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Association between maternal urinary speciated arsenic concentrations and gestational diabetes in a cohort of Canadian women

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ABSTRACT

Background: Epidemiological and toxicological evidence suggests that maternal total arsenic (As) levels are associated with an elevated risk of gestational diabetes (GDM). Uncertainty remains regarding the metabolic toxicity of specific arsenic species, comprised of both organic and inorganic sources of arsenic exposure.
Objectives: We assessed associations between speciated As and GDM using data from the Maternal-Infant Research on Environmental Chemicals (MIREC) Study.
Methods: Concentrations of speciated As [(inorganic (trivalent, pentavalent)), methylated arsenic species metabolites (monomethylarsonic acid (MMA), dimethylarsinic acid (DMA)), and organic (arsenobetaine)] were measured in first trimester maternal urine samples. GDM cases were identified in accordance with Canadian guidelines. Multivariable regression models were used to estimate associations between speciated As and GDM, evaluate potential interaction between speciated As exposures, and assess fetal sex-specific findings.
Results: Among 1243 women who had a live, singleton birth and no previous history of diabetes, 4% met the diagnostic criteria for GDM. Our analyses focused on DMA and arsenobetaine as these were the subtypes with detectable concentrations in at least 40% of samples. Compared to women in the lowest tertile of DMA (< 1.49 μg As/L), women with concentrations exceeding 3.52 μg As/L (3rd tertile) experienced an increased risk of GDM (aOR = 3.86; 95% CI: 1.18, 12.57) (*p*-value for trend across tertiles = 0.04). When restricted to women carrying male infants, the magnitude of this association increased (aOR 3rd tertile = 4.71; 95% CI: 1.05, 21.10).
Conclusions: These results suggest a positive relation between DMA and GDM; potential differences in risk by fetal sex requires further investigation.

1. Introduction

Exposure to inorganic arsenic (iAs), a globally ubiquitous contaminant, can produce toxic effects within multiple organ systems (IARC, 2012; Kuo et al., 2017; Quansah et al., 2015; Wang et al., 2014). Several studies have reported that total arsenic levels during pregnancy are associated with an increased risk of adverse maternal metabolic outcomes such as gestational diabetes mellitus (GDM) (Ettinger et al., 2009; Farzan et al., 2016; Peng et al., 2015; Shapiro et al., 2015; Xia et al., 2018). Total arsenic is comprised of numerous inorganic and organic As compounds and metabolites; the degree and type of toxicity induced by exposure to these species is heterogeneous (Molin et al., 2015).

Inorganic arsenic, found in drinking water and some foods (e.g. rice, seaweed), largely consists of arsenate (pentavalent arsenic (As(V))) and, to a lesser extent, arsenite (trivalent arsenic (As(III))). Upon ingestion,

Abbreviations: As, arsenic; AsB, arsenobetaine; As(III), arsenite; As(V), arsenate; BMI, body mass index; Cd, cadmium; DMA, dimethylarsinic acid; GCT, glucose challenge screening test; GDM, gestational diabetes mellitus; iAs, inorganic arsenic; IGT, impaired glucose tolerance; LOD, limit of detection; MMA, monomethylarsonic acid; OGTT, oral glucose tolerance test; SG, specific gravity

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arsenate and arsenite are either metabolized and methylated in the liver to both monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) or excreted unchanged in urine (National Academic Press, 2013; Watanabe and Hirano, 2013). Organic As, primarily found in seafood, is comprised of arsenosugars, arsenolipids, and arsenobetaine (AsB). In contrast to the well-established toxicity of inorganic As, organic arsenic compounds have historically been thought to be relatively nontoxic and excreted largely unchanged in urine (Aylward et al., 2014; Molin et al., 2015).

Research investigating the relationships between levels of individual As species and GDM is lacking. We examined the association between maternal first trimester urinary speciated As levels and measures of glucose intolerance using data from a Canadian pregnancy cohort. Our primary outcome was GDM and our secondary outcomes were i) diagnosis of impaired glucose tolerance (IGT) or GDM and ii) results of glucose challenge screening test (GCT). In light of previous evidence suggesting that risk of GDM may differ according to fetal sex (Jaskolka et al., 2015), we also evaluated effect modification by fetal sex.

2. Methods

2.1. Study population

The Maternal-Infant Research on Environmental Chemicals (MIREC) study is a Canadian longitudinal study of 2001 women (Arbuckle et al., 2013) who were recruited between 2008 and 2011 at 10 different sites in 6 Canadian provinces. Our study population was comprised of women over the age of 18, with singleton, live births, no preexisting diabetes and complete urinary arsenic and glucose testing data ($n = 1243$). This study received ethical approval from Health Canada, St. Justine's Hospital (Montreal, QC), and all participating sites. All participants gave informed consent prior to participation.

2.2. Exposure assessment: maternal urinary speciated arsenic

Concentrations of the following arsenic species were measured in first trimester maternal urine samples: arsenite, arsenate, monomethylarsonic acid (MMA), dimethylarsinic acid (DMA), and arsenobetaine (AsB). Details regarding urinary arsenic measurement have been described elsewhere (Bélanger and Dumas, 2010; Ettinger et al., 2017). Briefly, urine samples were analyzed using HPLC coupled with ICP-MS with a limit of detection (LOD) of 0.01 μmol/L (0.75 μg As/L). The limit of quantification (LOQ) was 0.0013, 0.0016, 0.0020, and 0.0009 μmol/L for AsB, DMA, trivalent, pentavalent, and MMA respectively. The concentrations of the various species were expressed as μg As/L by dividing the concentration in μmol/L by 0.01335. Due to the percentage of samples below the limit of detection (< 50% detectable for all species other than DMA), we were not able to calculate total inorganic arsenic exposure or primary and secondary methylation indices. For exploratory purposes, we created a measure of inorganic arsenic by summing MMA, trivalent, pentavalent, and DMA and determined that the correlation coefficient between this summary measure and DMA was 0.98. Based on this finding, we concluded that DMA was the appropriate and most precise estimate of inorganic arsenic exposure. Maternal cadmium (Cd) levels, included as a potential confounder in this study, were measured in whole blood using inductively coupled plasma mass spectrometry (PerkinElmer ELAN ICP-MS DRC II). Analyses for both cadmium and arsenic were performed at the Toxicology Centre of the Quebec Institute of Public Health, accredited by the Standards Council of Canada.

