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Association between maternal urinary chromium and premature rupture of membranes in the Healthy Baby Cohort study in China☆

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Chromium exposure from increasing industrial releases has become a threat for pregnant women due to the potential health effects on vulnerable embryos. Previous studies have suggested that maternal chromium exposure is associated with adverse birth outcomes, but no epidemiological research has been conducted to examine the relationship between chromium exposure and premature rupture of membranes (PROM). This study aimed at investigating the association of maternal urinary chromium exposure levels with PROM and was performed with 5408 pregnant women recruited from 2012 to 2014 in the city of Wuhan, China. Maternal urinary chromium collected before labor was adjusted with creatinine, and its association with PROM was evaluated using logistic regression. Each one unit increase in the natural logarithm transformed maternal urinary chromium concentration (μg/g creatinine), an odds ratio (OR) of 1.47 [95% confidence interval (CI): 1.36, 1.58] for PROM was observed. Compared to the lowest tertile of maternal urinary chromium, PROM was positively correlated with increased urinary levels of chromium (adjusted OR = 1.42; 95% CI: 1.09, 1.84 for the medium tertile; adjusted OR = 2.77; 95% CI: 2.18, 3.52 for the highest tertile). Additionally, the association of chromium with PROM appeared to be more significant among male infants (adjusted OR = 3.52; 95% CI: 2.51, 4.94 for the highest tertile) than female infants (adjusted OR = 2.16; 95% CI: 1.52, 3.06 for the highest tertile) (p for interaction = 0.05). Our large birth cohort showed an association between maternal urinary chromium levels and PROM, and the association may differ by infant gender. Further studies from different populations are needed to confirm the observed association.

1. Introduction

Chromium, a naturally occurring mineral that persists in the earth's mantle, is extensively utilized to produce a variety of industrial metal alloy products (Wilbur et al., 2012). As a result, large amounts of chromium contaminant are released into the environment (Kotas and Stasicka, 2000). China is the largest chromium slag producing country in the world (Gao and Xia, 2011), and chromium pollution has become a huge environmental threat (Chai et al., 2009). Chromium has two primary valences and one is trivalent chromium, which is essential; whereas the other is hexavalent chromium, which is toxic (Wilbur et al., 2012). High chromium exposure may pose a significant risk for human health (Achal et al., 2013), since previous epidemiological studies have shown

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that chromium is linked to adverse effects on humans, such as mouth ulcers, indigestion, acute tubular necrosis, vomiting, abdominal pain, kidney failure and even death (Beaumont et al., 2008).

Pregnant women are known to be more susceptible to environmental contaminant exposures than the general population. In animal studies, evidence has shown that gestational exposure to higher levels of chromium caused abortion, lower birth weight, and adverse consequences on skeleton development and the reproductive system (Wilbur et al., 2012). In human studies, chromium exposures during pregnancy have been related to elevated risk of premature labor, low birth weight (Berry and Bove, 1997) (Xia et al., 2016), and congenital deformities (Eizaguirre-Garcia et al., 2000). However, the effect of maternal chromium exposure on premature rupture of membranes (PROM) has not yet been studied.

PROM, referred to membrane rupture spontaneously ahead of the onset of labor (Ural and Nagey, 1998), is one of the main causes of preterm deliveries and is related to chorioamnionitis, umbilical cord compression, placental abruption, and sepsis (Vuadens et al., 2003). Besides, PROM has been linked with not only short-term neonatal consequences but also long-term adverse neurodevelopmental outcomes (Clark and Varner, 2011). PROM occurring spontaneously at less than 37 gestational weeks is regarded as preterm PROM (Robertson et al., 1992). Preterm PROM is the major contributor to neonatal prematurity (Parry and Strauss, 1998), and is the main factor resulting in significant perinatal morbidity and mortality (Mercer, 2003; Ural and Nagey, 1998).

