Environmental Research 137 (2015) 215–221

Contents lists available at ScienceDirect

Environmental Research

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

The critical fetal stage for maternal manganese exposure

Ming-Song Tsai [a,b,c], Kai-Wei Liao [d], Chia-Huang Chang [d], Ling-Chu Chien [e], I-Fang Mao [f], Yen-An Tsai [d], Mei-Lien Chen [d,*]

[a] Department of Obstetrics and Gynecology, Cathay General Hospital, Taipei, Taiwan
[b] School of Medicine, Fu Jen Catholic University, Taipei, Taiwan
[c] School of Medicine, Taipei Medical University, Taipei, Taiwan
[d] Institute of Environmental and Occupational Health Sciences, School of Medicine, National Yang Ming University, Taipei, Taiwan
[e] School of Public Health, Taipei Medical University, Taipei, Taiwan
[f] Department of Occupational Safety and Health, Chung Shan Medical University, Taichung, Taiwan

ARTICLE INFO

Article history:
Received 14 July 2014
Received in revised form
1 December 2014
Accepted 3 December 2014

Keywords:
Erythrocyte manganese
Birth outcomes
Birth weight
Head circumference
Chest circumference
Critical stage of pregnancy exposure

ABSTRACT

Prenatal exposure and the health effects of that exposure have been intensively studied for a variety of environmental pollutants and trace elements. However, few studies have compared susceptibilities among the three trimesters of gestation. Manganese (Mn) is a naturally occurring and abundant trace element in the environment. Although the effects of Mn on animals are well documented, knowledge of the effects of Mn exposure on pregnant women and fetuses remains limited. A longitudinal study was conducted by collecting blood samples during all three trimesters, and Mn exposure was completely characterized during gestation. The aims of this study were to examine the effects of maternal Mn exposure on neonatal birth outcomes and to explore the critical stage of these effects.

In total, 38, 76 and 76 samples were obtained from singleton pregnant women in their first, second and third trimesters, respectively. The cohort of pregnant women was selected at a medical center in northern Taiwan. Erythrocyte samples were collected during the first, second and third trimesters of gestation. Erythrocyte Mn concentrations were measured by inductively coupled plasma mass spectrometry. Neonatal birth outcomes were evaluated immediately after delivery. A multivariate regression model was used to determine the associations between maternal Mn levels in erythrocytes in each trimester and neonatal birth outcomes.

The geometric mean concentrations of Mn were 2.93 μg/dL, 3.96 μg/dL and 4.41 μg/dL in the first, second and third trimesters, respectively. After adjusting for potential confounders, a consistently negative association was found between maternal Mn levels throughout the three trimesters and birth outcomes. Log-transformed Mn levels in maternal erythrocytes in the second trimester were significantly associated with neonatal birth weight, head and chest circumferences, respectively ($\beta = -556.98$ g, $p = 0.038$; $\beta = -1.87$ cm, $p = 0.045$; $\beta = -2.74$ cm, $p = 0.024$). Despite the limited sample size in the first trimester, negative effects of maternal Mn levels on birth weight ($\beta = -1108.95$ g, $p < 0.01$) and chest circumference ($\beta = -4.40$ cm, $p = 0.019$) were also observed.

1. Introduction

In recent years, the maternal transfer of environmental pollutants to fetuses has raised concern. During gestation, fetuses are generally considered to be highly vulnerable to environmental pollutants. These pollutants include metals such as mercury (Hg), lead (Pb), arsenic (As) and manganese (Mn) (Andersen et al., 2000; Murata et al., 1999; Schantz et al., 2003). Metropolitan Taipei is a basin located in northern Taiwan. Industrial emissions are low, but this city has a population of 2.61 million and 6633 motor vehicles per square km (Taiwan EPA, 2013b). With a high motor vehicle density, automobile emissions contribute predominantly to air pollution. Taiwan completely banned leaded gasoline in February 2000, and thus, the presence of other metals, such as Mn, in fuel has become an issue of relative concern. Airborne Mn was reported to be 19.1 ng/m^3 in Taiwan, which is higher than the concentrations reported in Italy (13 ng/m^3) and Spain (14 ng/m^3) (Fang et al., 2003; Querol et al., 2001; Ragosta et al., 2008). This high Mn level may reflect the high background level of Mn in soil, which could be another source of Mn pollution. According to the Taiwan environmental water quality information system,

* Correspondence to: 155, Sec. 2, Linong Street, Taipei 112, Taiwan. Fax: +886 2 28278254.
E-mail address: mlchen7239@gmail.com (M.-L. Chen).

http://dx.doi.org/10.1016/j.envres.2014.12.010
0013-9351/

groundwater Mn levels in Taipei have exceeded the recommended limits in water throughout the past decade (Taiwan EPA, 2013a). A previous study has indicated that fetal cord blood is affected by ambient air (Lin et al., 2012).

Mn is a naturally occurring and abundant trace element in the environment and is an essential trace nutrient for humans. Maintaining trace element levels in the body within optimal ranges is important, as either deficiency or intake exceeding the recommended daily intake can be associated with risks. Mn is found in all tissues and is required for amino acid, protein and carbohydrate metabolism. Mn is involved in the functioning of numerous organ systems and is needed for normal immune function, digestion and bone growth (Aschner and Aschner, 2005). The WHO recommends a Mn intake of 2–9 mg per day for adults (World Health Organization, 1994). In 2002, the Institute of Medicine set adequate intake levels for Mn at 1.8 mg/day for women (IOM, 2002).

