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Maternal and cord blood manganese (Mn) levels and birth weight: The MIREC birth cohort study

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ABSTRACT

Epidemiological studies have hypothesized that both insufficient and excess blood manganese (Mn) levels during pregnancy are associated with reduced fetal growth. This literature is characterized by inconsistent results and a limited focus on women with exposures representative of the general North American population. We examined the relationship between maternal and cord blood Mn levels and fetal growth among women enrolled in the Maternal-Infant Research on Environmental Chemicals Study (MIREC). Mothers with singleton, term infants and complete maternal first and third trimester blood Mn data were eligible for inclusion in the present study (n = 1519). Mean birth weight and odds ratios of small for gestational age (SGA) births according to maternal and cord blood Mn levels (low (< 10), referent (10– < 90), high (≥90) percentiles) were estimated. We also evaluated the association between the ratio of cord and maternal blood Mn and birth weight. Women with low (< 0.82 μg/dL) maternal blood third trimester Mn levels had infants that weighed an average of 64.7 g (95% CI: −142.3,12.8) less than infants born to women in the referent exposure group. This association was strengthened and became statistically significant when adjusted for toxic metals (lead, mercury, arsenic, and cadmium) [−83.3 g (95% CI: −162.4, −4.1)]. No statistically significant associations were observed in models of maternal first trimester or cord blood Mn. A one unit increase in the cord/maternal blood Mn ratio was associated with a 29.4 g (95% CI: −50.2, −8.7), when adjusted for maternal and neonatal characteristics. Our findings motivate additional research regarding the relation between Mn exposure and fetal growth. Further inquiry is necessary to determine whether an exposure threshold exists, how growth related effects of maternal and fetal Mn may differ, and how concurrent exposure to other toxic metals may impact the association between Mn and growth.

1. Introduction

Manganese (Mn), a naturally occurring metal and an essential micronutrient, is necessary for optimal fetal development (Mistry and Williams, 2011). Experimental studies demonstrate that insufficient developmental Mn exposure may impair growth, bone formation, immune function, metabolism (Aschner and Aschner, 2005; US ATSDR, 2012; Yoon et al., 2011), and neurodevelopment (Erikson et al., 2008). Similarly, epidemiologic research has reported that prenatal Mn deficiency is associated with adverse effects on neurodevelopment (Chung et al., 2015) and growth (Wood, 2009). Excess Mn has been associated with adverse childhood neurological outcomes as demonstrated in reviews of both experimental (Erikson et al., 2008) and human studies (Bjørklund et al., 2017). In addition, excess Mn has been associated with both reduced (Molina et al., 2012; Sanchez et al., 1993; Torrente et al., 2002) and excess birth weight (Betharia and Maher, 2012) in

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experimental studies.

In humans, it is well known that maternal blood Mn concentrations rise throughout pregnancy (Arbuckle et al., 2016), most likely to meet the increased demand for micronutrients necessary for fetal growth (Tholin et al., 1995; Zota et al., 2009); higher levels in umbilical cord blood have also been reported (Arbuckle et al., 2016; Zota et al., 2009). Mn is rapidly metabolized and cleared (US ATSDR, 2012); trimester specific measurements, therefore, are likely representative of recent exposure. The observed increases in Mn throughout pregnancy are primarily driven by pregnancy-related physiological changes (ie increased absorption) rather than increased exposure (Tholin et al., 1995). The main Mn sources in the general population typically come from diet and naturally occurring Mn in air, soil, and water. Anthropogenic sources of Mn, such as from power plants and other industrial operations, also contribute to environmental Mn exposure (US ATSDR, 2012; Health Canada, 2013).

Considering putative Mn adverse effects at low and high exposure, epidemiologists have hypothesized that the relation between Mn and birth weight is characterized by an inverse U-shaped curve. Cohort studies from the US (Zota et al., 2009), China (Chen et al., 2014; Guan et al., 2013), and Korea (Eum et al., 2014) and one case-control study from China (Xia et al., 2016) have reported curvilinear associations between either maternal or cord blood Mn levels and birth weight. Further, in a retrospective cohort study conducted in California, USA, elevated outdoor airborne Mn concentrations were associated with low birth weight (Basu et al., 2014). Similar associations between Mn and birth weight were not found in cohort studies from China (Yu et al., 2013) and Costa Rica (Mora et al., 2015) or a Spanish cross-sectional study (Bermúdez et al., 2015). One of the challenges of this limited body of literature is the inconsistency in timing (3rd trimester versus delivery) and the matrix of Mn measurement (urinary, whole blood, and ambient air). Also, studies with exposure levels representative of the general North American population are limited (Basu et al., 2014; Takser et al., 2004).

