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Maternal exposure to nickel in relation to preterm delivery

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HIGHLIGHTS

- This is the largest population-based study to assess nickel exposure in pregnant women.
- Maternal exposure to nickel was associated with decreased gestational age.
- An increase of 16% in odds ratios for preterm delivery was observed as urinary nickel level elevated.

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ABSTRACT

Prior studies have suggested the reproductive effects of nickel; however, few epidemiological studies have investigated the associations of maternal exposure to nickel with preterm delivery. To investigate prenatal exposure to nickel as a risk factor for preterm delivery (< 37 weeks) in a large birth cohort. A total of 7291 pregnant women participated in the study were recruited between September 2012 and October 2014 in the longitudinal Healthy Baby Cohort (HBC) in Wuhan, China. Inductively Coupled Plasma Mass Spectrometry was employed to examine levels of nickel in urine from pregnant women collected before labor. The median urinary creatinine-corrected nickel was 5.05 creatinine μg/g with an inter-quartile range of 2.65–9.51 creatinine μg/g. We adjusted for potential confounders and found that each doubling in concentration of maternal urinary nickel was associated with an increase of 16% in adjusted odds ratios (ORs) for preterm delivery (95% CI: 1.08, 1.24). The associations were consistent for both spontaneous and iatrogenic preterm delivery. Our findings suggest that higher maternal urinary nickel concentrations were associated with an increased risk of preterm delivery.

1. Introduction

Nickel, a naturally occurring metal element, is widespread in the environment (ATSDR, 2005). Due to the unique properties about physical and chemical, nickel and its compounds are used in a wide variety of manifold industrial and commercial products (ATSDR, 2005). The high consumption of nickel nowadays inevitably leads to the environmental pollution, which becomes a great threat to public health (Aleksandra and Urszula, 2008). The general population is widely exposed to nickel through air, water, and food. The known health-related adverse effects of nickel exposure include allergic contact dermatitis, pulmonary fibrosis, and increased risk of cancer (Denkhaus and Salnikow, 2002; Berge and Skyberg, 2003; Hamann et al., 2013).

Nickel can transfer readily across the placenta barrier and appear in fetal blood and amniotic fluid (Sunderman, 1977; Klopov, 1998; Hou et al., 2011). Animal studies have reported that nickel-

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induced embryotoxicity and fetotoxicity (Sunderman et al., 1977, 1978; Saini et al., 2013), including decreased fetal body weight, malformations, and death (Saini et al., 2014a, 2014b). All those observations lead to the increase of the interest in the effects of nickel on fetuses and infants in humans, since the fetuses and infants are considered more sensitive and vulnerable to environmental threats compared with adults (Barker, 2004). The majority of previous research regarding nickel exposure during pregnancy and adverse birth outcomes were conducted in occupationally exposed people or residents living in contaminated area (Odland et al., 1999, 2004; Vaktskjold et al., 2006; Vaktskjold et al., 2007, 2008), and suggested a significantly increased likelihood of congenital malformations and prematurity associated with nickel exposure (Chashschin et al., 1994; Quansah and Jaakkola, 2009). However, studies on the associations and nickel exposure at environmental levels and birth outcomes are limited (Guo et al., 2010; Zheng et al., 2014).

Preterm delivery, defined as born alive occurring before 37 completed weeks (WHO, 2016) is a continued health concern internationally (Goldenberg et al., 2008; Lawn et al., 2010). Premature is considered as the leading cause of neonatal mortality and morbidity, and is associated with significant financial burden and pose serious health issue to mothers and neonates (Wen et al., 2004; Soilly et al., 2014). Furthermore, the potential negative impact also extends to later life periods and may have long-term medical, psychological, behavioral, and social outcomes (Bhutta et al., 2002; Allin et al., 2006a, 2006b; Moster et al., 2008; Yang et al., 2010).

The underlying mechanism of preterm delivery remains largely unexplained, despite some potential risk factors have been identified to be associated with an increased risk of preterm delivery. Oxidative stress and inflammatory response are thought to play a role in the etiology of premature labor (Buonocore et al., 2002). Some animal studies indicated that nickel triggers oxidative stress through modification in the antioxidant capacity and could directly induce lipid peroxidative damage to the placental membrane (Chen and Lin, 1998; Kakela et al., 1999). Furthermore, nickel is capable of evoking an inflammatory response (Viemann et al., 2007). These previous studies give us biologic plausibility to hypothesize that maternal exposure to higher levels of nickel during pregnancy may contribute to preterm delivery.