The cause of PROM has been shown to be multifactorial. Maternal exposure to environmental factors, such as air pollution, has also been reported to be associated with PROM (Dadvand et al., 2014; Wallace et al., 2016). The underlying mechanism of membrane rupture remains unknown. However, oxidative stress and inflammatory response have been shown to be involved and to play pivotal roles in inducing PROM by damaging the collagen content of fetal membranes (Fortunato et al., 2000; Longini et al., 2007; Simhan and Canavan, 2005; Wall et al., 2002). Previous studies have indicated that the pathophysiology of chromium includes oxidative stress that can enhance reactive oxygen species production and cause membrane damage (Stohs et al., 1999). Furthermore, chromium can increase the production of pro-inflammatory cytokines (Granchi et al., 1998), which can result in the impairing and rupturing of membranes (Challis et al., 2009). Through these mechanisms, chromium exposure during pregnancy may also possibly have an impact on PROM and preterm PROM. Therefore, in the present study, we investigated the association of maternal exposure to chromium with PROM and preterm PROM based on our large mother-child birth cohort in China. As far as we know, it is the first epidemiological study in humans to evaluate the association between chromium, PROM and preterm PROM.

2. Materials and methods

2.1. Study participants

The Healthy Baby Cohort (HBC) is a prospective birth cohort study that recruited pregnant women at the Wuhan City Municipal Medical and Health Center for Women-Children in central China. Wuhan City Municipal Medical and Health Center for Women-Children is the main maternal and child health hospital in Wuhan City, and the majority of pregnant women who reside in Wuhan would give birth their babies in this hospital. Pregnant women were invited to participate in HBC during admission to the hospital while waiting for delivery, and the participation rate (number of participants/number of potentially eligible women) was over 78%. The details of the cohort have been described in previous studies (Yang et al., 2016).

A total of 11,311 pregnant women were recruited between September 2012 and October 2014, and 7364 of these pregnant women who donated maternal urine samples were included in this study. For this analysis, we excluded participants who continued smoking ($n = 7$) and drinking ($n = 2$) during pregnancy, since evidence has shown smoking or drinking during pregnancy has adverse effects on fetal growth, and the small number of this smoking or drinking group did not allow them to be treated as covariates. We also excluded women who delivered a newborn with congenital malformations ($n = 62$), which may be the result of an abnormal pregnancy. For women who gave birth twice in the study period, we excluded the second delivery record ($n = 3$). Moreover, in accordance with World Health Organization guidelines to avoid too concentrated or too dilute creatinine concentrations in the urine samples (WHO, 1996), urinary samples with creatinine more than 3 g/L and less than 0.3 g/L ($n = 1882$) were excluded as well. Finally, this left 5408 pregnant women for the present study.

All participants of the birth cohort were ensured to have a full understanding of the research procedure and assigned written informed consent when enrolled. Ethics approval for our study was acquired by the Ethical Committee of Tongji Medical College, Huazhong University of Science and Technology, and the study hospital.

2.2. Data collection and outcomes

All members of the study population were interviewed face-to-face after delivery by experienced trained nurses to gather socioeconomic information (e.g., maternal age, educational background, and occupational status) and daily life habits (alcohol and tobacco use). Passive smoking during pregnancy was assessed as pregnant women who reported exposure to second-hand smoke in the household or workplace (Vardavas et al., 2016). The pre-pregnancy body mass index (pre-BMI) of the participants was computed based on their self-reported weight and height before pregnancy, and was categorized into three levels (underweight: < 18.5 kg/m^2, normal: 18.5–23.9 kg/m^2, overweight: ≥ 24 kg/m^2) according to the standard BMI cutoffs which were suitable for the Chinese (Zhou, 2002). Reproductive and medical histories, including current maternal diseases, and maternal pregnancy complications, were acquired from medical records. Maternal gestational week was determined by last menstrual period (LMP) and ultrasound information. If these two methods differed by over 7 days, the gestational age was based on the ultrasound data for the concerns of reliability of recalled LMP estimate.

PROM was referred to membrane rupture spontaneously ahead of the onset of labor. The diagnosis of PROM was confirmed by the visualization of amniotic fluid passing from the cervical canal to the vagina with a pH greater than 6.5 for vaginal fluid (amniorrhea). PROM was classified as preterm PROM when the rupture occurred before 37 weeks of gestation.

2.3. Urine sample collection and chromium exposure measurement

Urine sample collection from the women was obtained within 3 days before delivery at the time when they were admitted to hospital (the range of gestational age of urine collection was 32.0–42.0 weeks, mean 39.2 weeks). For the pregnant women with self-reported amniorrhea or bloody show before they were admitted to hospital, urine samples were not collected if they underwent vaginal delivery because amniorrhea or blood may influence the analysis of metals in urine; while urine samples were collected through the urinary catheter before the women were