Environment International 106 (2017) 127–134

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Associations between toxic and essential trace elements in maternal blood and fetal congenital heart defects

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ARTICLE INFO

Keywords:
Heart anomalies
Teratogen
Trace elements
Risk factor
Environment

ABSTRACT

Prenatal exposure to toxic trace elements, including heavy metals, is an important public health concern. Few studies have assessed if individual and multiple trace elements simultaneously affect cardiac development. The current study evaluated the association between maternal blood lead (Pb), cadmium (Cd), chromium (Cr), copper (Cu), mercury (Hg), and selenium (Se) levels and congenital heart defects (CHDs) in offspring. This hospital-based case-control study included 112 case and 107 control infants. Maternal peripheral blood draw was made during gestational weeks 17–40 and used to determine trace element levels by inductively coupled plasma mass spectrometry. Multivariable logistic regression was used to assess associations and interactions between individual and multiple trace elements and fetal CHDs, adjusted for maternal age, parity, education, newborn gender, migrant, folic acid or multivitamin intake, cigarette smoking, maternal prepregnancy body mass index, and time of sample collection. Control participants had medians of 2.61 μg/dL Pb, 1.76 μg/L Cd, 3.57 μg/L Cr, 896.56 μg/L Cu, 4.17 μg/L Hg, and 186.47 μg/L Se in blood. In a model including all measured trace elements and adjusted for confounders, high levels of maternal Pb (OR = 12.09, 95% CI: 2.81, 51.97) and Se (OR = 0.25, 95% CI: 0.08, 0.77) were harmful and protective predictors of CHDs, respectively, with positive and negative interactions suggested for Cd with Pb and Se with Pb, respectively. Similar associations were detected for subgroups of CHDs, including conotruncal defects, septal defects, and right ventricle outflow tract obstruction. Our results suggest that even under the current standard for protecting human health (10 μg/dL), Pb exposure poses an important health threat. These data can be used for developing interventions and identifying high-risk pregnancies.

1. Introduction

Congenital heart defects (CHDs), structural abnormalities of the cardiovascular system characterized by anatomical departures of the heart and great vessels from normal, are the most common birth defects in newborns, affecting 6 to 12 per 1000 live births worldwide (Donofrio et al., 2014). CHDs remain the leading cause of morbidity, mortality, and disability in neonates and children, associated with lifelong physical and mental comorbidities, and involving substantial financial expenses (Donofrio et al., 2014). Over the past decade, a growing body of epidemiological literature has shown that a multitude of noninherited risk factors may increase the risk of CHDs, including maternal illnesses like pregestational diabetes, maternal medication exposures, environmental exposures, and paternal exposures, while periconceptional multivitamin or folic acid intake may reduce the risk (Donofrio et al., 2014). Environmental pollutants, including toxic trace elements such as heavy metals, may play a contributing role (Di Renzo et al., 2015).

Heavy metal pollution in China and trace element deficiencies constitute an important public health concern. Lead (Pb) exposure is

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http://dx.doi.org/10.1016/j.envint.2017.05.017
Received 18 December 2016; Received in revised form 19 May 2017; Accepted 19 May 2017
Available online 20 June 2017

widespread. The public may be exposed to Pb through contaminated food, water, house dust, and through industrial activities such as metal recycling and the battery industry (Barbosa et al., 2005). In Guangdong, daily exposure also exists through consumption of cultured fish, rice paddy soil, and atmospheric pollution (Liang et al., 2016; Yang et al., 2004; Zeng et al., 2016). Maternal exposure to Pb during pregnancy has been associated with a higher probability for congenital abnormalities among offspring (Liu et al., 2015). Exposure to other trace elements were also reported to increase the likelihood for congenital abnormalities, such as cadmium (Cd) and chromium (Cr), that are associated with modern industrial processes, and are absorbed in significant quantities from cigarette smoke (Thompson and Bannigan, 2008; Gil et al., 2011). Exposure of experimental animals to oral or parenteral Cd causes a wide range of embryo abnormalities, conditional on the stage of exposure and the administered dose (Thompson and Bannigan, 2008). Selenium (Se) is an essential element, required for anti-oxidant enzyme activities, and deficiency can occur with inadequate dietary intake. Detectable traces of Se in drinking water were associated with a lower frequency of any CHD than was observed among children exposed to drinking water without detectable Se levels (Zierler et al., 1988). Other findings further indicated that maternal Se deficiency during pregnancy might contribute to neural tube defects (NTDs) in offspring (Cengiz et al., 2004).

Like Cd, chromium (Cr) exposure mostly results from modern industrial process and cigarette smoking (Gil et al., 2011). Human data showed a suggestive but not necessarily causal association between higher parental Cr exposure and increased CHDs, even at levels approaching but not exceeding the 0.05 mg/L action level for protecting human health (Goldberg et al., 1990). Copper (Cu) is an essential element required in trace concentrations for normal physiology. Yet, the relation between maternal plasma Cu concentrations and birth defects in offspring is unclear as few data are available to address the risk. A small case-control study reported higher serum Cu among the mothers of elective terminations with NTDs, relative to matched live births without a defect (Cengiz et al., 2004). Seafood consumption is the most important source of mercury (Hg) exposure among non-occupationally exposed populations (Wells et al., 2016). A suggestive association was found between higher placental Hg and higher NTD risk in offspring from a Chinese population (Jin et al., 2013).