Given limited data on the effects of maternal exposure to nickel at environmental levels on pregnancy duration, we conducted a large population-based prospective birth cohort study to examine the associations of maternal exposure to nickel with preterm delivery among 7291 pregnant women in Hubei province of China.

2. Materials and methods

2.1. Study population

The population in the present investigation were drawn from the Healthy Baby Cohort (HBC) study, which is an ongoing prospective cohort study was designed to examine potential role of environmental chemicals on the health of mothers and their offspring. Details of the HBC study have been described in previous reports (Xia et al., 2016). In brief, a total of 11,311 pregnant women who delivered a liveborn singleton were recruited from medical center, Wuhan Medical and Health Center for Women and Children, China, between September 2012 and October 2014. For this study, we restricted the analysis in pregnant women with urine samples for nickel measurements (n = 7303). We further excluded women who continued smoking (n = 7) and drinking (n = 2) during pregnancy. For women who participated in the cohort with more than one pregnancy during the study period (n = 3), we chose the first delivery record. Finally, a total of 12 pregnant women were excluded, leaving 7291 participants were analyzed in this study.

Ethical approval for the study was obtained from ethics committee of the School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, and the study medical center. All participating population provided their written informed consents prior to any study-related activities.

2.2. Data collection and outcomes

Standardized face-to-face interviews were conducted at the hospital by experienced trained nurses. The questionnaire consists of information about maternal demographic and socioeconomic (e.g., maternal age at enrollment, maternal height, self-reported maternal pre-pregnancy weight, pregnancy-induced hypertension, education, occupation, family annual income, iron, and folic acid supplement use) and lifestyle factors (e.g., smoking, passive smoking status, and alcohol consumption). The pre-pregnancy body mass index (BMI) of women was calculated based on their self-reported weight and height before pregnancy. Medical records were reviewed to collect additional data on delivery and disease. All the pregnant women in this study had ultrasound examinations in the first trimester. To corroborate gestational age, we used a first-trimester ultrasound to estimate the length of gestation instead of self-reported last menstrual period.

Based on clinical presentation, preterm delivery was further classified into two subtypes: (1) spontaneous preterm delivery (following spontaneous labor or preterm premature rupture of the membranes) and (2) iatrogenic preterm delivery.

2.3. Sample collection and urinary nickel measurement

We collected urine samples from participants in trace element-free polypropylene cups during hospital admissions waiting for delivery (the range of gestational age of urine collection was 29.0–42.0 weeks, mean 38.8 weeks). All urine samples were frozen at −20 °C until needed for the assay. For the preparation of the urine analysis of nickel, urine samples were defrosted at ambient temperature and homogenized by shaking, each 1 ml of the urine samples was incubated with 4 ml 3% HNO_3 for overnight nitrification, then the resulting sample was processed by ultrasound at 40 °C for 1 h. The urinary concentrations of nickel were determined using inductively coupled plasma mass spectrometry (ICP-MS) (Agilent 7700×, Agilent Technologies, Santa Clara, CA, USA). A comprehensive account of operation conditions of inductively coupled plasma mass spectrometry were the same as described previously reported (Xia et al., 2016). The detection limit (LOD) of nickel was 0.003 μg/L, and samples below LOD were substituted by the value of LOD divided by the square root of two. The certified reference standards for urinary metal (SRM2670a, National Institute of Standards and Technology, USA) was used as the external quality control in each batch to evaluate the instrument performance, and the concentrations measured were within the certified range (5%). Urinary nickel concentrations were corrected by urinary creatinine to control for variations in urine dilution, and expressed as μg/g creatinine.

2.4. Statistical analysis

The analysis of Wilcoxon signed-rank test was used to compare urinary creatinine-corrected nickel concentrations among different categories of sociodemographic characteristics. To test if there was a positive or negative association, we first included both nickel and gestational age as continuous variables in the statistical models. Given that clinical or population significance of an exposure related