2.3. Outcome assessment: measures of glucose intolerance

As described in our previous work (Shapiro et al., 2015), impaired glucose tolerance and gestational diabetes cases were identified using guidelines from the Canadian Diabetes Association and the Society of Obstetricians and Gynaecologists of Canada (Berger et al., 2002; Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, et al., 2013). Results of GCT and oral glucose tolerance tests (OGTT) were recorded via chart review. Diagnosis was based on a two-step approach using results from both the GCT and OGTT. The criterion for GDM was a 1-hour 50 g GCT ≥10.3 mmol/L or at least two elevated OGTT values. Women were assigned a diagnosis of IGT if one of the OGTT cut-off values was met or exceeded. The 75 g OGTT cut-off values were 5.3 mmol/L for fasting glucose, 10.6 mmol/L one hour post glucose, and 8.9 mmol/L two hours post glucose. Cut-off values for a 100-g OGTT were 5.8 mmol/L for fasting glucose, 10.6 mmol/L one hour post glucose, 9.2 mmol/L two hours post glucose, and 8.0 mmol/L three hours post glucose.

We evaluated the a diagnosis with either GDM or IGT as a secondary outcome because it closely resembles a diagnosis of GDM according to guidelines adopted by the International Association of Diabetes and Pregnancy Study Groups (International Association of Diabetes and Pregnancy Study Groups Consensus Panel, 2010) and the Canadian Diabetes Association (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee et al., 2013). This less conservative GDM classification was not used in MIREC because the guidelines had not been adopted at the time that participants were undergoing prenatal screening. Analysis of the association between As and GCT results, our other secondary outcome, facilitated insight regarding potential sub-diagnostic changes in glucose tolerance.

2.4. Statistical analysis

Descriptive statistics were performed for all exposures, outcomes, and potential covariates. Since several urinary As species were seldom detected, we only analyzed the association with impaired glucose tolerance and gestational diabetes for As species that were detected in at least 40% of samples (i.e., DMA and AsB). Samples below the LOD were defined as the LOD/√2. Descriptive statistics for arsenic species are presented as specific gravity standardized concentrations according to the formula adapted from Just et al. (2010):

$$Pc = Pi\left[\frac{SGm - 1}{SGi - 1}\right]$$

where *Pc* is the *SG* standardized concentration, *Pi* is the observed concentration, *SGi* is the specific gravity of the sample and *SGm* is the median SG in the cohort.

We calculated the percent of GDM cases among women with detectable vs non detectable levels of arsenic species and determined statistical significance with the chi-square test. This portion of our analyses was limited to species where at least 10% of samples had detectable concentrations (DMA, AsB, and arsenite). We then used multivariable logistic regression to calculate odds ratios and 95% confidence intervals of the association between arsenic species (DMA or AsB) and i) GDM and ii) GDM or IGT. Linear regression was used to assess the association between As exposure and a continuous measure of GCT.

We evaluated DMA as a categorical variable, defined by tertiles, and a continuous variable. AsB was dichotomized at the LOD due to the high number of samples with undetectable concentrations. Due to the right skewed distribution, DMA was natural log transformed prior to analysis as a continuous variable. Based on knowledge of GDM risk factors (Casagrande et al., 2018) and predictors of urinary arsenic within the MIREC cohort, models were adjusted for the following potential confounders: maternal age, race, education, parity, and pre-pregnancy BMI (Ettinger et al., 2017). Based on previous reports of possible associations between maternal cadmium levels and GDM (Liu et al., 2018; Shapiro et al., 2015) and potential for co-occurring exposure (Olmedo et al., 2013), we also adjusted for maternal first trimester blood Cd levels. To account for varying urine dilution, the

specific gravity of each urine specimen was included in all models as a covariate. We present results from three models: unadjusted, adjusted for potential maternal confounders, and additionally adjusted for co-occurring arsenic metabolites (ie, either DMA or AsB). The third model (adjusted for DMA or AsB) was done to account for co-occurring As exposure. In addition, we evaluated additive and multiplicative interaction between DMA and AsB. Additive interaction was calculated using the relative excess risk due to interaction (RERI) (Richardson and Kaufman, 2009) and confidence intervals were calculated using the method described by Zou (2008) DMA and AsB were dichotomized at the lowest tertile (1.49 μg As/L) and LOD (0.75 μg As/L) respectively. Multiplicative interaction was evaluated by calculating the *p*-value of the product term. To assess potential effect modification by fetal sex, we conducted a stratified analysis and calculated the p-value for the sex * exposure product terms in models of the association between each arsenic species and both GDM (logistic regression) and GCT (linear regression). Due to small numbers in the stratified analysis, we estimates model parameters using penalized likelihood.

