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Lead exposure at each stage of pregnancy and neurobehavioral development of neonates

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ABSTRACT

Purpose: Our pilot studies showed that there was a significant relationship between blood lead levels of women at the first trimester and scores of neonatal behavioral neurological assessment (NBNA). This study went further (1) to determine particular neurotoxicity during a specific trimester, (2) to analyze "safe" levels of Pb in neonates, and (3) to identify influencing factors for prenatal Pb exposure.
Method: A total of 415 mothers with newborn located Shenzhen, Guangdong, China participated in the study: 219 in the high lead group [blood lead levels (BLLs) at first trimester $\geq$ 4.89 μg/dl] and 196 in the low lead group [BLLs $\leq$ 1.96 μg/dl]. The maternal BLLs at each stage of pregnancy and delivery were measured by atomic absorption spectrophotometry, equipped with a graphite furnace. The developmental functioning of newborns was assessed with NBNA in 3 days. The children's birth outcome and the rest of information was obtained from their medical records or a comprehensive questionnaire from their parents, which contained demographic characteristics, lifestyle, IQ, occupation and influencing factors for lead exposure during and before first trimester, etc.
Results: Of 415 newborns, 332 (80.00%) had complete data collection for all variables at four-stage follow-up. The maternal mean BLL at first trimester for 332 newborns was 3.98 ± 1.15 μg/dl (0.38–15.86 μg/dl) and the geometric mean (GM) was 3.63 ± 0.35 μg/dl (95%CI: 2.98–4.32 μg/dl). In total, about 4.82% of newborns had maternal BLLs > 10 μg/dl. Significant inverse associations have been found between the maternal BLLs at the first trimester and the NBNA scores ($P < 0.05$). Drinking milk and supplements of Ca, Fe, or Zn are protective factors of high BLLs (OR = 0.363, $P < 0.05$).
Conclusion: Our study demonstrate that fetal lead exposure as low as 5 μg/dl has an adverse effect on neurodevelopment, most expressed during the first trimester and best arrested by measuring maternal BLLs. The collective evidence indicates that screening and intervention after the first trimester may be too late to prevent the fetal neurotoxic effects.

1. Introduction

Despite remarkable successes in recent decades in abating key sources and pathways of exposure, lead remains an important pediatric environmental health problem in both developed and developing countries (Bellinger, 2013). Lead is a ubiquitous environmental pollutant that can cross the placental and blood–brain-barriers and induce neurotoxicity. Even exposure to low doses of toxic lead has been found to be dangerous (Papanikolaou et al., 2005; Yu et al., 2011). Recent studies prompted to reduce the amount of lead exposure deemed safe during childhood, suggesting that the current screening guideline (10 μg/dl) might be a risk management tool for protecting children from lead poisoning (Bellinger, 2013; Papanikolaou et al., 2005; Bellinger, 2008; CDC, 2012).

A related issue about the neurotoxic effect of fetal lead exposure has received less concern. This issue has emerged as a potentially large pediatric health problem because of three recent insights. Firstly, the skeleton accumulates lead as the major endogenous

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source. About 95% of Pb is contained in the adult skeleton. Pb can persist in bone for decades after exposure. Endogenous lead exposure is an important independent predictor of adverse health outcomes (Cretacci and Parsons, 2010; Gulson et al., 2003). Secondly, during pregnancy, maternal bone turnover is high, providing calcium for the developing fetal skeleton. As a consequence, mothers with higher lead burdens release more lead from bone. With Pb crossing the placenta and blood–brain barriers, fetuses are at risk of in-utero Pb exposure (Bijoor et al., 2012). Lastly, Pb is highly and selectively toxic to the central nervous system (CNS). The developing CNS is a prime target for the disruptive effects of in-utero Pb exposure, as the brain undergoes its most rapid period of maturation during fetal life. Therefore, fetuses are more vulnerable to lead exposure (Bijoor et al., 2012; Goyer, 1990; Wan et al., 1996). However, across studies of the neurodevelopmental impacts of fetal lead exposure, a lot of inconsistency is still existed, e.g., some have shown an inverse association (Bellinger et al., 1987; Shen et al., 1998) and some have not (Cooney et al., 1989; McMichael et al., 1988). Some studies measured maternal BLLs during the second and third trimesters and at delivery (Baghurst et al., 1987; Schnaas et al., 2006), whereas others did in the first or second trimester (Dietrich et al., 1987), in mid-pregnancy and at delivery (Wasserman et al., 1997), or at delivery only (Cooney et al., 1989; Ernhart et al., 1986). Some studies relied solely on umbilical cord blood lead level as the index of prenatal exposure (Bellinger et al., 1987). The inconsistency across these studies might be attributed to no strictly discriminating prenatal and postnatal lead exposure and the variability in the assessment and timing of does to the fetus (Hu et al., 2006). The toxicokinetics of lead in the maternal–fetal unit are poorly understood. Although research has shown the adverse effects of childhood at low lead exposure, the "safe level" and the critical windows of greatest susceptibility are still in question. A pooled analysis has revealed that BLLs as low as 5 μg/dl can be associated with disturbances in early mental growth in children (Lanphear et al., 2005). Studies suggest that lead exposure in the third trimester, especially around week 28, may be more strongly associated with decreased cognitive development (Schnaas et al., 2006), whereas others found that the impacts were most strongly associated with first trimester BLLs (Hu et al., 2006). Further, there is still no clear safe screening guideline to reduce lead burden before pregnancy or to limit fetal exposure during pregnancy (Leiba et al., 2010). Until now, the impact of prenatal lead exposure on neurodevelopment remains unclear in terms of consistency, the trimester of greatest vulnerability, and the "safe level" for estimating fetal lead exposure. To assess fetal low lead exposure effects at each stage of pregnancy, more evidence is needed from cohort studies on neurocognitive deficits, especially from relatively large child population and low lead exposure from which to sample. China is the most populous developing country in the world, with increasing annually 20 million newborns considered to be the most susceptible to lead toxicity. Shenzhen city is one of the most economically developed areas in China. BaoAn district in Shenzhen city suffers intermediate environmental contamination. Our pilot studies showed that there was a significant relationship between blood lead levels of women at the first trimester and scores of neonatal behavioral neurological assessment (4.86 μg/dl) and scores of NBNA (neonatal behavioral neurological assessment) ($r = -0.331$) (Yan et al., 2010).

