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Associations between prenatal lead exposure and birth outcomes: Modification by sex and GSTM1/GSTT1 polymorphism

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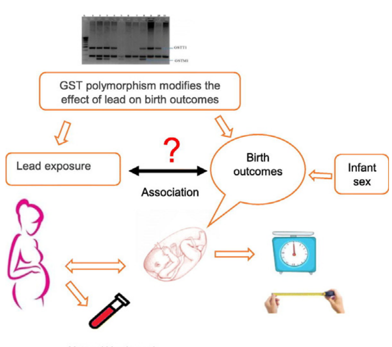
HIGHLIGHTS

- Lead concentrations were determined in both maternal blood and cord blood.
- Relation of lead with birth outcomes was explored in 782 mother-newborn pairs.
- GSH-related genes may modify the lead-birth outcomes relationship.
- Effect of GSH genes on lead-birth outcomes relationship differed by neonatal sex.

GRAPHICAL ABSTRACT



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ABSTRACT

Maternal lead exposure is associated with poor birth outcomes. However, modifying effects of polymorphism in glutathione S-transferases (GST) gene and infant sex remain unexplored. Our aim was to evaluate whether associations between prenatal lead and birth outcomes differed by maternal GST genes and infant sex. Prospective data of 782 mother-child pairs from Mothers and Children's Environmental Health (MOCEH) study were used. The genotyping of GST-*mu 1* (GSTM1) and *theta-1* (GSTT1) polymorphisms was carried out using polymerase chain reaction. Multivariable linear regression was used to examine whether the association between blood lead (BPb) level and birth outcomes (birthweight, length, and head circumference) varied by maternal GST genes and sex. We did not find a statistically significant association between prenatal BPb levels and birth outcomes; in stratified analyses, the association between higher BPb level during early pregnancy and lower birthweight ($\beta = -224$ per square root increase in BPb; 95% confidence interval (CI): -426, -21; false discovery rate $p = 0.036$) was significant in males of mothers with GSTM1 null. Results were similar for head circumference model ($\beta = -0.78$ per square root increase in BPb; 95% CI: -1.69, 0.14, $p = 0.095$), but the level of significance was borderline. Head circumference model showed a significant three-way interaction among BPb during early pregnancy, GSTM1, and sex ($p = 0.046$). For combined analysis with GSTM1 and GSTT1, GSTM1 null and GSTT1 present group showed a significant inverse association of BPb with birthweight and head

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circumference in males. Our findings of the most evident effects of BPb on the reduced birthweight and head circumference in male born to the mother with GSTM1 null may suggest a biological interaction among lead, GST genes and sex in detoxification process during fetal development.

1. Introduction

Despite progress in reducing blood lead (BPb) levels in general population over the past several decades, the health risks associated with low-level exposure to lead still continuous because of its widespread use (Lin et al., 2011). In particular, lead can have adverse effects on birth outcomes when its exposure occurs in the prenatal period (Needleman, 2004). However, previous studies on the association of BPb concentration in pregnancy with the birth outcomes have reported mixed results at all levels of exposure; while some have linked lead exposure and birth outcomes (Nishioka et al., 2014; Xie et al., 2013), others have not (McMichael et al., 1986; Taylor et al., 2016). Poor birth outcomes remain a major public health concern as they are known to be associated with poor developmental, behavioral, and metabolic disorders that may persist into adult life (Fisher et al., 2006).

There are several sources of BPb levels in general population, such as household lead piping, lead-laden home dust accumulation, dirt floors, proximity to dirt streets, lead-related industries, smoking, or intense traffic way (Azayo et al., 2009; Martins et al., 2014; Shen et al., 1997). The Centers for Disease Control and Prevention (CDC) identifies pregnant women with certain dietary and lifestyle risk factors are at increased risk of lead exposure in the United States (Centers for Disease Control and Prevention, 2010). Korean pregnant women may be particularly at increased risk of lead exposure due to the consumption of the typical Asian diet based on rice, fish, vegetables, regular coffee, and alcoholic drinks (Kim et al., 2016; Park and Lee, 2013). The mean BPb level among childbearing Korean women was 1.6 μg/dL in 2008–2009 (Korea Centers for Disease Control and Prevention, 2012), and the level in the United States was 1.2 μg/dL in 2003–2004 (National Center for Health Statistics, 2005). Changes in BPb concentrations during pregnancy have been observed in several studies (Hertz-Picciotto et al., 2000; Nishioka et al., 2014; Rothenberg et al., 1994): a decrease (1.1 μg/dL) in mean BPb from week 12 to week 20 of gestation and an increase (1.6 μg/dL) in mean BPb from week 20 to delivery have been demonstrated in Mexico city (Rothenberg et al., 1994). The mechanism of such U-shaped changes in BPb during pregnancy is not known but may be related to alterations in gastrointestinal absorption and bone storage of lead during pregnancy (Gulson et al., 1997). There is a larger demand of calcium during pregnancy that results in a greater bone mobilization (Kovacs and Kronenberg, 1997), releasing lead stored in bone into circulation and resulting in an endogenous source of prenatal exposure. Lead in maternal blood can readily pass through the placenta and enter the fetus circulation, making the fetus vulnerable to the effects of lead exposure (Nashashibi et al., 1999). Therefore, even low-level lead exposure early in life may impair infant growth and development (Bellinger, 2008).

