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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

in a laboratory that was specifically designed and dedicated to trace element analysis.

Blood (500 μL) and cord blood (250 μL) samples were diluted, 20-fold, 40-fold, or 50-fold in a diluent containing 0.5% (v/v) NH_4OH and 0.1% (v/v) octylphenol ethoxylate. The samples diluted 1/20, 1/40, or 1/50 have corresponding limits of detection (LOD), respectively, of: 0.225 μg/L (3.0 nmol/L), 0.449 μg/L (6 nmol/L), or 0.599 μg/L (8 nmol/L). External calibration curves were prepared by diluting the corresponding volume of human blood (from healthy volunteers) with diluent and then spiking with different volumes of 1 mg/L multi-elements standard solution (SCP Science, PlasmaCal ICP-MS Verification Standard 1; 5% HNO_3, #141-110-011). The internal standards for the calibration curve and the blood samples analysis were ^{89}Y (for ^{75}As). Internal quality assurance was ensured by running validated reference materials (QMEQAS08B05, QMEQAS08B08, QM-B-Q1108 and QM-B-Q1201: human blood from the Quebec Multi-element External Quality Assessment Scheme (QMEQAS) inter-laboratory comparison scheme) after calibration, after every 10th sample as well as at the end of each analytical sequence.

Meconium was thawed and homogenized and a sample (500 mg) was predigested at room temperature in a Teflon bomb for three hours under acidic conditions (2 mL HNO_3). The bombs were then sealed and placed at 110 °C for 18 h to complete the digestion. The digest was diluted 50-fold with an aqueous solution (diluent) containing 0.002% (m/v) L-(+)-cystein and 100 μg/L Au. External calibration curves were prepared in 2% (v/v) HNO_3 containing 0.002% (m/v) L-(+)-cystein and 100 μg/L Au by spiking with different volumes of 1 mg/L multi-elements standard solution (SCP Science, PlasmaCal ICP-MS Verification Standard 1; 5% HNO_3, #141-110-011). The internal standards for calibration standards and meconium samples were ^{89}Y (for ^{75}As). Internal quality assurance was ensured by running standard reference materials (SRM 1577b: bovine liver from the National Institute of Standards and Technology (NIST) Gaithersburg, MD USA) and validated reference materials (QM-H-Q1101: human hair from the Quebec QMEQAS external quality assessment scheme) after calibration, after every 10th sample and at the end of each analytical sequence.

Blood, cord blood, and meconium were analyzed using a single-quadrupole inductively coupled plasma mass spectrometry (ICP-MS) Elan DRC-II system (Perkin Elmer, Norwalk CT, USA). Limits of detection (LOD) for blood and meconium, respectively, were: 0.225 μg/L and 0.02 μg/g.

Urine (100 μL) was diluted 1/10 with solvent of elution then injected on instrument with no prior sample preparation steps. Arsenic species (arsenite (As-III), arsenate (As-V), dimethylarsinic acid (DMA), monomethylarsonic acid (MMA), arsenobetaine (AsB)) were measured by HPLC coupled with ICP-MS (Varian 820-MS, Varian Inc., Palo Alto CA, USA) with limits of detection (LOD) equal to 0.75 μg As/L (0.01 μmol/L) according to the method of Bélanger and Dumas (2010). Specific gravity was measured in thawed urine samples by refractometry (UG-1, Atago # 3461, Atago U.S.A. Inc., Bellevue WA, USA) to control for urine dilution.

2.3. Statistical analysis

Descriptive statistics, including sample size, detection limit, percentage of observations below the limit of detection (LOD), minimum, median, 95th percentile, maximum, geometric mean, and associated 95% confidence interval were calculated for arsenic biomarkers. Spearman correlation coefficients were calculated between biomarkers when at least 50% of the data were above the LOD.

Due to the non-normality of the data, the Wilcoxon signed rank test or sign test was used to test whether the medians of the 1st and 3rd trimester blood measurements were equal. Arsenic values below the LOD were defined as left-censored and methods to account for left-censoring were implemented.

The geometric mean from a lognormal random variable with censoring was calculated using the parametric maximum likelihood (ML) method and compared to the empirical median from the nonparametric Kaplan-Meier (KM) approach (Helsel, 2012; Nysen et al., 2012). The Greenwood estimate of variance was used for determination of Kaplan-Meier confidence intervals. The parametric and nonparametric censoring methods were used only for biomarkers with at least 50% of the data above the LOD. Justification for including contaminants with up to 50% censoring is provided in Helsel (2012).