Therefore, the main objectives of this study were (1) to determine particular neurotoxicity during a specific trimester, (2) to analyze "safe" levels of Pb in neonates, and (3) to identify influencing factors for prenatal Pb exposure. To avoid the methodological limitations of retrospective studies, our present study has the following advantages: the time sequence, a reduced recall and selection bias (i.e., minority sample attrition), obtaining BLLs by subsequent measurements during each trimester and delivery, and finishing NBNA in 3 days.

2. Materials and methods

2.1. Study subjects

Referring to the study design of Bellinger et al. (1987), at BaoAn district Maternal and Child Health Center prenatal clinic located in Shenzhen city, between January 2009 and 2010 January, 3686 early-pregnant women (10–14 weeks) were voluntarily recruited. The following exclusion criteria were applied to the mothers: non-resident of the city; planning to leave the area within 5 years; daily consumption of alcoholic beverages; addiction to illegal drugs; continuous use of prescription drugs; diagnosis of multiple pregnancy, preeclampsia, renal or heart disease, gestational diabetes, and use of corticosteroids (Hu et al., 2006). In addition, newborns also had to satisfy the following criteria: absence of a medical condition considered to be a risks factor for development difficulty (e.g., Down's syndrome, cleft palate, gestational age <5 weeks; maternal consent to be contacted). In recruiting our longitudinal sample from this population, all mothers were informed about the nature and the aims of the study and given information on ways to minimize lead exposure. All signed a letter of informed consent. The research protocol was approved by the Medical Ethics Committee of the hospital and our University. Trained staff screened the potential subjects for eligibility via structured face-to-face interview to ensure that they met the criteria. In the end, 2306 blood specimens were collected and measured at first trimester. On the basis of distribution of blood lead levels (BLLs): below the 25th percentile (low), and above the 75th percentile (high), the two exposure groups (high lead group: BLLs $\geq$ 4.89 μg/dl, $n = 219$; low lead group: BLLs $\leq$ 1.96 μg/dl, $n = 196$) were established. They were followed up at the mid-pregnancy (20–24 weeks), late pregnancy (30–34 weeks), delivery and 3 days postpartum (testing NBNA). The infants whose mother had BLLs between 25th and 75th quartile were excluded from the following NBNA test. At the mid-pregnancy, 26 participants withdrew owing to abortion (high, $n = 2$; low, $n = 1$), transferred to another hospital (high, $n = 5$; low, $n = 4$), and withdrew voluntarily (high, $n = 8$; low, $n = 6$). At the late pregnancy, 29 participants withdrew owing to obstetric complications (high, $n = 7$; low, $n = 5$), transferred to another hospital (high, $n = 6$; low, $n = 4$), and withdrew voluntarily (high, $n = 3$; low, $n = 4$). At the four-stage follow-up (3 days postpartum testing NBNA), more strict exclusion criteria were then used and another 28 participants were excluded: 5 for premature delivery (high, $n = 3$; low, $n = 2$), 3 for postterm pregnancy (high, $n = 2$; low, $n = 1$), 4 for low birth weight (high, $n = 2$; low, $n = 2$), 2 for fetal macrosoma (high, $n = 1$; low, $n = 1$) 10 for neonatal jaundice (high, $n = 4$; low, $n = 6$) and 4 withdrew voluntarily (high, $n = 2$; low, $n = 2$). As a result, 332 mother-newborn pairs completed the four-stage research: 174 in the high lead group and 158 in the low lead group. The other 83 subjects failed to complete the study for above-mentioned reasons.

2.2. Blood sample collection and analysis

Using a strict research protocol, fasting blood samples were obtained from the antecubital vein of each trimester periods and umbilieal cord blood by trained nurses in a lead-free, heparinized vacutainer. Collection tubes were refrigerated and transported to the Center Laboratory at Public Health College of our University no later than 24 h for lead analyses. BLLs were measured by atomic absorption spectrophotometry, equipped with a graphite furnace (Varian AA-DUO). Our laboratory has participated successfully in a CDC-administered quality-control program (Blood Lead Proficiency