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Maternal arsenic exposure and birth outcomes: A birth cohort study in Wuhan, China☆

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ABSTRACT

Maternal arsenic exposure leads to adverse birth outcomes, but the critical window of this susceptibility keeps unclear. To determine whether the associations between maternal arsenic exposure and birth outcomes were trimester-specific, we conducted a birth cohort study of 1390 women from 2014 to 2016 in Wuhan, China. We examined associations between total urinary arsenic concentrations in three trimesters and birth weight, birth length and the risk of small for gestational age (SGA), and the differences of these associations across trimesters using generalized estimating equations. Maternal urinary arsenic concentrations varied across trimesters and were weakly correlated. Arsenic concentrations in the 3rd trimester, but not in the 1st and 2nd trimesters, were associated with birth outcomes. For each doubling of arsenic levels in the 3rd trimester, birth weight was decreased 24.27 g (95% confidence interval (CI): −46.99, −1.55), birth length was decreased 0.13 cm (95% CI: −0.22, −0.04), and the risk for SGA birth was increased 25% (95% CI: 1.03, 1.49). Further, stratified analyses indicated that these associations were only observed in female infants. Our findings indicate maternal arsenic levels in the 3rd trimester seemed to have significant impacts on birth outcomes, and also emphasize the public health interventions relevance to arsenic exposure in late pregnancy.

1. Introduction

As a widely distributed semi-metallic element, arsenic occurs through natural processes across the earth's crust with higher concentrations in some areas, such as Bangladesh, West Bengal India, and Northern Chile (Smedley and Kinniburgh, 2002). Inorganic arsenic easily dissolves into the groundwater which may supplies drinking water. People are also likely to be exposed to arsenic from ingesting contaminated foods or soil (ATSDR, 2007).

Arsenic easily crosses the placenta (Concha et al., 1998; Hall et al., 2007), and its adverse impact of prenatal exposure to inorganic arsenic at high levels has been well established, such as spontaneous abortion, elevated neonatal mortality and impaired fetal growth (Quansah et al., 2015). It is worth mentioning that chronic exposure to arsenic at low levels (e.g. under 10 μg/L in drinking water -the maximum contaminant level of inorganic arsenic set by the World Health Organization) is more wide spread and may also pose health risks (Almberg et al., 2017; Amini et al., 2008; Bloom et al., 2014). However, the impact of exposure to arsenic at low levels (IARC, 2004) on fetal development has currently not been fully elucidated. The associations between reduced birth weight and higher arsenic concentrations in maternal urine (Gilbert-Diamond et al., 2016), blood (Claus et al., 2016), or cord blood (Remy et al., 2014) have been found in some areas with relatively low arsenic exposure, while other studies such as those from Taiwan (Chou et al., 2014) or Japan (Shirai et al., 2010) reported maternal arsenic exposure had no effect on birth size.

A meta-analysis reported that arsenic was associated with

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reduced birth weight. However, given that most of the reviewed studies assessed arsenic exposure at delivery, the precise biologic window across the entire pregnancy of arsenic exposure in utero keeps unclear. Pregnancy is a period of dynamic growth and change for the developing fetus. Growing evidence has supported the sensitive windows of prenatal chemical exposure. The hazards of arsenic exposure at different pregnancy periods on pregnancy outcomes could be various (Selevan et al., 2000). Therefore, the limited, contradictory findings of epidemiological studies on low-level arsenic and birth outcomes may be related to the variability in the timing of exposure assessment. The inconsistency across the studies also emphasizes the significance of precisely identifying critical exposure periods of vulnerability of fetus to arsenic exposure.

Arsenic absorbed into the body is metabolized and expelled mainly through the urine, and can be measured in the blood, urine, hair, or nails. Blood or urine were usually used as biological media to assess low-level arsenic exposure (ATSDR, 2007). However, with the short biological half-lives of arsenic-4 days in urine and a few hours in blood, respectively (Hughes, 2006), it is of great importance to measure repeated arsenic levels in different stages to provide accurate exposure estimates over entire pregnancy.

In the present study, our aim is to examine the associations between maternal arsenic exposure and birth outcomes, across three different trimesters, in a prospective birth cohort in Wuhan, China.