The aforementioned elements cross the placenta and are thus transferred from mother to a developing fetus (Caserta et al., 2013). Possible biological mechanisms underlying their teratogenic effects include oxidative damage to the DNA and modification of epigenetic patterns (Hansen, 2006; Valinluck et al., 2004; Pilsner et al., 2009; Ercal et al., 2001). Moreover, complex antagonistic interactions between Se and toxic trace elements have been reported in previous studies. For example, Se may exert an antagonistic effect on Pb induced expression of inflammatory factors and heat shock proteins genes (Zheng et al., 2016), the cataractogenic effects of Hg may be offset by Se (Lemire et al., 2010), and Se has been identified as a potential countermeasure against Cd inducted toxicity (Zwolak and Zaporowska, 2012).

To date, biomarker based observational studies of gestational trace element exposures and human CHDs remain sparse. There are even fewer data available to assess the simultaneous effects of multiple trace elements, and their interactions with respect to CHDs. Given the widespread nature of the exposures and tantalizing results from the few studies published to date, additional investigation is necessary. The current study was designed to address the existing data gap with an investigation of the individual and combined effects of Pb, Cr, Cd, Cu, Hg, and Se, on the occurrence of CHDs among mother-infant pairs in southeastern China.

2. Materials and methods

2.1. Study design and subjects

This is a hospital-based case-control study conducted from December 2012 to September 2013 at one provincial general hospital in China. Pregnant women receiving routine prenatal care in the hospital obstetric department mostly reside in the Pearl River Delta Region of Guangdong Province. Both pregnant women treated by the hospital's obstetrics department as well as mothers treated at other hospitals in the Pearl River Delta Region are referred to the Department of Fetal Echocardiography in our institute if a CHD is suspected following an obstetric ultrasound examination. In 2001, the cardiovascular institute reported 92% sensitivity and 95% specificity for echocardiogram detection of fetal CHDs (Pan et al., 2001). Consecutive singleton fetuses diagnosed with defined structural cardiac defects were recruited to the study at the time of the prenatal diagnosis, between 17 and 40 weeks. Among 1379 fetuses examined with fetal echocardiography, 170 of them were diagnosed with CHDs after review by two physicians specialty-trained in echocardiography. We excluded fetuses with: 1) only mitral or tricuspid valvular lesions or enlarged atrial septal defects ($n = 6$); 2) chromosomal malformations or syndromes, or CHDs co-existing with ex-cardiac birth defects ($n = 7$); 3) self-reported family history of CHDs ($n = 4$); 4) diabetes ($n = 8$); 5) multiple gestations ($n = 8$); and 6) prenatal CHD diagnosis not confirmed after delivery ($n = 3$). Of 134 eligible case 112 (84%) agreed to participate in our study. Each CHD case was matched by gestational age (± 3 months) and maternal age (± 5 years) to a control mother without diabetes or a family history of CHDs, who was undergoing routine prenatal consultation for a normal singleton fetus randomly selected from the obstetrics clinic, on the same day. Of 119 eligible controls, 107 agreed to participate in our study; a participation rate of 90%, which was not differ from that of cases.

All live births with a prenatal CHD diagnosis received B-mode echocardiographic examination to confirm the diagnosis after delivery. Live births without a prenatal CHD diagnosis were routinely evaluated before discharge to determine whether further investigation for a potential CHD was needed. At least two senior pediatric cardiologists confirmed each CHD case diagnosis after delivery, using computed tomography, cardiac catheterization, surgery, or autopsy (i.e., for cases of stillbirth and elective termination) as clinically necessary. CHD cases were coded based on the International Classification of Diseases version 10 (ICD-10) with codes Q20-Q28.

2.2. Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Guangdong General Hospital Human subjects committee (No. 2011120H) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Oral informed consent was obtained from the mothers of each fetus prior to study enrollment.

2.3. Classification of CHD case subtypes

Cases were classified into five cardiac phenotypes after modification based on prior reports (Leirgul et al., 2014), including: (i) conotruncal defects (d-transposition of the great arteries [TGA], tetralogy of Fallot [ToF], double outlet right ventricle [DORV], conoventricular ventricle septum defect [VSD], truncus arteriosus, and interrupted aortic arch [IAA] type B or type C); (ii) left ventricle outflow tract obstructions [LVOTO] (coarctation of aorta [CoA], aortic valve stenosis [vAS], and hypoplastic left heart syndrome [HLHS]); (iii) right ventricle outflow tract obstructions [RVOTO] (hypoplastic right heart syndrome [HRHS], tricuspid atresia, Ebstein anomaly, pulmonary atresia [PA] or valvular PA, and pulmonary valve stenosis [vPS] with or without septal defects);