Maternal characteristics considered in the analysis included: age group (<25, 25–29, 30–34, ≥35 years); parity (0, 1, ≥2); pre-pregnancy body mass index (BMI <25, 25≥BMI <30, BMI≥30); smoking status (current or quit during pregnancy, former, never); Canadian-born (yes, no) and region of birth; household income (≤$50K, >$50K–100K, >$100K); education level (high school, some college/college diploma, university degree); season of sample collection (fall, winter, spring, summer); fasting status (yes, no); and, for urine only, time of sample collection (6:00–9:00, 9:00–12:00, 12:00–15:00, 15:00–18:00, 18:00–24:00) and time since last urination (≤75, 76–120, 121–170, >170 min). Infant sex, maternal smoking status and season of sample collection were considered for cord blood and meconium. Summary statistics were reported for each variable group and statistical hypothesis testing was used to test for significant differences among the groups.

Urine concentrations in 1st trimester samples are presented both unadjusted and adjusted by urine specific gravity (SG) using the following formula (adapted from Just et al., 2010):

$$P_c = P_i\left[\frac{SG_m - 1}{SG_i - 1}\right]$$

where P_c is the SG-adjusted metabolite concentration, P_i is the observed metabolite concentration, SG_i is the specific gravity of the ith urine sample and SG_m is the median SG for the cohort. One urine sample was excluded from the analysis because it was deemed too dilute (specific gravity =1.000, equivalent to water) and all chemical results were below the limits of detection. Three samples for which no specific gravity results were available were included in the unadjusted analyses, but excluded from adjusted analyses.

For blood arsenic, maximum likelihood estimation was employed to account for left−censored repeated measures (Jin et al., 2011)and hypothesis testing was performed using the data from both the 1st and 3rd trimesters, by means of likelihood ratio tests which follow a chi-square distribution. These methods were implemented where at least 50% of the observations were above the LOD. Confidence intervals were computed for geometric mean contaminant levels by demographic variables of interest, correcting for multiple pairwise comparisons (Bonferonni-adjusted) using Empirical Bayes estimates of the random effects (McCulloch et al., 2008). Hypothesis testing was performed to determine if there were significant differences in urinary arsenic levels by maternal characteristics with specific gravity treated as a covariate.

Statistical analysis was performed using SAS (Statistical Analysis System) Enterprise Guide 4.2 (SAS Institute, Cary NC, USA) and R (R Core Development Team) for analysis. For the censoring methods, functions from the R packages NADA and SURVIVAL and SAS procedure NLMIXED were used for analysis. Unless otherwise indicated, a 5% significance level (α=0.05) was implemented throughout.

3. Results

Table 1 shows descriptive statistics for total As in maternal blood, umbilical cord blood and meconium. Most pregnant women had detectable levels of arsenic in blood (92.5% and 87.3% greater than the LOD, respectively, for 1st and 3rd trimester samples); however, most samples were below the LOD for cord blood (50.9%) and especially meconium (93.9%). Concentrations of blood As in the 1st

Table 1
Descriptive statistics for total arsenic in maternal blood (µg/L), umbilical cord blood (µg/L), and meconium (µg/g).

					Kaplan-Meier			Maximum-Likelihood			95th	
Sample Type	N	LOD	% <LOD	Min	Median	95% CI[a]		GM	95% CI[b]		Percentile	Max
1st trimester blood	1938	0.225	7.5	<LOD	0.82	0.79	0.86	0.75	0.73	0.78	2.32	34.46
3rd trimester blood	1673	0.225	12.7	<LOD	0.69	0.65	0.73	0.67	0.64	0.69	2.77	32.96
Umbilical cord blood	1416	0.599[c]	50.9	<LOD	NA	NA	NA	NA	NA	NA	2.55	17.98
Meconium	1591	0.02	93.9	<LOD	NA	NA	NA	NA	NA	NA	0.02	0.55

LOD: Limit of detection
GM: Geometric mean
NA: Indicates that the estimate is 'not applicable' due to a high level of censoring
[a] 95% Confidence Intervals (CI) computed using Greenwood's estimate of the standard error.
[b] 95% CI computed using the Maximum likelihood method.
[c] Upper limit of detection; cord blood LODs ranged from 0.225 to 0.599 depending on sample dilution prior to instrument analysis.

trimester of each woman tended to be higher than her paired sample from the 3rd trimester, with the median of the differences between 1st and 3rd trimester As in blood of 0.11 µg/L ($p < 0.0001$); however, the paired samples were only modestly correlated (Spearman r=0.41, $p < 0.0001$).

