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Prenatal maternal stress in relation to the effects of prenatal lead exposure on toddler cognitive development

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ABSTRACT

Objective: To evaluate the effects of maternal lead exposure during pregnancy on toddler cognitive development and the potential effect modification by maternal stress.
Methods: We conducted a prospective birth-cohort study in Shanghai from 2010 to 2012 and investigated 225 mother-infant pairs. The mothers were recruited in mid-to-late pregnancy and children were followed up until 24–36 months old. A self-administered Symptom Checklist-90-Revised Scale (SCL-90-R) was used to assess maternal emotional stress during pregnancy. Maternal whole blood lead levels were measured during gestational weeks 28–36. The toddlers' cognitive levels were assessed using the Gesell Development Scale. Multiple linear regression models were established to explore the main effects of prenatal lead exposure on toddlers' cognitive abilities and the modifying effects of maternal stress. Covariate information was collected through interviews, questionnaires and medical records.
Results: The mean maternal blood lead concentration was 3.30 (95%CI: 3.05, 3.57) μg/dL. After adjusting for relevant confounders, no significant associations of maternal blood lead concentrations with toddlers' cognitive levels were observed in all five domains of the Gesell scale ($P > 0.05$). However, the interaction between prenatal maternal blood lead and stress was significant in the domains of adaptive behavior, language and social behavior. When stratified by maternal stress levels, compared with non-significant associations ($P > 0.05$) among low (P1-P75) prenatal stress group, adverse associations between maternal blood lead concentrations (log10-transformed) and toddlers' cognitive levels were observed among high (P75-P100) prenatal stress group in the domains of language ($\beta = -33.82$, 95%CI: −60.04, −7.59), social behavior ($\beta = -41.00$, 95%CI: −63.11, −18.89) and adaptive behavior ($\beta = -17.93$, 95%CI: −35.83, −0.03).
Conclusion: Prenatal maternal stress may exacerbate the deleterious effects of prenatal exposure to lead on toddler cognitive development.

1. Introduction

Maternal exposure to chemical, physical and emotional risk factors during pregnancy affects children's health in both the short and long term and may be a potential origin of diseases into adulthood (Gaspar et al., 2015; Lertxundi et al., 2015; Xu et al., 2015)

Lead exposure remains a pediatric problem both in developed and developing countries (Brink et al., 2016; Li et al., 2014). Previous studies demonstrated that prenatal lead exposure alone impaired the unborn child's brain, causing cognitive dysfunction, attention deficits, early high school dropout, and a higher rate of juvenile delinquency later in life (Bellinger, 2008). Scientific evidence showed that no safe level of exposure to lead existed and that developmental impairments in the fetus may be induced at a blood lead level lower than 10 μg/dL (Silver et al., 2016). The United States Centers for Disease Control issued guidelines regarding the management of lead exposure in pregnant and lactating women, recommending that blood lead levels in pregnant women should be below 5 μg/dL (Burns and Gerstenberger, 2014).

The developmental neurotoxicity induced by prenatal stress has been observed in epidemiological studies and animal experiments. Prenatal stress would impair the neurodevelopment of the fetus and exert its detrimental and long-lived effects, including mental and psychomotor deficits in children (Richetto and Riva, 2014). A study conducted in London demonstrated that the levels of prenatal stress predicted mental development of infants at ages of 14 to 19 months old (Bergman et al., 2007). Prenatal maternal stress appeared to be a potential determinant of delay in motor and

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mental development in infants at 8 months of age (Huizink et al., 2003).

Previous animal experiments demonstrated that prenatal stress may exacerbate the negative effects of prenatal lead exposure on the stress responsivity (Virgolini et al., 2006), learning ability (Cory-Slechta et al., 2010), and cognitive development in the offspring (Cory-Slechta et al., 2004). Compared with single exposures, mixed exposures of neurotoxic chemicals and social hazards occur more often and pregnant women can hardly avoid the risk of concurrent exposure. Considering the complexity of maternal exposure, especially the susceptibility of the low socio-economic-status population to maternal concurrent exposure to stress and lead during pregnancy, as well as the extreme vulnerability of the fetus to these two prenatal risks, researches on the effects of prenatal combined exposure to lead and stress may have more practical values than those only considering the effects of a single exposure.

Stress is a state of threatened homeostasis. Although previous studies investigated the interaction between adverse circumstances (poverty, social distress or low self-esteem) and lead exposure on child neurodevelopment (Bellinger, 2000; Dietrich et al., 1987; Moodie et al., 2013; Surkan et al., 2008; Tong et al., 2000; Winneke and Kraemer, 1984; Xu et al., 2015), few human studies focused on the interaction effects of prenatal lead and stress exposures on child cognitive development. Therefore, in this study, we performed a prospective birth-cohort study to examine the effects of prenatal lead exposure on the cognitive abilities of toddlers and to identify whether maternal stress would exacerbate deleterious effects induced by lead.