2. Materials and methods

2.1. Study population

Women were enrolled in the prospective birth cohort from the Wuhan Women and Children Medical Care Center in Wuhan, Hubei, China between October 2014 and March 2016. We invited pregnant women who went to the hospital for their first prenatal visit and met the following criteria to participate in this study: 1) residents of Wuhan who do not intend to move out the city for the foreseeable future; 2) conceived a singleton baby and less than 16 weeks of pregnancy; and 3) plan to have prenatal checkup and deliver at the study hospital. Enrolled mothers were invited to provide urine samples in three pregnancy trimesters. For the present study, we restricted the analyses to pregnant women with at least two urine samples from two different trimesters ($n = 1390$), due to the purpose of investigating the trimester-specific associations of maternal arsenic with birth outcomes. We excluded 432 participants without urine samples or just available of one urine sample. All participants signed informed consent forms. Both of the ethics committee of the Tongji Medical College, Huazhong University of Science and Technology, and the study hospital-Wuhan Women and Children Medical Care Center approved the research protocol.

2.2. Urine sample collection and arsenic measurement

Pregnant women provided spot urine samples when they visited the hospital for prenatal care in each trimester. The gestational ages (mean ± SD) when we collected urine samples in the 1st, 2nd, and 3rd trimester were 12.7 ± 1.2, 23.9 ± 2.9, 34.4 ± 4.4 weeks, respectively. Among the 1390 participants, 1362 (84%) provided urine samples in three different trimesters, and the other 18 women provided two urine samples in two trimesters. The numbers of women with urine samples in the 1st, 2nd, and 3rd trimester were 1378, 1380, and 1383, respectively.

We used polyethylene containers to collect urine samples and stored them at −20 °C until further processing. The concentrations of total urinary arsenic, including organic arsenic and inorganic arsenic (As^{3+} and As^{5+}) were determined using Inductively Coupled Plasma Mass Spectrometry (ICP-MS) (Agilent 7900, Agilent Technologies, Santa Clara, CA, USA). We prepared and analyzed the urine samples according to the previously described methods (Jie et al., 2016). Repeated samples from one woman were determined in the same batch. In each batch, we used National Institute of Standards and Technology (Gaithersburg, Maryland) Standard reference material (SRM) as an external control, and the levels measured were kept in the manufacture-recommended range (5%). For the sample with arsenic concentration below the limit of quantitation (LOQ, 0.02 μg/L) ($n = 1$), we replaced the value with the LOQ divided by the square root of 2 for analyses.

In order to control the urine dilution, we used specific gravity (SG) to adjust arsenic concentrations with an average SG of 1.015 mg/L based on urine arsenic × (1.015−1)/(measured SG-1). SG measurement was conducted using a refractometer (Atago PAL-10S, Atago, Tokyo, Japan), immediately after thawing of urine samples for arsenic analyses. We excluded samples with SG values < 1.01 ($n = 3$).

2.3. Birth outcomes

Birth outcomes in this study included birth weight, birth length and the small for gestational age (SGA) births. Medical records at delivery provided us information of birth length and birth weight. Immediately after birth, experienced obstetric nurses measured nude newborns and recorded the values by standardized procedures. The infants with birth weight less than the 10th percentile in the specific gestational age and sex group were identified as SGA. Percentiles of birth weight were calculated based on all available live births in the study hospital according to a global reference (Mikolajczyk et al., 2011) and percentiles for boy and girl infants were calculated separately. For women whose gestational age and ultrasound-based gestational age were within 7 days, we identified the gestational age by the duration (in weeks) between the date of the last menstrual period (LMP) and birth date. For participants whose menstrual cycle were irregular or who were not sure about the date of LMP, we estimated the gestational age based on the ultrasound-based LMP by experienced obstetricians.

2.4. Covariates

Information on maternal height, pre-pregnancy body weight (self-reported), body weight at delivery, and maternal health during pregnancy, including gestational diabetes mellitus and hypertension disorders during pregnancy were abstracted from medical records. All participants were interviewed face-to-face by specially trained nurses at the study hospital. Demographic information (ethnicity, age, marital status, and residence), socioeconomic characteristics (women's and husbands' occupation, education, and annual family income), and lifestyle habits (alcohol use, smoke, and multivitamin supplement during pregnancy) were collected during the interviews.

2.5. Statistical analysis

We firstly compared the baseline characteristics (demographic, socioeconomic characteristics and lifestyle factors) of the 1390 included participants with those of the 432 excluded women. We then calculated the distributions of urinary arsenic and SG-adjusted arsenic concentrations. We used log2 transformed (log_2) SG-adjusted arsenic in the subsequent analyses to meet the requirements of normal distributed residuals.

To evaluate the variability of urinary arsenic across the three