Given the larger percentage of non-detects in the cord blood, we examined the correlations between maternal As levels and cord blood levels only for those samples above the LOD and found poor correlations of 0.19 (n=762) with 1st trimester maternal blood, 0.29 with 3rd trimester maternal blood (n=701) and 0.05 (n=681) with 1st trimester DMA. While the sensitivity of detectable maternal blood As or urinary DMA to predict detectable levels in cord blood was very good (96.6% and 93.5% for 1st and 3rd trimester blood, respectively and 86.5% for DMA, the specificity was poor (<22%) (data not shown).

Table 2 shows how total As in 1st and 3rd trimester blood (combined) varied by maternal characteristics. Significantly higher maternal blood As concentrations were observed in women who were older, foreign-born, nulliparous, former or never smokers, university educated, and blood sample collection in spring (compared to the fall). A further analysis of country of birth revealed significant differences between Canadian women and women born in Asia and Europe (Table 3). In addition, women who identified as Asian (Chinese, south

Table 2
Differences in total arsenic (µg/L) in 1st and 3rd trimester blood by maternal characteristics.

Characteristic	Group Variable	N[a]	GM[b]	95% CI[c]	Differences[d]	p-value
Age (years)	<25	244	0.59	(0.51, 0.69)	A	0.0001
	25–29	848	0.68	(0.62, 0.73)	AB	
	30–34	1290	0.71	(0.67, 0.76)	BC	
	≥35	1229	0.77	(0.72, 0.82)	C	
Parity	0	1604	0.74	(0.70, 0.79)	A	0.005
	1	1447	0.71	(0.67, 0.75)	AB	
	≥2	557	0.64	(0.59, 0.71)	B	
Pre-pregnancy BMI	Underweight to Normal (BMI <25)	2141	0.73	(0.70, 0.76)		0.1
	Overweight (25≤BMI <30)	720	0.71	(0.65, 0.77)		
	Obese (BMI≥30)	487	0.66	(0.60, 0.73)		
Canadian-born	No	677	0.84	(0.79, 0.90)	A	0.0001
	Yes	2934	0.69	(0.66, 0.71)	B	
Smoking status	Current	427	0.63	(0.56, 0.70)	A	0.002
	Former	974	0.75	(0.70, 0.81)	B	
	Never	2205	0.71	(0.68, 0.75)	B	
Household income	≤$50,000	618	0.69	(0.63, 0.75)		0.42
	$50,001–$100,000	1433	0.71	(0.67, 0.76)		
	>$100,000	1398	0.73	(0.68, 0.77)		
Education	High school or less	309	0.6	(0.53, 0.68)	A	<0.0001
	Some college	1031	0.68	(0.63, 0.72)	A	
	Undergraduate degree or higher	2267	0.75	(0.71, 0.78)	B	
Season	Fall	995	0.68	(0.64, 0.73)	A	0.006
	Winter	826	0.74	(0.69, 0.79)	AB	
	Spring	947	0.75	(0.70, 0.80)	B	
	Summer	843	0.69	(0.65, 0.74)	AB	
Fasting status	No	3532	0.71	(0.69, 0.73)		0.30
	Yes	69	0.78	(0.66, 0.93)		

[a] 1st and 3rd trimesters combined.
[b] Geometric means calculated using both 1st and 3rd trimester measurements.
[c] Confidence Intervals (CI) are corrected for multiple pairwise comparisons (Bonferroni-adjusted).
[d] Results of statistical hypothesis testing of differences by maternal group characteristics: letters shared in common between the groups indicate no significant difference, whereas groups that do not share a letter are significantly different from each other.

Table 3
Maternal blood arsenic levels[a] by region of birth.

Region	N	GM[b] (95% CI)[c]	Differences[d]	p-value
Africa	55	0.82 (0.56, 1.20)	AB	<0.0001
Asia	125	1.10 (0.85, 1.41)	A	
Caribbean	59	0.92 (0.63, 1.33)	AB	
Central or South America	83	0.71 (0.52, 0.97)	AB	
Eastern Europe	75	0.64 (0.46, 0.89)	AB	
Europe	168	0.96 (0.77, 1.19)	A	
Middle East	48	0.60 (0.40, 0.90)	AB	
US and Oceania	64	0.80 (0.56, 1.14)	AB	
Canada	2934	0.69 (0.65, 0.72)	B	

[a] 1st and 3rd trimester measurements combined.
[b] Geometric means calculated using both 1st and 3rd trimester measurements.
[c] Confidence Intervals (CI) are corrected for multiple pairwise comparisons (Bonferroni-adjusted).
[d] Results of statistical hypothesis testing of differences by maternal group characteristics: letters shared in common between the groups indicate no significant difference, whereas groups that do not share a letter are significantly different from each other.

Asian, Filipino, southeast Asian, Japanese, Korean), had a significantly higher blood As level (GM 0.913 µg/L) compared to non-Asian women (GM 0.701 µg/L). No significant differences were observed by pre-pregnancy BMI, household income, or fasting status.

Table 4 shows descriptive statistics for species of inorganic and organic arsenic in 1st trimester urine, both unadjusted and adjusted for specific gravity. Due to the high percentage of values below the limit of detection (>50%) for species other than DMA, estimates for the median and geometric mean were not applicable in most cases. DMA ranged from <LOD to 64.42 (95th percentile: 11.99) µg As/L and <LOD to 44.14 (95th percentile: 9.74) µg As/L when unadjusted and adjusted for specific gravity, respectively.

There was a weak but significant linear correlation between total arsenic in blood and specific gravity-adjusted DMA in urine (Spearman $r=0.33$, $p<0.0001$). Correlations were not calculated for the other urinary arsenic species with total blood arsenic since more than 50% of the samples were less than LOD for As-III, As-V, MMA and AsB.

Table 5 shows differences in dimethylarsinic acid (DMA) in 1st trimester urine by maternal characteristics when specific gravity is modeled as a linear covariate. Similar to what was observed for the blood measures, significant differences were observed for age, parity, country of birth, smoking, and education. In addition, lower maternal DMA concentrations were observed in women with pre-pregnancy BMI ≥30. There were no significant differences with fasting status or time since last urination.

4. Discussion

Among a large, geographically diverse sample of pregnant women across ten sites in Canada, arsenic was frequently detected in maternal blood (92.5% and 87.3%, respectively in 1st and 3rd trimesters), while urinary arsenic species were less commonly detected. Arsenic species in 1st trimester urine were <LOD for most samples except for DMA which was above the LOD for over 85% of samples. This is consistent with concurrent data from females aged 20–39 years in the Canadian Health Measures Survey (CHMS)(Cycle 2: 2009–2011) which found urine levels <LOD for As^{3+}(76.06% <LOD), As^{5+}(100% <LOD), MMA (77.66% <LOD), and AsB (41.49% <LOD) (Health Canada, 2013). In the CHMS, DMA was detected in almost 94% of samples with a geometric mean (95% CI) of 3.5 (2.6–4.7) µg/L compared to greater than 85% detection in our cohort with a geometric mean of 2.3 (2.2–2.4) µg/L, not adjusted for specific gravity. Similarly, the inorganic arsenic species were mostly undetected in urine in the US NHANES 2009–2010 analysis, with similar detection limits (CDC, 2015).

While the percentages of women with detectable blood arsenic in a national survey and in MIREC were similar, Canadian women of reproductive age (20–39 years) from 2007 to 2009 had a geometric mean (GM) of 0.88 µg/L and 95th percentile of 4.0 µg/L (Health Canada, 2010), compared to a GM of 0.75 µg/L and 95th percentile of 2.32 µg/L in MIREC 1st trimester blood. Among infants born to these women, greater than 50% and 93% of samples, respectively, were <LOD for total arsenic in umbilical cord blood and meconium. An analytical method with a lower detection limit in meconium would have yielded more precise data for those samples <LOD, as arsenic has been measured in meconium in studies with lower detection limits in Japan (median 0.03 ppb) (Yang et al., 2013), Taiwan (GM 33 µg/kg) (Jiang et al., 2014) and China (median 37.78 ng/g) (Peng et al., 2015).

In general, urinary arsenic has been the more common biomarker of exposure for the measurement of total arsenic or speciated metabolites used in epidemiologic studies possibly due to the non-invasive mode of sample collection. However, as discussed in detail below, the lack of consistent methods may limit interpretability and comparisons across studies. We note below that blood arsenic has been more

Table 4
Descriptive statistics for speciated arsenic (µg As/L) in 1st trimester urine, unadjusted and adjusted for specific gravity.

					Kaplan-Meier			Maximum-Likelihood			95th	
Arsenic Species	N	LOD	% <LOD	Min	Median	95% CI[a]		GM	95% CI[b]		Percentile	Max
Arsenous acid (As-III)	1933	0.75	84.1	<LOD	NA	NA	NA	NA	NA	NA	1.95	23.97
As-III adjusted[c]				<LOD	NA	NA	NA	NA	NA	NA	3.25	24.10
Arsenic acid (As-V)	1933	0.75	98.5	<LOD	NA	NA	NA	NA	NA	NA	NA	22.47
As-V adjusted[c]				<LOD	NA	NA	NA	NA	NA	NA	NA	15.58
Monomethylarsonic acid (MMA)	1933	0.75	92.5	<LOD	NA	NA	NA	NA	NA	NA	0.82	11.24
MMA adjusted[c]				<LOD	NA	NA	NA	NA	NA	NA	3.25	9.74
Dimethylarsinic acid (DMA)	1933	0.75	14.1	<LOD	2.40	2.26	2.53	2.30	2.20	2.41	11.99	64.42
DMA adjusted[c]				<LOD	2.39	2.30	2.47	2.57	2.49	2.65	9.74	44.14
Arsenobetaine (AsB)	1933	0.75	51.2	<LOD	NA	NA	NA	NA	NA	0.81	29.51	1573.03
AsB adjusted[c]				<LOD	0.77	NA	0.89	0.79	NA	0.89	33.79	889.11

LOD: Limit of detection.
NA: Indicates that the estimate is 'not applicable' due to a high level of censoring.
[a] Confidence Intervals (CI) computed using Greenwood's estimate of the standard error.
[b] Confidence Intervals (CI) computed using the Maximum likelihood method.
[c] Adjusted for urine specific gravity.

Table 5
Differences in dimethylarsinic acid (μg As/L) in 1st trimester urine by maternal characteristics with specific gravity modeled as a linear covariate.

Characteristic	Group Variable	N	% <LOD	GM	95% CI[a]	Differences[b]	p-value
Age (years)	<25	132	14.4	1.76	(1.49, 2.09)	A	<0.0001
	25–29	448	14.5	2.18	(1.99, 2.39)	AB	
	30–34	693	15.0	2.38	(2.21, 2.56)	B	
	≥35	660	12.9	2.45	(2.28, 2.64)	B	
Parity	0	853	12.3	2.54	(2.39, 2.70)	A	<0.0001
	1	780	15.6	2.15	(2.02, 2.29)	B	
	2+	298	15.4	2.09	(1.89, 2.31)	B	
Pre-pregnancy BMI	BMI <25	1136	14.0	2.44	(2.32, 2.57)	A	<0.0001
	25≤BMI <30	392	14.3	2.24	(2.05, 2.44)	AB	
	BMI≥30	265	14.7	1.89	(1.69, 2.11)	B	
Canadian-born	No	363	9.6	3.14	(2.92, 3.37)	A	<0.0001
	Yes	1570	15.2	2.15	(2.08, 2.23)	B	
Smoking status	Current	229	13.5	2.00	(1.78, 2.24)	A	0.006
	Former	530	14.5	2.32	(2.15, 2.51)	AB	
	Never	1172	14.1	2.37	(2.25, 2.49)	B	
Household income	≤$50,000	336	11.6	2.16	(1.96, 2.38)	A	0.004
	$50,001–$100,000	767	14.9	2.25	(2.11, 2.39)	A	
	>$100,000	739	14.1	2.48	(2.33, 2.65)	A	
Education	High school or less	173	12.7	1.96	(1.71, 2.24)	A	<0.0001
	Some college	555	16.8	2.00	(1.85, 2.15)	A	
	Undergraduate degree or higher	1203	13.1	2.52	(2.40, 2.65)	B	
Season	Fall	563	17.6	2.14	(1.97, 2.32)	A	0.012
	Winter	470	12.6	2.31	(2.11, 2.53)	A	
	Spring	447	13.4	2.48	(2.27, 2.72)	A	
	Summer	453	12.1	2.35	(2.15, 2.58)	A	
Fasting status	No	1868	14.4	2.30	(2.23, 2.38)		0.64
	Yes	39	10.3	2.18	(1.73, 2.74)		
Time of urine sample collection	6:00–9:00	28	17.9	4.62[c]	(2.94, 7.26)		0.15
	9:00–12:00	827	17.1	4.93[c]	(4.57, 5.32)		
	12:00–15:00	659	12.9	4.57[c]	(4.23, 4.93)		
	15:00–18:00	379	10.3	4.73[c]	(4.27, 5.25)		
	18:00–24:00	38	7.9	4.04[c]	(2.90, 5.61)		
Time since last urination (minutes)	≤75	504	18.9	2.17	(1.99, 2.37)		0.26
	76–120	607	12.9	2.35	(2.17, 2.54)		
	121–170	272	16.5	2.38	(2.12, 2.68)		
	>170	453	9.5	2.31	(2.11, 2.53)		