In recognition of higher reported rates of GDM (Hedderson et al., 2012) and higher urinary As levels among Asian compared to non-Asian women (Awata et al., 2017a, 2017b; Ettinger et al., 2017), we conducted a sensitivity analysis of the study population stratified according to Asian race. We examined this relation using the continuous measure of DMA due to the relatively low number of Asian women in the population ($n = 76$).

All analyses were performed in SAS v 9.3 (SAS Institute Inc. Cary, USA) and R v. 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Among 1243 women with live, singleton births, no previous history of diabetes, and complete arsenic and glucose tolerance data, 4.0% were classified as having GDM and 8.3% were classified as having combined GDM and IGT. The women in the present analysis were on average older than 30 years of age, of normal BMI, non-smokers, white, and were of moderate to high socioeconomic status (annual household income > $50,000) (Table 1).

Details regarding descriptive statistics of maternal urinary speciated arsenic concentrations have been reported previously (Ettinger et al., 2017). Briefly, the percent of detectable concentrations for arsenite, arsenate, MMA, DMA, and AsB was 15.9, 1.7, 7.8, 85.8, and 48.8 respectively. Median (IQR) DMA and AsB concentrations (μg As/L) were 2.32 (1.12–4.49) and LOD (LOD-3.52) respectively. Median (IQR) specific gravity standardized DMA and AsB concentrations (μg As/L) were 2.40 (1.65–3.82) and LOD (LOD- 3.66) respectively. The Kendall's tau correlation between continuous measures of DMA and AsB was 0.31 ($p < 0.05$). Median DMA concentrations were slightly higher among women with GDM (3.22 μg As/L) than women without GDM (2.32 μg As/L). Similarly, women with GDM had higher median AsB concentrations than women with normal glucose tolerance (GDM AsB = 1.87 μg As/L; no GDM AsB = 0.63 μg As/L).

The prevalence of GDM was higher among women with detectable versus undetectable As concentrations, yet these differences were not statistically significant. Among women with detectable DMA, AsB, or arsenite concentrations, GDM prevalence was 4.2, 5.3, and 4.7%. Comparatively, 2.4, 2.6, and 3.8% of women with undetectable DMA, AsB and arsenite concentrations met the criteria for GDM diagnosis. Using a chi-square test, these differences in GDM prevalence were not observed to be statistically significant.

A one unit increase in natural log transformed DMA, which corresponds to a nearly threefold increase in urinary DMA concentrations, was associated with elevated odds of GDM in the unadjusted and adjusted models, though the confidence interval in the adjusted results included the null value (aOR = 1.38, 95% CI: 0.92, 2.07). The odds were attenuated when adjusted for arsenobetaine (Table 2). In models examining the association with a diagnosis of either GDM or IGT, no evidence of association or trend were observed (data not shown).

Compared to women in the lowest tertile of DMA, those with DMA in the highest tertile (> 3.52 μg As/L) were at an increased risk of GDM (aOR: 3.86 95% CI: 1.18, 12.57, test for trend *p*-value = 0.04). This risk

Table 1
Characteristics of MIREC participants with speciated As data ($n = 1243$).

	Total		Normal Glucose		GDM	
	N	%	N	%	N	%
Maternal age (y)						
< 29	367	29.5	345	30.3	9	19.2
30–34	454	36.5	411	36.1	22	46.8
≥35	422	34.0	384	33.7	16	34.0
Race						
White	1006	80.9	935	82.0	25	53.2
Other	237	19.1	205	18.0	22	46.8
Pre-pregnancy BMI (kg/m^2)						
< 25	718	62.4	682	64.2	18	42.9
25- < 30	249	21.6	224	21.1	12	28.6
≥30	184	16.0	157	14.8	12	28.6
Education						
High school or less	103	8.3	96	8.4	6	12.8
Some college	345	27.8	298	26.2	15	31.9
Undergrad or higher	794	63.9	745	65.4	26	55.3
Parity						
Nulliparous	559	46.5	512	44.9	23	48.9
Parous	643	53.5	628	55.1	24	51.1
Smoking						
Current	62	5.0	56	4.9	4	8.5
Former	343	27.6	315	27.7	9	19.2
Never or quit during pregnancy	837	67.4	768	67.4	34	72.3
Household income (CAD)						
≤50,000	200	16.8	176	16.1	11	24.4
50,001–100,000	496	41.6	451	41.3	20	44.4
≥ 100,000	495	41.6	465	42.6	14	31.1

Note: MIREC, Maternal Infant Research on Environmental Chemicals; As, arsenic; BMI, body mass index; Missing: BMI $n = 92$, education $n = 1$, income $n = 52$, smoking $n = 1$.

Table 2
Odds ratios of association between maternal urinary speciated As (μg As/L) and gestational diabetes mellitus.

	GDM OR (95%CI)[a]				
	No. GDM	No. normal glucose	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Ln DMA	42	1049	1.38 (1.03,1.87)	1.38 (0.92,2.07)	1.18 (0.74,1.88)
DMA					
≤1.49	6	331	1.0	1.0	1.0
1.49– ≤ 3.52	16	365	2.42 (0.94,6.25)	3.21 (1.12,9.23)	2.75 (0.92,8.19)
> 3.52	20	353	3.13 (1.24,7.88)	3.86 (1.18,12.57)	2.88 (0.79,10.46)
Test for trend *p*-value			0.02	0.04	0.18
AsB					
< LOD	14	525	1.0	1.0	1.0
≥LOD	28	524	2.00 (1.04,3.85)	1.96 (0.97, 3.96)	1.53 (0.71, 3.28)

Note: Ln DMA, natural log transformed dimethylarsinic acid; AsB, arsenobetaine; GDM, gestational diabetes.