In animal studies, inadequate dietary intake and Mn deficiency are accompanied by impaired growth, bone formation, skeletal and birth defects (Keen et al., 1999). In contrast, excessive Mn exposure is potentially neurotoxic (Wood, 2009). Female rats exposed to high levels of Mn experience fewer pregnancies, and increased fetal death is observed among mice exposed to high Mn levels (Colomina et al., 1996; Elbetieha et al., 2001; Laskey et al., 1982; Sanchez et al., 1993). The primary targets of Mn toxicity are the brain and the central nervous system (ATSDR, 2000). A previous study demonstrated that young animals absorb approximately 70% of ingested Mn through the intestine, whereas adults absorb only 1–2% (Lonnerdal et al., 1987).

Although Mn deficiency causes numerous biochemical and structural abnormalities, low-level and long-term Mn exposure may decrease neuromotor function. Epidemiologic studies suggest that Mn exposure, even at a low level, may affect the growth and neurodevelopment of neonates, particularly with respect to birth weight, achievement and intelligence quotient (Bhang et al., 2013; Claus Henn et al., 2010; Khan et al., 2012; Zota et al., 2009). One study found that children aged 6–12 years exhibited lower cognitive performance when they had high Mn levels in their hair (Menezes-Filho et al., 2011). Another study reported that exposure to Mn was adversely associated with neurodevelopment in utero (Lin et al., 2013). In adults, overexposure has been associated with cognitive, psychiatric, learning and memory problems (Guilarte and Chen, 2007).

Mn is primarily obtained by the general population through dietary intake, as it is a natural component of many foods and beverages, such as leafy vegetables, nuts, grains and tea. Inhalation is another common source of human exposure in environmental and occupational settings. For neonates and infants, food is the major source of absorption, and they are more vulnerable than adults to Mn exposure through the intestines (Lonnerdal, 1994; Lucchini and Kim, 2009). Mn has been reported to cross the placenta via an active transport mechanism to enter the fetus, and it crosses the blood–brain barrier in fetuses at a rate that is four times higher than that in adults (Mena, 1974; Rossipal et al., 2000). Although the effects of Mn on animals are well documented, the effects of Mn exposure on pregnant women and fetuses remain poorly characterized.

To date, several prenatal studies have focused on the adverse effects of toxicant exposure during specific stages of pregnancy (Huang et al., 2009; Yolton et al., 2011). In our previous study, we demonstrated that intrauterine nonylphenol exposure during pregnancy, particularly in the second trimester, is adversely associated with fetal body length at birth (Tsai et al., 2013). We collected complete exposure data from pregnant women in three trimesters of the gestational period as well as fetal development data and neonatal birth data. Therefore, this study examines a useful cohort for exploring the susceptibility associated with prenatal exposure to environmental pollutants. The objective of the present longitudinal cohort study was to examine the relationship between maternal Mn exposure and birth outcomes and to determine the critical time periods for Mn exposure.

2. Materials and methods

2.1. Study subjects

Pregnant women were recruited at an obstetrics clinic in northern Taiwan. The research protocol was approved by the Institutional Review Board (IRB) of Cathay General Hospital, Taipei, Taiwan. After informed consent was obtained, pregnant women who had undergone Down syndrome screening in the first trimester of gestation were invited to participate in the study between March and December 2010. Women carrying fetuses with structural abnormalities or chromosomal defects, as detected by second-trimester amniocentesis, were excluded from the study. In total, 235 pregnant women were invited to participate in this study. Of these women, 85.5% ($N=201$) agreed to participate, and 71.5% ($N=168$) were followed until delivery. Thirty-eight women provided specimens in the first, second and third trimesters. An additional 38 women provided specimens only in the second and third trimesters. In total, 38, 76, and 76 pregnant women provided erythrocyte samples in the first, second and third trimesters, respectively (Fig. 1).

Each woman was asked to complete a structured questionnaire, consisting of information on sociodemographic characteristics (age, weight, height and education), lifestyle (smoking, drinking, exercise, vitamin use and medication) and dietary consumption (such as meat, vegetables, fruit, tea and coffee). Information on personal and family disease histories, allergies and reproductive histories was acquired from the hospital's information system. Maternal body weight was measured during each prenatal clinic visit. Maternal weight gain in each trimester was calculated by subtracting the pre-pregnancy body weight from the weight at the end of each trimester.

2.2. Erythrocyte Mn measurements

Maternal erythrocyte samples were collected at the first-trimester (gestational weeks 10–13) Down syndrome screening,

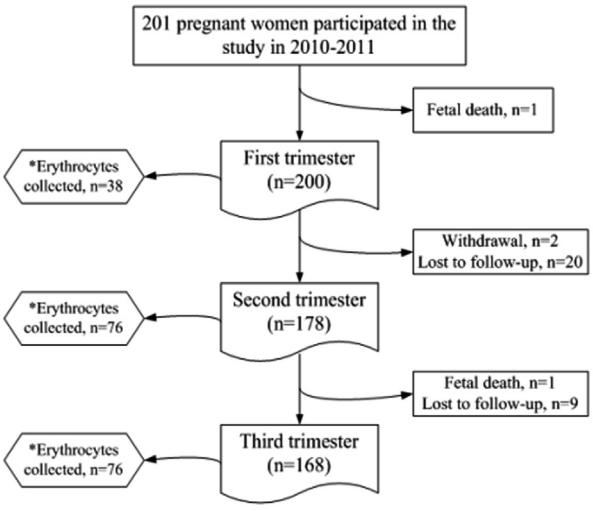

Fig. 1. Follow-up of pregnant women.