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Maternal exposure to arsenic and cadmium and the risk of congenital heart defects in offspring

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ABSTRACT

Hair arsenic and cadmium from 339 women with congenital heart defect (CHD)-affected pregnancies (case women) and 333 women with normal live births (control women) in China were estimated using inductively coupled plasma mass spectrometry. The median levels of hair arsenic and cadmium in the case women were 98.30 (74.30–136.30) ng/g and 14.60 (8.30–32.50) ng/g, respectively, which were significantly higher than the levels in the control group ($P < 0.05$). Arsenic concentrations ≥62.03 ng/g were associated with increased risk for almost every CHD subtype, with a dose-response relationship. However, only the group with the highest cadmium levels (≥25.85 ng/g) displayed an increased risk of CHDs (AOR 1.96; 95% CI 1.24–3.09), with a 2.81-fold increase found for the occurrence of conotruncal defects in their offspring. Furthermore, an interaction between arsenic and cadmium was observed. Our findings suggest that maternal exposure to arsenic and cadmium may be a significant risk factor for CHDs in offspring. Cadmium may have an enhancing effect on the association between arsenic and the risk of CHDs in offspring.

1. Introduction

Congenital heart defects (CHDs), abnormalities in cardiac architecture and function that arise before birth, are the most common cause of infant death from birth defects [1]. The prevalence of CHDs varies widely around the world. The most commonly reported incidences of CHDs are 8 per 1000 live births in the United States [2], 6.9 per 1000 births in Europe and 9.3 per 1000 births in Asia [3]. Despite the high prevalence and improvements in diagnostics, the causes of CHDs are largely unknown. Accumulating evidence has indicated that interactions between environmental and genetic factors may contribute to CHDs, and an increasing number of studies have demonstrated the potential role of environmental elements as a risk factor in CHD cases [4].

Exposure to arsenic and cadmium during pregnancy can increase the risk of poor birth outcomes, including low birth weight and small birth size [5–7]. Studies have shown that prenatal arsenic exposure is inversely associated with birth weight in Bangladesh [6] and Inner Mongolia [8]. In a study of a Japanese group, it was suggested that even a low-level cadmium burden in the general population has a negative effect on birth weight [9]. A few epidemiological studies have also shown that exposure to arsenic and cadmium during pregnancy was associated with birth defects [10,11]. In a Chinese study group, 215 pregnant women in two counties in Shanxi Province with different prevalence levels of neural tube defects were studied, and their results showed that blood levels of cadmium were higher in Yushe County, which has a higher prevalence of neural tube defects [11]. However, Jin et al. found that a higher concentration of cadmium was associated with a decreased risk of neural tube defects. They also found that there was no difference in placental arsenic concentrations between the cases of neural tube defects and control subjects [12]. Although Zierler et al. found that arsenic exposure through drinking water during pregnancy was associated with a threefold increase in the occurrence of coarctation of the aorta in offspring in an early case–control

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study [10] and that there was no association with patent ductus, conotruncal and ventricular septal defects, there is little evidence that maternal exposure to arsenic or cadmium is correlated with CHDs in offspring.

We performed a case–control study to detect concentrations of arsenic and cadmium in maternal hair specimens collected during pregnancy. The objective of the present study was to investigate the relationship between maternal exposure to arsenic and cadmium and CHDs in offspring in a Chinese population.

2. Materials and methods

2.1. Study design and subjects

The case and control women were recruited from four different maternal and children's hospitals in China from February 2010 to October 2011. The inclusion criteria for cases and controls were described in a previous study [13]. A case was defined as a pregnant woman whose fetus had been diagnosed with a CHD using echocardiography, with the CHD confirmed after birth. Pregnant women from the same hospitals who conceived healthy children without congenital malformations were selected as controls. In this study, cases and controls were recruited between the gestational ages of 14 and 40 weeks after the following exclusion criteria were applied [14]: pregnant women who had multi-fetal pregnancies or unclear diagnoses, pregnant women who had a family history of CHDs, pregnant women with dyed hair, pregnant women whose babies were diagnosed with a chromosomal abnormality (including chromosome numerical abnormalities and chromosome structural aberrations) or syndrome (such as Down's syndrome, trisomy 18 syndrome and trisomy 13 syndrome), and pregnant women who were unwilling or unable to participate in the study. After excluding and matching, we had 339 cases and 333 controls.

