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Maternal lead exposure and risk of congenital heart defects occurrence in offspring

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ABSTRACT

Maternal lead exposure may be harmful to fetal development. However, sufficient evidence was lacked about the risk on cardiac development in offspring. To explore the association between maternal lead exposure and risks of congenital heart defects (CHDs) occurrence in fetuses, a case–control study was adopted during pregnant women making antenatal examinations. The maternal hair lead levels were measured by using inductively coupled plasma mass spectrometry (ICP-MS), and logistic regression analysis was used to calculate the odds ratio (OR). Three hundred and sixteen cases and 348 controls were eligible to the study. The median level of lead in maternal hair of case (0.670 ng/mg) was significantly higher (AOR 3.07, 95% CI 2.00–4.72) than that of the control (0.461 ng/mg), including the CHD cases with or without extracardiac malformations (AOR 3.55, 2.94, respectively). Maternal lead exposure is associated with the risk of some subtypes of CHDs occurrence in offspring. The potential dose–response relationship is also presented.

1. Introduction

Congenital heart defects (CHDs) are the most prevalent type of recognized structural birth defects among newborns. The incidence of moderate and severe forms of CHD is about 6–8 per 1000 live births [1]. The environmental factors combined with inherent genetic susceptibility contribute to the etiology of most CHDs [2]. However, there remain relatively few recognized non-inherited, modifiable risk factors for CHDs occurrence [3].

Heavy metal pollution has become a serious health concern in recent years. As a common toxic trace element, lead widely exists in our environment including a main source of non-occupational exposure [4]—the air, soil, water and even inside our homes [5]. An increasing studies show lead exposure is undeniable dangerous to health, especially the reproductive health [6]. Either paternal or maternal lead exposure may increase the risks of spontaneous abortion [7–9] and pregnancy hypertension [10]. Lead material may do harm to injury on brain and nerve systems development [11], abnormal neurobehavioral [12], mental retardation [13] and cognitive developmental delays in children [14,15]. Furthermore, when maternal exposed to lead during pregnancy, high risks were found for miscarriage [16], premature [17], low birth weight [18], small fetal size or small head circumference [19] and congenital malformation, such as neural tube defects [20–22], oral cleft [22] and musculoskeletal defects [23]. These evidences had suggested

Abbreviations: AOR, adjusted odds radio; BMI, Bbody mass index; CHD, congenital heart defect; CI, confidence interval; COR, crude odds radio; ICP-MS, inductively coupled plasma mass spectrometry; Pb, lead.

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that the developing fetus is thought to be at increased risk from maternal lead exposure.

Our previous study showed significant risks for cardiac defects if the pregnant woman moved into a new house within 1 month after decoration at either 3 months before pregnancy (AOR: 2.38, 95% CI: 1.03–5.48) or during first trimester (AOR: 4.00, 95%: 1.62–9.86) [24]. Renovation, repair or painting activities can create toxic lead dust by using deteriorating lead-based paint [5]. These results suggest that the risk to fetal CHDs may attribute to maternal lead exposure. However, research on associations between maternal lead exposure and the risk of cardiac defects in human offspring is still sparse [25–27], with inconsistent positive or negative results. For this reason, we focused on lead exposure and CHD. Because there is a limitation of exposure level assessment using self-reported, industrial hygiene assessment or job exposure matrix in these studies, a significant gap in knowledge understanding the association between maternal lead exposure and risks of CHDs is an important area needing more quantitative data and evidence from human studies.

In 2009, we conducted a program of the study on interaction between environmental risk factors and genetic factors on CHDs occurrence in offspring. The program developed the protocol about the collection of clinic data and biologic sample, based on case–control design [24,28,29]. This study is a part of the program, which aims to obtain the evidence about the association between the maternal lead exposure and the risk of occurrence for CHDs and its subtypes in offspring, as well as to explore the dose–response relationship.

2. Materials and methods

2.1. Study design and study population

The case–control study was performed in February 2010 to October 2011 at four maternal and child hospitals in China. A total of 1032 mothers were recruited during this study period. Eligible fetuses with cardiac defects diagnosed prenatally were recruited as case group. For a case, one or two pregnant control without any malformations in offspring was selected in the same hospital with gestation ages within 2 weeks differ from the case fetus.

