論文の内容の要旨

論文題目：**Impact of Prenatal Heavy Metals Exposure on Birth Outcomes and Newborns Leucocytes Telomere Length in Myanmar**

（妊娠期における重金属暴露が出生アウトカム及び新生児の白血球テロメア長に与える影響：ミャンマーにおける研究）

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ABSTRACT

Introduction: Arsenic, cadmium and lead are well-known environmental contaminants and their toxicity at low concentrations is a target of scientific concern. Through trans-placental exposure, these metals can accumulate in fetal tissues, extending the risk of fetal toxicity. Meanwhile, heavy metals exposure appears to modify telomere length (TL), which may predispose a person to adverse health risks. Information on newborn TL is important because TL later in life is mainly influenced by TL at birth, meaning that having a short or long TL is greatly defined before adulthood. However, the determinants of TL at birth are unclear. This study aimed to examine the extent of heavy metals contamination among a Myanmar population. This study also identified the potential effects of prenatal heavy metals exposure on birth outcomes among pregnant women and newborns in Myanmar. In addition, this study determined whether prenatal heavy metals exposure has an impact on newborn leucocyte TL.

For a better understanding of the etiologic pathway, this study also determined whether heavy metals-induced TL shortening triggers the occurrence of adverse birth outcomes.

Methods: A birth-cohort study was conducted among 419 pregnant women and their newborns in Ayeyarwady Region, Myanmar. At their first visit during the third trimester, face-to-face interviews were performed using a pretested structured questionnaire and maternal spot urine samples were collected. Cord blood samples were collected by local skilled birth attendants at the time of delivery during follow-up after one to three months from the first visit. Urinary arsenic, cadmium, lead and selenium concentrations were measured by inductively coupled plasma mass spectrometry (ICP-MS) and adjusted for creatinine. TL was measured by quantitative real-time polymerase chain reaction and relative TL was calculated as the ratio of telomere repeats product to a single-copy gene (T/S ratio). We examined the extent of environmental exposure of arsenic, cadmium and lead during pregnancy and their associations with adverse birth outcomes, including low birth weight (birth weight < 2500 g regardless of gestational age at birth) and preterm delivery (any delivery before 37 weeks of gestation regardless of birth weight) using multivariable logistic regression analysis and adjusting for confounders. Associations between prenatal heavy metals exposure and TL were also assessed by the quartiles stratification of heavy metals concentrations using linear regression. Later, both bivariate and multivariate logistic regressions were performed to determine whether a shorter TL was associated with risks of adverse birth outcomes.

Results: The median values of adjusted urinary arsenic, cadmium, selenium and lead concentrations were 74.2, 0.9, 22.6 and 1.8 μg/g creatinine, respectively. The mean gestational age was 38.5 weeks (standard deviation (SD) = 1.9). Birth weight ranged from 1510 g to 6300 g with an average value of 3171.7 g (SD = 493.0). The median relative TL of the study population was 0.9 (interquartile range (IQR), 0.5 - 1.3). Multivariable logistic regression revealed that an increased risk of low birth weight was associated with higher maternal urinary cadmium exposure (lowest vs highest quartile, adjusted odds ratio (AOR) = 4.79, 95% confidence interval (CI): 1.25, 18.37, $p = 0.022$) after adjusting for maternal age, maternal education, the baby's sex, smoking status, primigravida, antenatal visits and selenium concentration. However, maternal heavy metals concentration was not significantly associated with preterm delivery. There was a strong and independent inverse association between prenatal arsenic (lowest vs highest quartile, coefficient = - 0.13, 95% CI: - 0.22, - 0.03, $p = 0.002$), cadmium (lowest vs highest quartile, coefficient = - 0.19, 95% CI: - 0.30, - 0.08, $p < 0.001$) and lead exposure (lowest vs highest quartile, coefficient = - 0.11, 95% CI: - 0.20, - 0.02, $p = 0.020$), and newborn TL, even after adjusting for maternal age, education, ethnicity, smoking status, parity, gestational age, mode of delivery, the baby's sex, birth weight and selenium concentration. Newborn TL was not significantly associated with any adverse birth outcome.

Conclusions: The present study determined that Myanmar mothers are highly exposed to cadmium. Prenatal maternal cadmium exposure was associated with an increased risk of low

birth weight. This is also the first study to determine the impact of prenatal heavy metals exposure on newborn TL. The present study also identified that arsenic, cadmium and lead exposure could shorten TL even *in utero* exposure. Since the TL at birth could predict the TL later in life, future public health measures should integrate interventions to reduce heavy metals contamination, with special emphasis on pregnant women. However, the risk of adverse birth outcomes was not associated with newborn leucocyte TL.

Keywords: heavy metals, birth outcome, telomere length, newborn, Myanmar