2. Methods

2.1. Study design and participants

In this Shanghai Stress Birth Cohort study, 398 mother-infant pairs were enrolled in prenatal clinics of maternity hospitals during mid-to-late pregnancy in 2010. Mother-infant pairs were followed-up until 24–36 months postpartum from 2010 to 2012. During pregnancy, a face-to-face interview was conducted at an antenatal examination to record maternal demographic information, including maternal age, family monthly income, education, occupation, marital status, family structure and health status. Symptom Checklist-90-Revised (SCL-90-R) was used to assess maternal emotional stress. The maternal blood lead concentration was examined at 28–36 weeks of gestation. The children's birth information was collected from medical records. When the children were around 24–36 months of age, interviews were conducted again to collect both maternal postnatal information and the toddlers' information, and the Gesell Development Scale was used to assess each infant's cognitive ability. The exclusion criteria included severe complications of pregnancy, infants with an Apgar score at 5 min of 7 or less, maternal psychiatric disorders based on the maternity medical record, and twin pregnancies (Lin et al., 2017). A total of 398 mother-child pairs were recruited, among which 173 pairs were lost to follow-up (flow chart shown in Fig. 1). Therefore, this resulted into 225 mother-child pairs. Among these study pairs, only 139 toddlers had prenatal maternal blood lead data, and the remaining 86 toddlers didn't have prenatal maternal blood lead data due to their mothers' unwillingness to be drawn blood. Therefore, this study included a total of 139 mother-child pairs. No significant difference was observed in the demographic information of mothers and children between participants who were followed-up and who were lost to follow up.

This study received ethics approval from the Institutional Review Boards of Xinhua Hospital affiliated with the Shanghai Jiao Tong University School of Medicine. The women were informed of the study aims and procedures and signed appropriate informed consent forms before enrollment.

2.2. Measures

2.2.1. Maternal prenatal stress levels

The emotional stress quantifies an individual's reaction to a traumatic event, and refers to mother's feelings, e.g. irrational fear, hopelessness, and irritation, often along with the associated elevation of glucocorticoids. Previous studies investigating maternal stress during pregnancy have applied measures of maternal emotional stress (Beydoun and Saftlas, 2008; Mohler et al., 2006; Tillett, 2011), and the SCL-90-R was considered a good measure of maternal emotional stress levels (Mohler et al., 2006; Tillett, 2011). The levels of psychological symptoms reflected the levels of emotional stress. SCL-90-R is a 90-item self-reported symptom inventory oriented to measure levels of psychological symptoms or emotional stress. The SCL-90-R has nine primary symptom dimensions including somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism, and the Global Severity Index (GSI) is used to describe the overall psychological distress level. A higher GSI score indicates a greater level of emotional stress (Derogatis and Unger, 2010). The Chinese version of SCL-90-R has been repeatedly demonstrated to be valid and consistent as a measure of recent emotional stress levels (Tan et al., 2015).

2.2.2. Maternal blood lead levels

Five milliliters of maternal whole blood were collected during mid-to-late pregnancy, and sampling procedures and containers were kept lead-free. The maternal blood lead level during mid-to-late pregnancy was tested using atomic absorption spectrometry (PinAAcle 900Z, PerkinElmer) with a limit of detection of 0.01 μg/dL (Dietrich et al., 2001). All the blood lead levels were above the limit of detection.

2.2.3. Toddler cognitive development

The toddlers' cognitive levels were assessed using the Gesell Development Scale by the two experienced examiners. For assessing reliability, the kappa index and the paired *t*-test result showed that the inter-rater agreement was very good. The Gesell Development Scale has 5 domains, including gross motor, fine motor, adaptive behavior, language, and social behavior. Higher developmental quotient (DQ) scores mean higher cognitive levels (Zhu et al., 2014). The Chinese version of the Gesell Development Scale has been widely used in previous studies (Jin et al., 2014).

2.2.4. Covariates

The covariates included maternal age at enrollment, economic status, maternal education, gestational week, child sex, birth weight and age. The information on covariates was collected through interviews and medical records.

2.3. Statistical analyses

The associations of the demographic characteristics of the study participants with DQ scores were analyzed using linear regression models. The unadjusted and adjusted associations between maternal blood lead concentrations (log10-transformed) and DQ scores were evaluated. Previous studies suggested potential interaction effects of prenatal lead exposure with prenatal maternal stress on neurodevelopment using animal experiments (Cory-Slechta et al., 2010, 2004; Virgolini et al., 2006, 2008), therefore, the models with the interaction term between maternal blood lead levels and stress were estimated to assess the modifying