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Arsenic levels among pregnant women and newborns in Canada: Results from the Maternal-Infant Research on Environmental Chemicals (MIREC) cohort

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ABSTRACT

Arsenic is a common environmental contaminant from both naturally-occurring and anthropomorphic sources and human exposure can be detected in various tissues. Its toxicity depends on many factors including the chemical form, valence state, bioavailability, metabolism and detoxification within the human body. Of paramount concern, particularly with respect to health effects in children, is the timing of exposure as the prenatal and early life periods are more susceptible to toxic effects. The Maternal-Infant Research on Environmental Chemicals (MIREC) cohort was established to obtain national-level biomonitoring data for approximately 2,000 pregnant women and their infants between 2008 and 2011 from 10 Canadian cities. We measured total arsenic (As) in 1st and 3rd trimester maternal blood, umbilical cord blood, and infant meconium and speciated arsenic in 1st trimester maternal urine. Most pregnant women had detectable levels of total arsenic in blood (92.5% and 87.3%, respectively, for 1st and 3rd trimester); median difference between 1st and 3rd trimester was 0.1124 µg/L ($p < 0.0001$), but paired samples were moderately correlated (Spearman $r=0.41$, $p < 0.0001$). Most samples were below the LOD for umbilical cord blood (50.9%) and meconium (93.9%). In 1st trimester urine samples, a high percentage (>50%) of arsenic species (arsenous acid (As-III), arsenic acid (As-V), monomethylarsonic acid (MMA), and arsenobetaine (AsB)) were also below the limit of detection, except dimethylarsinic acid (DMA). DMA (>85% detected) ranged from <LOD to 64.42 (95th percentile: 11.99) µg As/L. There was a weak but significant correlation between total arsenic in blood and specific gravity-adjusted DMA in urine (Spearman $r=0.33$, $p < 0.0001$). Among this population of pregnant woman and newborns, levels of arsenic measured in blood and urine were lower than national population figures for Canadian women of reproductive age (20–39 years). In general, higher arsenic levels were observed in women who were older, foreign-born (predominantly from Asian countries), and had higher education. Further research is needed to elucidate sources of exposure and factors that may influence arsenic exposure in pregnant women and children.

1. Introduction

Arsenic (As) is a ubiquitous metalloid that is present in the environment from both naturally-occurring and anthropomorphic sources. Environmental contamination is a worldwide concern resulting in human exposure to both inorganic and organic forms. Human exposure generally occurs from the consumption of inorganic arsenic in drinking water and diet (National Research Council [NRC] 2013). Organic arsenic is formed through biological reactions with inorganic arsenic in aquatic environments resulting in human exposure to

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organic arsenicals mainly from seafood. Arsenic toxicity depends on many factors including its chemical form, valence state, bioavailability, metabolism and detoxification within the human body (National Research Council (NRC), 2013; Vahter and Concha, 2001).

The complex chemistry and toxicokinetics of arsenic affect the availability and choice of exposure biomarkers. Measurements of total arsenic in human tissues represent the sum of both the inorganic and organic species. Laboratory analytical advances and availability of a standard reference material containing both inorganic and organic arsenic species allows for more complex speciated arsenic measurements (Le et al., 2000; Xie et al., 2006).

Although the toxicity and health effects of arsenic species are still being elucidated, some of the methylated metabolites of inorganic arsenic are thought to be the most toxic to humans (Cohen et al., 2006). Once ingested, greater than 90% of inorganic arsenic (As) is absorbed by the gastrointestinal tract with As^{5+} reduced to As^{3+} in blood and metabolized by the liver to monomethylarsonic acid (MMA-V). This, in turn, is reduced to the highly reactive/highly toxic monomethylarsinic acid (MMA-III) which is methylated again to dimethylarsinic acid (DMA) and excreted in urine within a few hours (National Research Council (NRC), 2013; Watanabe and Hirano, 2013). The organoarsenicals, primarily arsenobetaine and arsenocholine, are generally thought to be absorbed and excreted untransformed, thus considered non-toxic. Correlations have been reported between fish and shellfish consumption and urinary concentrations of arsenobetaine (Lovreglio et al., 2012; Rivera-Núñez et al., 2012). However, research now suggests that arsenobetaine may also be formed endogenously in humans (Molin et al., 2015). One study has suggested that arsenobetaine is a human metabolite of DMA or inorganic arsenic from food, or both (Newcombe et al., 2010).

The International Agency for Research on Cancer (IARC) classifies inorganic arsenic as a group-1 human carcinogen and associations have been found with lung, bladder, skin, kidney, liver and prostate cancer (IARC (International Agency for Research on Cancer), 2012). A range of non-carcinogenic effects, including cardiovascular disease (Tsuji et al., 2014), hypertension (Abhyankar et al., 2012), and diabetes (Wang et al., 2014), have also been observed. Low-level environmental exposure has been associated with impaired glucose tolerance during pregnancy (Ettinger et al., 2009; Shapiro et al., 2015). Arsenic is known to cross the placenta and prenatal exposure is associated with adverse birth and developmental outcomes (National Research Council (NRC), 2013; Vahter, 2009).