All CHD cases were divided into two groups, the "isolated" group (with only cardiac malformations or intracardiac defects) and the "complex" group (CHD cases associated with other congenital extracardiac defects). The "isolated" group was divided into six subtypes based on the anatomic lesion as described in a previous study [15]: (1) septal defects, (2) conotruncal defects, (3) left ventricular outflow tract obstructions, (4) right ventricular outflow tract obstructions, (5) anomalous pulmonary venous returns, and (6) other heart defects.

2.2. Structured interview

Prior to initiating the case–control study, the Ethics Committee of Sichuan University reviewed and approved the study protocol and informed consent forms (No. 2010004). Women were interviewed after informed consent was obtained. The structured interviews elicited information about each woman's demographic characteristics, living environment, lifestyle, environmental and occupational exposures, reproductive history, family health history, medication use, and diet and nutritional supplement use from 3 months before conception to 3 months after conception.

2.3. Hair sample collection and laboratory assessment

Hair samples were collected after the interviews. Approximately 5 cm of long hair weighing 2 g was cut from the occipital region of the head close to the scalp. First, each hair sample was soaked and washed to remove surface dust and grease. Next, 100 μg of each sample was microwave-digested (CEM, US) at 180 °C, and then 5 ml of HNO_3 was added. After being heated to near dryness, 2% HNO_3 was added to dilute it to 2 ml. The diluted samples were stored at 4 °C for the analysis. The arsenic and cadmium contents were analyzed as described previously [14] by inductively coupled plasma mass spectrometry (ICP-MS) using the Agilent 7500cx ICP/MS system (Agilent Technologies) equipped with a G3160B I-AS integrated autosampler. The limits of detection for arsenic and cadmium were 0.01 and 0.0003 μg/g, respectively. To check the data, certified human hair reference material (GBW09101) obtained from the Shanghai Institute of Nuclear Research was used as a standard.

2.4. Statistical analysis

The differences in demographic information and maternal characteristics between the case and control groups were compared using a Chi-square test. The distributions of arsenic and cadmium are presented as medians (inter-quartile range, IQR). The Mann–Whitney *U* test was used to compare the differences in arsenic and cadmium levels between the case and control groups.

The risks of CHDs associated with exposure to arsenic and cadmium were estimated using a crude odds ratio (COR) and adjusted odds ratio (AOR). The precision of the estimation was assessed by calculating the 95% confidence interval (95% CI) using logistic regression. The potential confounding effects were maternal age, previous pregnancies, gestational age, folic acid supplementation, body mass index (BMI), and paternal smoking.

We divided all of the subjects into four levels by quartile (presented as the first quartile of exposure, low, medium and high), and the first quartile of arsenic (≤62.03 ng/g) and cadmium (≤7.23 ng/g) exposure were considered references. The interactions between each level of arsenic and cadmium were analyzed in multiplicative model by multivariate logistic regression model [16]. The strength of the interaction was calculated using a variable regression coefficient (β). The interaction coefficient (γ) was the ratio of two log odds ratios (ORs). Arsenic was considered the main effect factor, and the formula for the interaction coefficient (γ) was as follows:

$$\gamma = \beta(\mathrm{As}_n\mathrm{Cd}_n)/\beta\mathrm{As}_n\mathrm{Cd}_{(\mathrm{none})}$$

In this formula, when γ is >1, it suggests that cadmium has an amplification effect on arsenic; when γ is <1, it suggests that cadmium has a diminishing effect on arsenic; when $\gamma = 1$, it suggests that cadmium has no effect on arsenic.

A two-sided *P* value of <0.05 was considered statistically significant. Statistical analyses of the data were performed using SPSS Version 20.0.

3. Results

3.1. Characteristics of participants

A final total of 339 case and 333 control subjects were included in the study. The group of case mothers included 237 cases (69.9%) with isolated cardiac defects (intracardiac defects) and 102 cases (30.1%) associated with other congenital extracardiac defects. Of those with intracardiac defects, 186 cases (78.5%) had simple CHDs (only one simple CHD, such as a ventricular septal defect) and 51 cases (21.5%) had complicated CHDs (at least two distinct CHDs, such as transposition of the great vessels with outflow tract obstruction). The most common isolated cardiac defect subtype was conotruncal defects (99, 41.8%), followed by septal heart defects (62, 26.2%), right ventricular outflow tract obstructions (58, 4.5%), left ventricular outflow track obstructions (51, 21.5%), other heart defects (21, 8.9%) and anomalous pulmonary venous returns (8, 3.4%). The maternal and paternal characteristics of the cases and controls are displayed in Table 1. Cases and controls were significantly different in maternal age, gestational age, folic acid supplementation and paternal smoking status. Cases and controls were similar with respect to maternal cosmetic use, but cases were more likely to have been exposed to chemicals (pesticide, insecti-