[a] Model 1 = unadjusted, Model 2 = adjusted for maternal age, specific gravity, education, pre-pregnancy BMI, parity, race, ln Cd, Model 3 = Model 2 + As (AsB in DMA model, DMA in AsB model).

Table 3
Odds ratios of association between maternal urinary speciated As (μg As/L) and gestational diabetes stratified by fetal sex.

	No. GDM	Males n = 565		No. GDM	Females n = 524	
		Model 2[a]	Model 3[b]		Model 2[a]	Model 3[b]
		OR (95% CI)	OR (95% CI)		OR (95% CI)	OR (95% CI)
DMA						
≤1.49	3	1.0	1.0	3	1.0	1.0
1.49–≤3.52	11	5.48 (1.49,20.14)	4.04 (1.05,15.62)	5	1.44 (0.33,6.21)	1.35 (0.30,6.04)
> 3.52	8	4.71 (1.05,21.10)	2.73 (0.53,14.19)	12	2.43 (0.51,11.74)	2.12 (0.38,11.96)
Test for trend p-value		0.08	0.43		0.22	0.34
AsB						
< LOD	7	1.0	1.0	7	1.0	1.0
≥LOD	15	2.74 (1.08,7.00)	2.01 (0.75,5.41)	13	1.50 (0.58,3.86)	1.19 (0.42,3.36)

Note: DMA, dimethylarsinic acid; AsB, arsenobetaine.
[a] Model 2: adjusted for maternal age, specific gravity, education, pre-pregnancy BMI, parity, race, ln Cd.
[b] Model 3: Model 2 + As(AsB in DMA model, DMA in AsB model.

was attenuated when adjusted for concurrent exposure to arsenobetaine (OR: 2.88 95% CI: 0.79, 10.46, test for trend p-value = 0.18). A similar pattern was observed for AsB. Compared to women with undetectable arsenobetaine concentrations, the magnitude of association was highest in the unadjusted GDM model (OR: 2.00 95% CI: 1.04, 3.85). The odds of GDM diminished incrementally when adjusting for covariates and DMA (Table 2). Neither DMA nor AsB was associated with the combined outcome of GDM or IGT (data not shown). The product term between AsB and DMA was not significant (p-value = 0.45) and the RERI was 1.83 (95% CI: −3.47, 5.28), indicating a greater than additive relation that was not statistically significant.

When stratified by infant sex, the magnitude of the association between both DMA or AsB and GDM was stronger among mothers with males than female infants (Table 3). Being pregnant with a male fetus and having higher DMA levels (2nd tertile) increased the odds of developing GDM by up to 5 times. Consistent with the total population, results were attenuated when adjusted for co-occurring arsenic species (AsB in DMA model, DMA in AsB model). The product terms for sex and AsB or DMA were not significant (sex ∗ AsB p-value = 0.88, sex ∗ DMA p-value = 0.19).

No association was observed between DMA levels and GCT results. Compared to undetectable AsB concentrations, detectable AsB concentrations were associated with slightly increased glucose challenge test results (β = 0.19; 95% CI:0.00,0.38); this result was minimally affected by adjustment for DMA (β = 0.22; 95% CI:0.01,0.43) (Table 4). When stratified by sex, the association between AsB and GCT results was positive and statistically significant among male infants but not among female infants (Table 5). No association was observed among either male or female in the DMA-GCT model estimates. The interactions between sex and AsB or DMA were not significant (sex ∗ AsB p-value = 0.67, sex ∗ DMA p-value = 0.81).

We observed that the rate of GDM was 9.5% among women who self-identified as Asian. The adjusted odds of GDM per unit increases in ln DMA was elevated but not statistically significant in the analyses restricted to Asians [OR = 2.42 (95% CI: 0.67, 8.74)] and when Asians were excluded [OR = 1.26 (95% CI: 0.80, 1.98)].

Table 4
Linear regression parameter estimates of association between maternal first trimester urinary speciated As levels (μg As/L) and glucose challenge test (mmol/L) results (n = 1063).

	Parameter estimates GCT (95% CI)		
	Model 1[a]	Model 2[b]	Model 3[c]
Ln DMA	0.05 (−0.05,0.14)	0.00 (−0.13,0.14)	−0.06 (−0.21,0.08)
AsB ≥ LOD	0.19 (0.01,0.37)	0.19 (0.00,0.38)	0.22 (0.01,0.43)

Note: Ln DMA, natural log transformed dimethylarsinic acid; AsB, arsenobetaine; GCT, glucose challenge test. Model estimates represent the change in GCT result per 1 ln unit increase in DMA or the change in GCT result per detectable vs undetectable AsB concentrations.
[a] Model 1: unadjusted.
[b] Model 2: adjusted for maternal age, specific gravity, education, pre-pregnancy BMI, parity, race, ln Cd.
[c] Model 3: Model 2 + AsB or DMA.

4. Discussion

In this cohort of Canadian women, women with elevated first trimester maternal urinary DMA experienced an increased risk of GDM. The magnitude of this increase was highest in models that were not adjusted for AsB. We did not identify any evidence of interaction between DMA and AsB, yet the small number of exposed cases may have precluded the ability to identify a synergistic or antagonistic effect. Detectable concentrations of AsB were positively associated with both GDM and glucose challenge test results, though the magnitude of the association with GCT was small and of questionable clinical significance. The association between DMA and GDM was stronger when restricted to women carrying male infants; however, these results were marked by wide confidence intervals. DMA exposure was not associated with changes in glucose challenge test results or with an increased risk of a less conservative definition of GDM (GDM or IGT).

Our findings are consistent with the few previous studies in the US (Ettinger et al., 2009; Farzan et al., 2016), and China (Peng et al., 2015; Xia et al., 2018) that have evaluated the relation between certain measures of total arsenic and GDM. In our previous analysis from the MIREC cohort, we observed a statistically significant association between total first trimester blood arsenic levels and GDM (Shapiro et al., 2015). Authors of the New Hampshire (NH) birth cohort study reported a statistically significantly association between arsenic and GDM when exposure assessment was based on toenail samples but not when using urinary samples. This NH study reported a lower LOD (ranging from 0.1 to 0.15 μg As/L for all species) with only 0.5% of samples with DMA concentrations below the LOD. It should be noted that the NH study was conducted in an area with known arsenic contamination of some private water supplies. While NH study (Farzan et al., 2016) did not report species specific concentrations, the median concentrations of urinary DMA in MIREC participants (2.32 μg As/L) were lower than reported in US NHANES (DMA = 3.5 μg As/L) (Aylward et al., 2014) and CHMS (3.8 μg As/L) (Health Canada, 2017) with similar detection limits.

A positive association between DMA and GDM is also consistent with biological mechanisms identified in experimental studies. Mice exposed to inorganic arsenic have been observed to exhibit impaired glucose tolerance and increased concentrations of arsenic metabolites

Table 5
Linear regression parameter estimates of association between maternal first trimester urinary speciated As levels (μg As/L) and glucose challenge test (GCT) (mmol/L) results stratified by fetal sex.

	Parameter estimates GCT (95% CI)					
	No. GDM	Males n = 553		No. GDM	Females n = 508	
		Model 2[a]	Model 3[b]		Model 2[a]	Model 3[b]
Ln DMA	21	0.06 (−0.11,0.24)	−0.04 (−0.23,0.15)	17	−0.09 (−0.30,0.13)	−0.13 (−0.36,0.11)
AsB ≥ LOD	14	0.35 (0.08,0.62)	0.37 (0.08,0.67)	11	0.05 (−0.22,0.33)	0.12 (−0.18,0.42)

Note: Ln DMA, natural log transformed dimethylarsinic acid; AsB, arsenobetaine; GCT, glucose challenge test. Model estimates represent the change in GCT result per 1 ln unit increase in DMA or the change in GCT result per detectable vs undetectable AsB concentrations.
[a] Model 2: adjusted for maternal age, specific gravity, education, pre-pregnancy BMI, parity, race, ln Cd.
[b] Model 3: Model 2 + AsB or DMA.

(Paul et al., 2007). As reviewed by Tseng et al. (Tseng, 2004), arsenic has multiple properties that may adversely affect glucose homeostasis. Two of the primary mechanistic pathways are increased oxidative stress and changes in gene expression. Oxidative stress may damage pancreatic beta cells and consequently inhibit glucose stimulated insulin secretion (Douillet et al., 2013; Walton et al., 2004). Our study highlights areas of scientific uncertainty regarding the roles of fetal sex, organic arsenic exposure, and arsenic methylation on GDM risk.

Recent literature suggests that both GDM risk and arsenic toxicity may differ by sex. A systematic review of 20 studies reported that women carrying a male fetus experienced a 4% higher risk of GDM (Jaskolka et al., 2015). In addition, an analysis of metabolic function during pregnancy found reduced beta cell function and a higher risk of GDM among women carrying a male fetus (Retnakaran and Shah, 2015). Maternal sex hormone levels may contribute to the cascade of physiological events involving fetal sex, glucose homeostasis, and arsenic toxicity. For example, higher circulating estradiol levels in mothers of female offspring (Toriola et al., 2011) may offer a protective effect on diabetes-related arsenic toxicity. Authors of an in vitro study of cancer cell cultures reported that arsenic may bind to estrogen and, in turn, negate the effects of both chemicals (Kumar et al., 2016). Consistent with the premise that the toxic effects of arsenic are mitigated by estrogen, arsenic exposed mice who underwent an ovariectomy were more likely to experience insulin resistance than mice who underwent a sham surgery (Huang et al., 2015). A recent Chinese cohort study reported a statistically significant interaction between fetal sex and maternal Cd levels in an analysis of GDM risk; women carrying males infants were at increased risk of GDM (Liu et al., 2018). Among MIREC participants, the number of GDM cases was not statistically different according to fetal sex (3.9% in female, 4.0% in male infants). DMA concentrations, on the other hand, were higher among women carrying a male infant (males = 4.48 ugl, females = 3.57 ugl) (p-value t-test of logged concentrations = 0.10). Due to the small number of GDM cases and resulting wide confidence intervals in the sex stratified analyses, these results are best viewed as exploratory. Our findings support the need for further investigation into the role of fetal sex in arsenic metabolism, toxicity, and maternal outcomes.

Results pertaining to AsB highlight questions about the potential toxicity of this organic species. Adjustment for AsB attenuated DMA model estimates; one interpretation of this result is that DMA risk estimates not adjusted for AsB may inflate the risk of GDM potentially attributable to inorganic As species (Aylward et al., 2014). Primary sources of urinary DMA concentrations are ingestion of rice and seafood (including shellfish and seaweed); these foods contain DMA as well as inorganic species which are metabolized to DMA (Guillod-Magnin et al., 2018; Molin et al., 2015). Analyses of NHANES data demonstrated that DMA concentrations rise subsequent to seafood ingestion (Navas-Acien et al., 2011) and that DMA is correlated with arsenobetaine (Aylward et al., 2014). Due to the moderate degree of correlation between these two species and the percent of undetectable AsB samples in our study, it is difficult to determine whether AsB has an effect on GDM or glucose challenge test results independent of DMA. The attenuation of DMA estimates in the AsB model could also be a consequence of modeling two moderately correlated exposures. Studies examining AsB as an independent outcome are sparse (Baek et al., 2017; Thomas et al., 2015). Authors of studies of the association between arsenic and GDM have either adjusted model estimates for AsB (Navas-Acien et al., 2008) or excluded AsB from analyses (Farzan et al., 2016). An analysis of the Korean National Health and Nutrition Examination suggest a possible association between AsB and glucose intolerance in men, though the authors of that study did not adjust for DMA (Baek et al., 2017). In a MIREC based analysis, Thomas et al. (2015) reported that AsB concentrations > 2.25 μg As/L were associated with a 65% increased risk of small for gestational age (SGA). Further inquiry regarding the potential independent association of health effects with AsB is, therefore, warranted.

Arsenic metabolism varies between individuals and populations due to genetic and phenotypic differences in metabolism, methylation, and availability of different species (Molin et al., 2015). Arsenic metabolism is also affected by pregnancy. The efficiency of arsenic methylation, and subsequent concentrations of metabolites such as DMA, is known to increase during pregnancy (Gardner et al., 2011). Pregnant women, therefore, may be particularly susceptible to DMA-related toxic effects. Genetic factors, namely polymorphisms of enzymes involved in arsenic metabolism (arsenic methyltransferase (AS3MT), DNA-methyltransferases) also affect methylation efficiency (Engstrom et al., 2013; Gardner et al., 2012). Pregnancy has been reported to have a greater effect on methylation efficiency than genotype (Gardner et al., 2012). Though we did not have the capacity to address inter-individual factors on arsenic metabolism in our study, our finding of a positive association between DMA and GDM is consistent with the notion that arsenic methylation is not a complete detoxification pathway (Khairul et al., 2017).

We also did not have capacity to account for the influence of diet, particularly rice and seafood intake, on model estimates. This issue is of particular interest for certain racial groups, such as Asians, where rice is a dietary staple. We attempted to account for race and diet by adjusting for race and conducting a sensitivity analysis among women who self-identified as Asian. Due to the composition of the MIREC study population, we were not able to more fully explore whether, compared to other groups, women of Asian race are more susceptible to the potentially adverse effects of As exposure on GDM risk. Authors of a recent analysis of a Chinese cohort reported that first trimester serum arsenic levels were significantly associated with a modestly elevated risk of GDM (Xia et al., 2018). Though the differences in arsenic measurement (serum versus urinary) preclude direct comparison, the magnitude of the association between maternal arsenic levels and GDM in this more homogenous population was comparable to findings among MIREC participants (Xia et al., 2018).

Strengths of this study are the relatively large sample size, ability to

control for multiple confounders, and availability of individual level arsenic data. Despite these strengths, our analysis was subject to some limitations. First, due to the percent of samples below the limit of detection, our analysis focused primarily on DMA and we had limited capacity to explore the association of the parent compounds or MMA with GDM. Although our study was hindered by the degree of undetectable samples, this is an issue common to measurement of urinary speciated arsenic. National biomonitoring studies in the US and Canada have reported similarly low detection rates for the speciated arsenic, particularly the inorganic compounds. Compared to a 15.9% detection rate in MIREC samples, trivalent arsenic was detected in 4% of NHANES (Aylward et al., 2014) and 24.4% of CHMS samples (Saravanabhavan et al., 2017). Detection rates for pentavalent arsenic are even lower; 2.2% in NHANES (Aylward et al., 2014) samples, 0.8% in CHMS samples (Saravanabhavan et al., 2017), and 1.7% in MIREC samples. To refine arsenic exposure assessment, future biomonitoring research may require more precise analytic methods or alternative matrices such as toenails. In addition to the issue with detection, our exposure assessment was based on one measure of As during the first trimester as a surrogate of relevant exposure throughout early pregnancy. In a study of repeated urinary As concentrations repeated over two years, the intraclass correlation of DMA was 0.47, indicative of a moderate degree of reproducibility (Kile et al., 2009). The timing and frequency of our exposure assessment is unlikely to introduce a notable source of bias, as the first trimester is a reasonable proxy for the critical window of exposure for GDM and any exposure misclassification is unlikely to differ according to GDM status. To assess potential confounding due to Cd exposure, we adjusted for maternal blood Cd levels. Adjustment for maternal urinary Cd levels may have been preferable due to use of the same biological matrix as arsenic, but Cd was not measured in the urine of MIREC participants. Another limitation of our study was the number of women with no glucose screening data. Since this information was extracted from chart review rather than collected as part of a MIREC study visit, data were only available from study centres that regularly perform screening on all patients. The potential selection bias resulting from this limitation is likely to be minimal because we did not observe any notable differences in study population characteristics between women with and without GDM data. Finally, due to the unique composition of the MIREC cohort, generalizability to other populations of diverse racial and socioeconomic status composition may be limited.

5. Conclusions

In this population of Canadian women, we observed a positive association between maternal first trimester urinary concentrations of DMA and clinically diagnosed GDM. This finding suggests that higher urinary DMA may be a risk factor for GDM and provides some support for evidence that methylation of inorganic As to DMA may not a complete detoxification pathway (Khairul et al., 2017). Due to the complexity of arsenic metabolism and inability to measure all parent compounds, sources of exposure, and correlated exposures, it is possible that the observed associations are driven by unmeasured confounders. Further research with more sensitive limits of detection is warranted to analyze risks associated with inorganic and organic As in pregnant women and to further investigate the potential modifying role of fetal sex on arsenic toxicity.

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Declaration of competing financial interests

The authors declare they have no actual or potential competing financial interests.

References

Arbuckle, T., Fraser, W., Fisher, M., Davis, K., Liang, C., Lupien, N., et al., 2013. Cohort profile: the maternal-infant research on environmental chemicals research platform. Paediatr. Perinat. Epidemiol. 27 (4), 415–425. https://doi.org/10.1111/ppe.12061. (PMID: 23772943).

Awata, H., Linder, S., Mitchell, L.E., Delclos, G.L., 2017a. Association of dietary intake and biomarker levels of arsenic, cadmium, lead, and mercury among Asian populations in the United States:NHANES 2011–2012. Environ. Health Perspect. 125 (3), 314–323. https://doi.org/10.1289/EHP28. (PMID: 27586241).

Awata, H., Linder, S., Mitchel, L.E., Delclos, G.L., 2017b. Biomarker levels of toxic metals among Asian populations in the United States: NHANES 2011–2012. Environ. Health Perspect. 125 (3), 306–313. https://doi.org/10.1289/EHP27. (PMID: 27517362).

Aylward, L.L., Ramasamy, S., Hays, S.M., Schoeny, R., Kirman, C.R., 2014. Evaluation of urinary speciated arsenic in NHANES: issues in interpretation in the context of potential inorganic arsenic exposure. Regul. Toxicol. Pharmacol. 69 (1), 49–54. 24582650. https://doi.org/10.1016/j.yrtph.2014.02.011.

Baek, K., Lee, N., Chung, I., 2017. Association of arsenobetaine with beta-cell function assessed by homeostasis model assessment (HOMA) in nondiabetic Koreans: data from the fourth Korea National Health and Nutrition Examination Survey (KNHANES) 2008–2009. Ann. Occup. Environ. Med. 29 (Jul 1), 1–11. https://doi.org/10.1186/s40557-017-0181-0. (PMID: 28702205).

Bélanger, P., Dumas, P., 2010. Fast determination of urine arsenic species by ion exchange chromatography and HPLC-ICP-MS using collision-reactive interface. At. Spectrosc. 31 (6), 175–181.

Berger, H., Crane, J., Farine, D., Armson, A., De La Ronde, S., Keenan-Lindsay, L., Leduc, L., 2002. Screening for gestational diabetes mellitus. J. Obstet. Gynaecol. Can. 24 (11), 894–912. 12417905. https://doi.org/10.1016/S1701-2163(16)31047-7.

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Thompson, D., Berger, H., Feig, R., Gagnon, R., Kader, T., et al., 2013. Diabetes and pregnancy. Can. J. Diabetes 37 (Suppl. 1), S168–S183. https://doi.org/10.1016/j.jcjd.2013.01.044. (PMID: 24070943).

Casagrande, S.S., Linder, B., Cowie, C.C., 2018. Prevalence of gestational diabetes and subsequent type 2 diabetes among U. S. women. Diabetes Res. Clin. Pract. 141 (Jul), 200–208. 29772286. https://doi.org/10.1016/j.diabres.2018.05.010.

Douillet, C., Currier, J., Saunders, J., Bodnar, W., Matousek, T., Styblo, M., 2013. Methylated trivalent arsenicals are potent inhibitors of glucose stimulated insulin secretion by murine pancreatic islets. Toxicol. Appl. Pharmacol. 267 (1), 11–15. https://doi.org/10.1016/j.taap.2012.12.007. (PMID: 23261974).

Engstrom, K., Hossain, M.B., Lauss, M., Ahmed, S., Raqib, R., Vahter, M., Broberg, K., 2013. Efficient arsenic metabolism — the AS3MT haplotype is associated with DNA methylation and expression of multiple genes around AS3MT. PLoS One 8 (1), e53732. https://doi.org/10.1371/journal.pone.0053732. (PMID: 23341986).

Ettinger, A.S., Zota, A.R., Amarasiriwardene, C.J., Hopkins, M.R., Schwartz, J., Hu, H., et al., 2009. Maternal arsenic exposure and impaired glucose tolerance during pregnancy. Environ. Health Perspect. 117 (7), 1059–1064. https://doi.org/10.1289/ehp0800533. (PMID: 19654913).

Ettinger, A.S., Arbuckle, T.E., Fisher, M., Lei, C., Davis, K., Cirtiu, C., et al., 2017. Arsenic levels among pregnant women and newborns in Canada: results from the maternal-infant research on environmental chemicals (MIREC) cohort. Environ. Res. 153, 8–16. https://doi.org/10.1016/j.envres.2016.11.008. (PMID: 27880879).

Farzan, S.F., Gossai, A., Chen, Y., Chasan-Taber, L., Baker, E., Karaga, S.M., 2016. Maternal arsenic exposure and gestational diabetes and glucose intolerance in the New Hampshire birth cohort study. Environ. Health 15 (1), 1–8. https://doi.org/10.1186/s12940-016-0194-0. (PMID: 27825389).

Gardner, R.M., Nermell, B., Kippler, M., Grandér, M., Li, L., Ekstrom, E.C., et al., 2011. Arsenic methylation efficiency increases during the first trimester of pregnancy independent of folate status. Reprod. Toxicol. 31 (2), 210–218. https://doi.org/10.1016/j.reprotox.2010.11.002. (PMID: 21078382).

Gardner, R.M., Engstrom, K., Bottai, M., Hoque, W.A., Raqib, R., Broberg, K., et al., 2012. Pregnancy and the methyltransferase genotype independently influence the arsenic methylation phenotype. Pharmacogenet. Genomics 22 (7), 508–516. https://doi.org/10.1097/FPC.0b013e3283535d6a. (PMID: 22547080).

Guillod-Magnin, R., Brüschweiler, B.J., Aubert, R., Haldimann, M., 2018. Arsenic species in rice and rice-based products consumed by toddlers in Switzerland. Food Addit. Contam. Part A. 35 (6), 1164–1178. https://doi.org/10.1080/19440049.2018.1440641. (PMID: 29448893).

Health Canada, 2017. Fourth Report on Human Biomonitoring of Environmental Chemicals in Canada. https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/environmental-contaminants/fourth-report-human-biomonitoring-environmental-chemicals-canada-page-4.html#a10-1, Accessed date: 7 September 2018.

Hedderson, M., Ehrlich, S., Sridhar, S., Darbinian, J., Moore, S., Ferrara, A., 2012. Racial/ethnic disparities in the prevalence of gestational diabetes mellitus by BMI. Diabetes Care 35 (7), 1492–1498. https://doi.org/10.2337/dc11-2267. (PMID: 22619080).

Huang, C., Yang, C., Chan, D., Wang, C., Huang, K., Wu, C., 2015. Arsenic exposure and

glucose intolerance/insulin resistance in estrogen-deficient female mice. Environ. Health Perspect. 123 (11), 1138–1145. https://doi.org/10.1289/ehp.1408663. (PMID: 25859628).
IARC, 2012. Arsenic, Metals, Fibres, and Dusts IARC Monographs on the Evaluation of Carcinogenic Risks to Human. Vol. 110c. https://monographs.iarc.fr/iarc-monographs-on-the-evaluation-of-carcinogenic-risks-to-humans-19/, Accessed date: 13 July 2018.
International Association of Diabetes and Pregnancy Study Groups Consensus Panel, 2010. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 33 (3), 676–682. https://doi.org/10.2337/dc09-1848. (PMID: 20190296).
Jaskolka, D., Retnakaran, R., Zinman, B., Kramer, C.K., 2015. Sex of the baby and risk of gestational diabetes mellitus in the mother: a systematic review and meta-analysis. Diabetologia 58 (11), 2469–2475. https://doi.org/10.1007/s00125-015-3726-1. (PMID: 26253767).
Just, A.C., Adibi, J.J., Rundle, A.G., Calafat, A.M., Camann, D.E., Hauser, R., et al., 2010. Urinary and air phthalate concentrations and self-reported use of personal care products among minority pregnant women in New York City. J. Expo. Sci. Env. Epidemiol. 20 (7), 625–633. https://doi.org/10.1038/jes.2010.13. (PMID: 20354564).
Khairul, I., Wang, Q.Q., Jiang, Y.H., Wang, C., 2017. Metabolism, toxicity and anticancer activities of arsenic compounds. Oncotarget 8 (14), 23905–23926. https://doi.org/10.18632/oncotarget.14733. (PMID: 28108741).
Kile, M.L., Hoffman, E., Hsueh, Y., Afroz, S., Quamruzzaman, Q., Rahman, M., et al., 2009. Variability in biomarkers of arsenic exposure and metabolism in adults over time. Environ. Health Persepct. 117 (3), 455–460. https://doi.org/10.1289/ehp.11251. (PMID: 19337522).
Kumar, S., Mukherjee, T.K., Guptasarma, P., 2016. Arsenic and 17- b -estradiol bind to each other and neutralize each other's signaling effects. Biochem. Biophys. Res. Commun. 477 (4), 575–580. https://doi.org/10.1016/j.bbrc.2016.06.087. (PMID: 27346132).
Kuo, C., Moon, K.A., Wang, S., Silbergeld, E., Navas-Acien, A., 2017. The association of arsenic metabolism with cancer, cardiovascular disease, and diabetes: a systematic review of the epidemiological evidence. Environ. Health Perspect. 125 (8), 087001. https://doi.org/10.1289/EHP577. (PMID: 28796632).
Liu, W., Zhang, B., Huang, Z., Pan, X., Chen, X., Hu, C., et al., 2018. Cadmium body burden and gestational diabetes mellitus: a prospective study. Environ. Health Perspect. 126 (2), 0270006. https://doi.org/10.1289/EHP2716. (PMID: 29425094).
Molin, M., Ulven, M., Meltzer, H.M., Alexander, J., 2015. Arsenic in the human food chain, biotransformation and toxicology – review focusing on seafood arsenic. J. Trace Elem. Med. Biol. 31, 249–259. https://doi.org/10.1016/j.jtemb.2015.01.010. (PMID: 25666158).
Navas-Acien, A., Silbergeld, E.K., Pastor-Barriuso, R., Guallar, E., 2008. Arsenic exposure and prevalence of type 2 diabetes in US adults. JAMA 300 (7), 814–822. https://doi.org/10.1001/jama.300.7.814. (PMID: 18714061).
Navas-Acien, A., Francesconi, K.A., Silbergeld, E.K., Guallar, E., 2011. Seafood intake and urine concentrations of total arsenic, dimethylarsinate and arsenobetaine in the US population. Environ. Res. 111 (1), 110–118. https://doi.org/10.1016/j.envres.2010.10.009. (PMID: 21093857).
Olmedo, P., Pla, A., Hernández, A.F., Barbier, F., Ayouni, L., Gil, F., 2013. Determination of toxic elements (mercury, cadmium, lead, tin and arsenic) in fish and shell fish samples. Risk assessment for the consumers. Environ. Int. 59 (Sep), 63–72. https://doi.org/10.1016/j.envint.2013.05.005. (PMID: 23792415).
Paul, D.S., Hernández-Zavala, A., Walton, F.S., Adair, B.M., