems at age 6 years were stronger for girls than for boys(Liu et al., 2014b). A lead-related increased risk for preterm delivery was only observed among male infants(Perkins et al., 2014). Furthermore, experimental studies have demonstrated that perinatal lead exposure results in sex-specific effects on amount of daily food intake, fat and weight values, and insulin responses across the murine lifespan (Faulk et al., 2014) and caused a sex- and tissue-specific effect on DNA methylation in mice(Sánchez-Martín et al., 2015). Additionally, it has been widely accepted that there are sex-specific differences in fetal growth(Vatten and Skjaerven, 2004; Di Renzo et al., 2007); for example, the birth weight percentiles of males are generally larger than those of females at birth. Therefore, it is plausible that prenatal lead exposure could differentially affect fetal growth in males and females. For instance, birth weight was found to be inversely associated with maternal lead levels in male newborns(Nishioka et al., 2014). However, to our knowledge, few studies have specifically examined the effects of cord blood lead concentrations on birth outcomes stratified by sex, or they have only considered sex/gender as a confounding variable (Al-Saleh et al., 2014; Dallaire et al., 2014).

Birth outcomes may be influenced by various factors, among which the nutritional supply to the developing fetus is paramount. Evidence from epidemiological and randomized controlled trials has shown that the consumption of whole foods, such as vegetables, fruit, low-fat dairy, and lean meats during pregnancy is beneficial to promoting an appropriate birth weight, and iron supplementation seems to increase birthweight(Grieger and Clifton, 2015). In contrast, another study found no significant correlation between dietary intake and pregnancy outcomes(Johnson et al., 1994). Moreover, maternal intake of some nutrients has been observed to play a role in reducing the adverse effects of lead during pregnancy. For example, maternal dietary intake of iron and vitamin D was negatively related to neonatal blood lead levels(-Schell et al., 2003), while vitamin E and ascorbic acid could protect the fetus against lead toxicity and/or free radical damage through antioxidant actions(West et al., 1994). However, diet is also a major source of lead in the general population(Martorell et al., 2011; Solenkova et al., 2014). The consumption of Chinese traditional popcorn and fried foods was found to be a risk factor for elevated blood lead levels among preschool children in Shanghai (Cao et al., 2014). According to a systematic review, the dietary intake of lead by the Chinese population was 1.232 μg/kg b. w./day, which was higher than actual dietary lead intake in France(0.20 μg/kg b. w./day in adults and 0.27 μg/kg b. w./day in children) and Canada(0.13 μg/kg b. w./day) (Jin et al., 2014). Thus, maternal dietary intake may be a potential confounder in the relationship between cord blood lead and fetal growth outcomes. Nevertheless, limited studies have investigated maternal dietary intake when exploring the effects of prenatal lead exposure on birth outcomes.

We therefore conducted a study of prenatal lead exposure and neonatal birth outcomes in mother-infant pairs in Shanghai, one of the most economically developed cities in eastern China. The aims of this study were: 1) to further probe the effects induced by prenatal lead exposure on neonatal birth outcomes, including birth weight, birth length, head circumference, and ponderal index; 2) to assess the sex differences in associations between cord blood lead levels and birth outcomes after adjusting for potential confounders.

2. Materials and methods

2.1. Study subjects and recruitment

The study was a cross-sectional multicenter survey conducted from September 2008 to October 2009. By stratified random sampling, ten hospitals located in 8 districts of Shanghai were selected for participant recruitment. Singleton pregnant women who had lived in Shanghai for at least 2 years, were aged 18 years or older, and were delivering at the selected hospitals were recruited. Pregnant women were excluded if they had chronic diseases before pregnancy, pregnancy complications, or a history of occupational heavy metal exposure. Infants who had severe disorders or congenital malformations at birth were also excluded. Before being enrolled in the study, all the participants were informed of the aims of the study and signed a written informed consent. The research protocol was approved by the Ethics Committee of Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine. Finally, a total of 1009 mother-infant pairs that met the eligibility criteria completed the questionnaires, and their umbilical cord blood samples were collected and analyzed. We calculated the power of the models in our study using PASS11, and our sample size achieved more than 97% power to detect an R-squared of 0.03 attributed to cord blood lead concentrations.

2.2. Data collection

A ten-minute questionnaire was administered to the pregnant women by specially trained nurses prior to delivery. The questionnaire collected demographic and socioeconomic information (e.g., age, education level, and monthly household income per capita), lifestyle habits before and during pregnancy (e.g., smoking, passive smoking, and alcohol consumption), potential sources of metal exposure and dietary intake frequency during pregnancy (e.g., milk, eggs, beef, pork and mutton). The participants were asked to complete the questionnaires individually, and the nurses then retrieved the questionnaires.

Neonatal anthropometry, including birth weight, birth length, and head circumference, was performed by trained delivery room staff with standardized equipment, and the results were recorded. Other infant characteristics (e.g., sex and mode of delivery) and maternal characteristics (e.g., height and weight before delivery, gestational age, parity and pregnancy complications) were extracted from the medical records. The mother's BMI before delivery was calculated as (pre-delivery weight; kg)/[(pre-delivery height; meters)^2]. The infant's ponderal index was calculated as [(birth weight; grams)/(birth length; centimeters)^3] × 100. The criterion for low birth weight was less than 2500 g, and preterm birth referred to a gestational age <37completed weeks.

2.3. Sample collection and blood lead analysis

After delivery, umbilical cord blood was collected in a lead-free tube containing lithium heparin anticoagulant. The samples were frozen at −80 °C until analysis. The cord blood lead levels were measured using graphite furnace atomic absorption spectrophotometry (Thermo Fisher Scientific, M6, USA). Quality control methods were used to ensure the accuracy of the results. Before the specimens were analyzed, a daily calibration curve (0–50 μg/dl) was formed with five standard concentrations. Then, low, medium and high lead level controls (Contox, Kaulson Laboratories, Inc., NJ, USA) were analyzed to examine the accuracy of the calibration. Only when the results of the control blood were within the scope of the standard value would the specimens be analyzed. In addition, each specimen was analyzed twice for cord blood lead, and the