As Mn is an essential nutrient and is widely occurring in food, all women have detectable concentrations of Mn. Biomonitoring studies in North America report geometric mean blood Mn concentrations in women of 9.5 μg/L (Health Canada, 2013) and 10.6 μg/L (Oulhote et al., 2014). In 2013, 6.7% of births in Canada were low birth weight (< 2500 g), a predictor of multiple adverse child health outcomes (Statistics Canada, 2016). Considering the potential public health burden of reduced fetal growth and in light of the inconsistent findings regarding Mn-related effects, we examined the association between *in utero* Mn exposure and fetal growth in a Canadian birth cohort. Mn exposure was assessed via maternal and cord blood Mn concentrations. We evaluated fetal growth using measures of birth weight and small for gestational age (SGA).

2. Methods

2.1. Study population

A total of 1983 women were recruited to the Maternal-Infant Research on Environmental Chemicals (MIREC) study from 10 Canadian sites between 2008–2011 during their first trimester of pregnancy, as previously described (Arbuckle et al., 2013, 2016). Whole blood samples were collected during the first and third trimesters as well as venous umbilical cord blood at delivery for environmental chemical analysis. Women were eligible for inclusion if they were < 14 weeks gestation at time of recruitment, ≥18 years of age, able to communicate in French or English, and planning to deliver in a participating hospital. Women with known fetal or chromosomal anomalies in the current pregnancy or with serious medical complications were excluded from the study (Arbuckle et al., 2013, 2016). Of the 1983 women with available questionnaire and chemical data, 1648 mothers had complete maternal first and third trimester blood Mn data. Among these women, 1519 participants had a singleton, live, term birth and were included in the present study. Of these, 1214 women had complete cord blood Mn data.

Data on maternal and neonatal variables were extracted from questionnaires administered by research personnel, and from hospital charts by trained research nurses and staff. Ethics approval was obtained from the Health Canada ethics review board as well as ethics review boards at participating hospitals at all study sites. Eligible women signed informed consent forms prior to participating in the study.

2.2. Measurement of maternal and cord blood Mn concentrations

Maternal and cord blood samples were analyzed for Mn using a single-quadrupole Perkin Elmer inductively coupled mass spectrometry at the Centre de toxicologie du Quebec, Institut national de santé publique du Québec (INSPQ), Quebec, QC, Canada following 17,025 ISO guidelines as previously described (Arbuckle et al., 2016). Internal quality control (IQS) was ensured by analyzing non-certified reference materials from the Quebec Multielement External Quality Assessment Scheme (QMEQAS) (QM-B-Q1108, QM-B-Q1201) after calibration, every 10th sample, as well as at the end of each analytical sequence. The QMEQAS program is operated by the Centre de toxicologie du Québec (Institut national de santé publique du Québec, Quebec, Canada). IQC recoveries ranged from 89 to 120%. Other metals such as cadmium (Cd), arsenic (As), lead (Pb) and mercury (Hg) were analyzed using the same analytical method and instrumentation as was used for Mn.

2.3. Outcome assessment: birth weight and small for gestational age (SGA)

Infant weight (g) at birth was abstracted from study participants' medical charts. SGA births were defined as below the 10th percentile of birth weight distribution for each gestational week and sex, based on Canadian standards (Kramer et al., 2001).

Potential confounders were identified as variables previously reported to be associated with birth weight or Mn concentrations (Zota et al., 2009). These included maternal age at delivery (≤24, 25–29, 30–34, ≥35 y), pre-pregnancy body mass index (BMI) according to WHO guidelines (World Health Organization, 2018), parity (nulliparous, parous), maternal education (high school diploma or less, some college or trade school, undergraduate university degree, graduate university degree), household income ($ ≤30,000, 30,001–50,000, 50,001–100,000, ≥100,000), race (Caucasian/non-Caucasian), maternal smoking (never or quit before pregnancy, quit when knew pregnant, current smoking), gestational age at time of blood sampling, and hemoglobin level (Wood, 2009). Pb, Cd, As, and Hg were also considered potential confounders (Arbuckle et al., 2016; Govarts et al., 2016)

2.4. Statistical analysis

Descriptive statistics were calculated for all variables. All Mn samples were above the limit of detection. Mn was not log-transformed as data were not characterized by skewed distributions. We calculated the mean difference in birth weight according to categories of maternal and neonatal characteristics. For continuous variables, we calculated the change in birth weight per unit increase in the continuously measured characteristic (e.g. gestational age, hemoglobin). To graphically depict the relationship between blood Mn and birth weight as continuous variables, we used unadjusted generalized additive models (GAM). Based on previous literature showing inverse U-shaped relationships between birth weight and Mn (Chen et al., 2014; Ettinger et al., 2009; Eum et al., 2014; Xia et al., 2016), we categorized Mn concentrations in maternal and cord blood into three groups: < 10th (low), 10– < 90th (middle), and ≥90th percentiles (high). We calculated the mean