[a] Confidence Intervals (CI) are corrected for multiple pairwise comparisons (Bonferroni-adjusted).
[b] Results of statistical hypothesis testing of differences by maternal group characteristics: letters shared in common between the groups indicate no significant difference, whereas groups that do not share a letter are significantly different from each other.
[c] Specific gravity-adjusted GM, as a significant interaction was observed between SG as a covariate and time of sample collection.

commonly used in studies conducted among pregnant women and their infants possibly because these subjects are already undergoing blood collection as part of their clinical care. While arsenic in blood is cleared within several hours of being absorbed, it may reach a steady state following chronic exposure (Hall et al., 2006; Hughes, 2006).

Maternal total blood arsenic, representing the sum of both inorganic and organic exposure, in the MIREC cohort ranged from <LOD to 34.5 (median 0.8) and 33.0 (median 0.7) μg/L, respectively, in the 1st and 3rd trimesters of pregnancy. These results are consistent with a birth cohort study carried out near the Tar Creek Superfund site in Oklahoma (USA) where total blood arsenic at delivery in 532 women ranged from <LOD to 24.1 (median 1.4) μg/L (Ettinger et al., 2009). A 2010 study in Shanxi, China that measured total blood arsenic using less sensitive atomic fluorescence spectrophotometry (AFS) among 212 women in the 1st and 2nd trimesters of pregnancy observed much lower levels ranging from 0.04 to 2.2 (median 0.5) μg/L (Jin et al., 2014). Levels in that study were significantly higher than the median among those with reported consumption of pork, meat, or mutton (24% higher) and use of coal as a cooking fuel (36% higher). We noted significantly higher As levels in Asians, similar to what has been reported in the U.S. NHANES 2011–2012 data (Awata et al., 2016a) where Asians had the highest daily fish and rice consumption across the racial/ethnic groups, with fish being the major contributor to total arsenic intake, while rice was the major contributor to inorganic arsenic dietary intake (Awata et al., 2016b).

In a study among women from the Salta province of Argentina, total blood arsenic ranged from 5.6 to 13 (median 11) μg/L in late (average 39 weeks) gestation (Concha et al., 1998). Arsenic in umbilical cord blood was similar (range 6–12, median 9 μg/L) to that in maternal blood with a significant correlation between the two measures, suggesting that arsenic was transferred to the fetus. We also found detectable arsenic in about 50% of umbilical cord blood samples at birth (range <LOD to 18 μg/L). Among those cord bloods with detectable As in our study, the correlation with the corresponding maternal blood As was poor; however the sensitivity of detectable As in maternal blood to predict detectable As in cord blood was very good,

supporting the notion of some fetal transfer.