Human and experimental studies have shown that the susceptibility of the developing embryo/fetus to environmental factors is dependent on the timing of exposures during critical windows of prenatal development (Selevan et al., 2000). Canada's Maternal-Infant Research on Environmental Chemicals (MIREC) cohort was established to obtain national biomonitoring data for pregnant women and their infants and to examine potential adverse health effects of prenatal exposure to priority environmental chemicals (Arbuckle et al., 2013). Previous analyses of associations between maternal blood As levels and health outcomes in the MIREC Study have reported no significant associations with small for gestational age births (Thomas et al., 2015), fetal markers of metabolic function (Ashley-Martin et al., 2015a) or immune function (Ashley-Martin et al., 2015b), or impaired glucose tolerance during pregnancy (Shapiro et al., 2015). However, maternal blood As was significantly associated with gestational diabetes (Shapiro et al., 2015) and urinary arsenobetaine levels were associated with a higher risk of small for gestational age births (Thomas et al., 2015).

MIREC has one of the richest sources of information to date on prenatal exposure biomarkers including measurements in maternal blood, urine, breast milk, and neonatal umbilical cord blood and meconium from nearly 2,000 mother-newborn pairs. Here, we present the MIREC arsenic exposure biomarker data for total arsenic in 1st and 3rd trimester maternal blood, umbilical cord blood, and infant meconium and speciated arsenic in 1st trimester maternal urine and examine differences in arsenic concentrations by selected maternal characteristics.

2. Materials and methods

2.1. Study population

MIREC enrolled 2,001 women in the first trimester of pregnancy between 2008 and 2011 from 10 cities in six Canadian provinces: Vancouver, Edmonton, Winnipeg, Sudbury, Ottawa, Kingston, Hamilton, Toronto, Montreal and Halifax. The study was reviewed and approved by the Research Ethics Board of Health Canada as well as the ethics committees at each of the 10 participating clinical study sites and collaborating institutions. Details on the cohort have been published previously (Arbuckle et al., 2013).

Briefly, women at least 18 years of age or older with English or French language ability, willing to provide a cord blood sample, and intending to deliver at a local hospital, were recruited between six and 13 weeks of pregnancy (<14 weeks gestation) and followed through pregnancy and up to ten weeks after a pregnancy (for breast milk collection). Women with histories of medical complications or known fetal abnormalities or chromosomal or major malformations in the current pregnancy, or those with a major chronic illness, threatened abortion, or illicit drug use were excluded. Biological samples of maternal blood and urine were collected at each trimester of pregnancy and at delivery, neonatal umbilical cord blood at delivery and meconium within the first few days after delivery. Extensive information was collected by interviewer-administered questionnaires and medical chart review on a number of variables, including: socio-demographic characteristics; maternal anthropometry; obstetrical history; and smoking. After data collection, 18 women asked to withdraw from the study and their data and biospecimens were destroyed. Additional loss to follow-up over the course of the pregnancy was due to: withdrawals from the study (N=48), fetal demise (N=41), therapeutic abortion (N=13), mobility of the participants outside the study site (N=14) or the biospecimen was not collected.

2.2. Laboratory methods

Blood was collected in 6-mL K_2 EDTA tubes at the 1st and 3rd trimester visits using standard phlebotomy procedures. Umbilical cord blood was collected at delivery using a S-Monovette® (Sarstedt, Germany), and meconium was collected within the first two days after delivery using a Mère Hélène® bioliner (Mère Hélène, Quebec, Canada) inserted in the diaper. All whole blood and meconium samples were aliquotted and stored in Sarstedt® tubes. First trimester (median gestational age 12.4, range 6.1–14.9 weeks) urine samples were collected in 125-mL Nalgene® containers (Thermo-Fisher Scientific Inc., Rochester NY, USA), aliquoted into 30-mL Nalgene® containers, frozen at −20 °C within 2 h of collection and shipped on dry ice to the MIREC coordinating center in Montreal where they were stored at −30 °C. Potential contamination of the collection materials was assessed by pre-screening for trace metals. Field blanks using water (Steril.O reagent grade deionized distilled water) were collected and tested to assess for possible contamination during the collection, processing, transportation and storage procedures.

Samples were shipped in batches for analysis to the Centre de Toxicologie du Québec, Institut national de Santé Publique du Québec (INSPQ) (http://www.inspq.qc.ca/ctq/), which is accredited by the Standards Council of Canada under ISO 17025 and CAN-P-43. The accuracy and precision of the analyses are evaluated on a regular basis through the laboratory's participation in external quality assessment programs. Samples were received at the laboratory, registered into the laboratory information management system, and stored at −20 °C until analysis. On the day before analysis, samples are placed at 4 °C to be thawed if necessary. Sample preparation and analysis were carried out