Oxidative stress has been proposed as a mechanism by which heavy metal, including lead, affects fetal growth (Lopes et al., 2016). Glutathione S-transferases (GST) play an essential role in the defense against oxidative stress as they catalyze the conjugation of glutathione with various reactive intermediates and also display peroxidase activities (Hayes and Strange, 2000). The GST (GSTs; GST *theta* 1, GSTT1; GST *mu* 1, GSTM1) genes are highly polymorphic in the human population (Schneider et al., 2004), which may be partly responsible for the interindividual differences in phenotypic variations of enzymatic activity. Of the GST *mu* class of isoenzymes, GSTM1 enzymes are the most widely expressed (Hayes and Strange, 1995). Thus, these GSTM1 null individuals may experience greater oxidative stress and, as a result, greater impairment in reproductive outcomes associated with lead exposure due to their inability to clear particular reactive compounds. Studies have demonstrated associations between genetic susceptibility in GST genes and reproductive outcomes, including birth weight, preterm delivery, and small-for-gestational births (Infante-Rivard et al., 2006; Nukui et al., 2004; Thompson et al., 2014).

Prior studies on the interactive effect of GST gene and heavy metals (lead and mercury) on health outcomes did not distinguish between male and female genders (Eum et al., 2013, 2015; Lee et al., 2010). It is likely that maternal lead exposure affects birth outcomes differently in male and female fetuses (Vahter et al., 2007). In order to advance understanding of mechanisms of the lead-birth outcomes relationship, it is important to consider the sex-dependent effects of lead. However, the interactive effects of lead, GST gene, and sex have not previously been examined. In this study, we used prospectively collected information on maternal or cord BPb level to examine differential associations between lead exposure and birth outcomes related to maternal GST polymorphisms and infant sex, hypothesizing that there is a combined association between these genes and sex and the birth outcomes.

2. Materials and methods

2.1. Study subjects

Participants in the current study were drawn from the Mothers and Children's Environmental Health (MOCEH) study. As described previously (Kim et al., 2009), MOCEH study had collected information on sociodemographic characteristics, lifestyle factors, medical history, and maternal anthropometry by trained interviewers, and birth outcomes of neonates were extracted from medical records. In this study, participants were restricted to those in which maternal and cord BPb levels were assessed, and birth outcomes measurements were performed. After excluding subjects lost to follow-up before birth ($n = 276$), 1475 participants were eligible for enrollment in the study. Of these 1475 women, 583 were excluded for the following reasons: multiple births and abortion ($n = 26$); congenital anomalies ($n = 4$); gestational diabetes and hypertension ($n = 55$); smoking ($n = 10$); and missing information on maternal age ($n = 52$), prepregnancy weight ($n = 83$), height ($n = 30$), education level ($n = 11$), gestational age ($n = 2$), parity ($n = 153$), urinary cotinine level ($n = 101$), GST genotype ($n = 19$), and dietary folate intake ($n = 110$). Of the remaining 794 participants, the missing information of lead levels and birth outcomes were removed. The final sample size was varied for different outcomes, ranging from 468 to 782 pregnant women and their infants. The details of final sample size are shown in the Supplementary file (Fig. S1). There were no significant differences in general characteristics of pregnant women at recruitment and their newborns at birth between the included and excluded participants (Table S1). This study was conducted under the approval of the ethics committee of the MOCEH. The MOCEH study was approved by three institutional review boards, namely Ewha Womans University, Dankook University Hospital, and Ulsan University Hospital. Written informed consent was obtained from all participants after explaining the purpose and procedures of the study.

2.2. Measurement of exposure

The measurement procedures for BPb level in the MOCEH study have previously been reported (Hong et al., 2014). The whole blood samples were collected during early pregnancy (12–20 gestational