In the Argentinian study, essentially all of the arsenic in the blood and urine of mothers in late gestation (as well as in newborn blood) was in the form of DMA which may indicate that arsenic methylation is increased during pregnancy (Concha et al., 1998). Interestingly, the increased methylation in late gestation was associated with lower arsenic concentrations in blood and higher concentrations in urine, compared with a few months postpartum, suggesting that methylation may be inhibited at higher exposure levels (Vahter, 2009). Arsenic methylation efficiency varies between individuals, as well as within individuals over time (Kile et al., 2009). In general, those with higher ratios of MMA to DMA in urine or blood are thought to be less efficient methylators and may be at greater risk for arsenic-related health effects (National Research Council (NRC), 2013). Women of childbearing age have been shown to be more efficient arsenic methylators than men and, among populations with relatively low exposure, methylation efficiency appears to increase across pregnancy (Gardner et al., 2011).

Laine et al. (2015) found negative associations between %MMA in maternal third trimester urine and birth weight and placental weight in a Mexican birth cohort where approximately half the mothers had elevated (>10 μg/L) drinking water arsenic. A recent meta-analysis of 16 studies, including several prospective birth cohort studies, revealed small but statistically significant increased risks of spontaneous abortion, stillbirth, and neonatal and infant mortality among populations highly-exposed to arsenic in drinking water; however, when the analysis was restricted to the seven highest quality studies, statistical significance was only achieved for infant mortality (Quansah et al., 2015). Inorganic arsenic in drinking water has been associated with adverse birth outcomes at relatively low levels of exposure (Bloom et al., 2014).

It has been suggested in highly-exposed populations such as Bangladesh that the immunosuppressive effects of prenatal As exposure (Ahmed et al., 2011, 2014) may increase the risk of infant morbidity and mortality from infectious diseases (Rahman et al., 2011). In a New Hampshire (USA) birth cohort with lower drinking water As exposure than the aforementioned Bangladesh studies, researchers also found increased risk of diarrhea and respiratory infections (Farzan et al., 2013) and altered immune cell and gene expression in cord blood (Nadeau et al., 2014) among infants of mothers with higher inorganic arsenic exposures in that population.

It is recognized that a host of biological and behavioral factors modify biomarkers of arsenic exposure and may be responsible for inter-individual differences in arsenic metabolism (Calderon et al., 2013; Hudgens et al., 2016). In addition to the state of pregnancy itself, it may be that underlying genetic susceptibility factors are responsible for differences in arsenic metabolism and toxicity. Arsenic methyltransferase (AS3MT) genotype has been shown to influence the arsenic methylation profile phenotype (Gardner et al., 2012; Engström et al., 2013). Other genetic and epigenetic mechanisms may also be responsible (Bailey and Fry, 2014). Although the influence of changes to arsenic methylation during pregnancy on child health outcomes is not well understood, it is clear that a better understanding of the effects of prenatal arsenic exposure, including factors associated with such exposure, is needed.

We also measured speciated arsenic in urine and found differences by maternal characteristics in the detected urinary arsenic species, namely DMA, both when unadjusted and adjusted for specific gravity. In general, higher levels were observed in women who were older, foreign-born, and had higher education. This may be due to differences in diet, such as consumption of green tea (Colapinto et al., 2016), seafood, fruit, grains, milk or rice consumption, which are known to influence arsenic exposure (DeCastro et al., 2014). Comparison of urinary arsenic levels, including examination of sources of exposure, across studies is limited by the lack of consistent methods for laboratory and statistical analysis and presentation.

Some studies have used creatinine to control for urinary dilution, but it is now recognized that urinary creatinine is affected by age, sex, body size, and diet, particularly protein intake, and adjustment by creatinine may provide higher values for urinary arsenic concentrations than specific gravity (Nermell et al., 2008). Urinary creatinine may also be affected by several disease processes; for example, among diabetics adjustment for creatinine has been found to overestimate arsenic concentrations (Yassine et al., 2012). We found that specific gravity was a highly significant covariate, indicating its importance to the analysis of urinary arsenic species. Additionally, modeling specific gravity as a covariate allows the urinary analyte concentration to be appropriately adjusted for urine dilution and the statistical significance of other variables in the model to be evaluated independently from the effects of specific gravity. It also provides additional model flexibility due to the ability to evaluate interaction terms in multiple regression analysis.

In summary, among this population of pregnant woman and newborns, levels of arsenic measured in blood and urine were lower than national population figures for women of reproductive age (20–39 years) in Canada. Further research is needed to elucidate sources of exposure and factors that may influence arsenic exposure in pregnant women and children. Future studies should take care to present results in a detailed and consistent manner to allow for comparisons over time and across populations.

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Human subjects' ethics review

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.

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