All live births of CHD cases and controls were ascertained through routine examination, heart auscultation and a thorough neonatal echocardiography performed by pediatric cardiologists within the first week after delivery. Stillbirth and abortion cases were also confirmed by autopsy report. Furthermore, all cases and controls were reviewed by an experts group composed of 6–7 national specialists from the fields of ultrasound, pediatrics, obstetrics and pathology to ensure the accuracy of the final diagnosis and that the patients met the inclusion criteria in the analysis. The information on clinic data and hair sample were collected when the pregnant women were recruited. The more detailed information about methodology in this study has been described elsewhere [24,28,29]. The study was approved by the Ethics Committee of Sichuan University (No. 2010004), and informed consent was obtained from each subject during the enrollment process.

Cases and controls with gestational ages from 14 to 40 weeks were selected to analyze in this study after the exclusion criteria for pregnant women as follows: (1) multi-fetal pregnancy; (2) CHD family history; (3) hair dye use; (4) fetuses diagnosed with chromosomal abnormality or hereditary syndrome; (5) the CHDs cases diagnosed unclear; (6) the mothers with mental disease or unwilling to participate in the study.

CHD cases were divided into two groups, namely cases with only CHDs referred to an abnormality with only cardiac malformation; and cases with CHDs and other noncardiac defects. Meanwhile, all cases with only CHDs were classified into six kinds of subtypes based on the anatomic lesion: (i) septal, (ii) conotruncal, (iii) right-sided obstructive, (iv) left-sided obstructive, (v) anomalous venous return and (vi) other cardiac structural abnormalities [24,28,29].

2.2. Questionnaire interview

Each participant had received a face-to-face interview when they were recruited during the antenatal examination. The structured questionnaire included information on the maternal demographic information, work and living environment, lifestyle exposures such as smoking habits and usage of hair dye, history of pregnancy, maternal diet and nutrition, life events and mental state, as well as history of maternal illness and drug use during the most critical period of 3 months before conception to the end of the first trimester. Information on potential confounders was obtained for covariate factors.

2.3. Hair samples collection

Hair samples were collected after the questionnaire interview. A pencil width lock of hair closed to the scalp was cut from the occipital region of the head using a fine pair of sterile steel scissors. The hair samples were kept in individual labeled sterile envelopes and then stored in −40 °C until analysis. The final test hair samples were included a 3–5 cm segment, about 0.1 g of hair closest to the scalp.

2.4. Hair sample preparation and analysis

The hairs of pregnant women in case and control groups were cut into 5 mm pieces and washed with acetone and water according to the procedure recommended by the IAEA Advisory Group to remove surface impurity and grease [30]. The washed samples were dried at about 50 °C to constant weight.

Each 100 mg of the hair sample was digested with microwave (CEM) at 180 °C following the manufacture's procedure in 5 ml of HNO_3. Then the digestion of samples was heated to near dryness on a heating plate, and subsequently diluted with 2% HNO_3 up to 2 ml. The diluted samples were stored at 4 °C for analysis. The mineral contents were measured by inductively coupled plasma mass spectrometry (ICP-MS), using Agilent 7500cx ICP/MS system (Agilent Technologies) equipped with a G3160B I-AS integrated autosampler. The samples were prepared and analyzed according to the method of Sun and Karimi [31,32]. The limit of detection (LOD) for Pb was 0.01 ng/mg. For checking our laboratory data, the certified reference material of human hair GBW09101, obtained from Shanghai Institute of Nuclear Research, was used.

2.5. Statistical analysis

A case–control analysis was performed to assess the potential effect using the database of identified cases and controls. Data analysis was performed using Statistical Package for Social Sciences (SPSS) version 16.0 software (SPSS Inc., IBM, Chicago, USA). Firstly, the composition ratio of potential factors was calculated. Differences in proportions between cases and controls were calculated using Chi-square test (two-tailed values of $P < 0.05$).

Whether the metric discrete variables were shown as mean ± standard deviation, geometric mean, range (minimum–maximum), and percentile values. Wilcoxon–Mann–Whitney was used to test for differences in lead levels between cases and controls.

The associations between lead exposure and risks of CHDs and various subtypes were assessed by calculating odds radio (ORs), and its 95% confidences interval (CI) using logistic regression model.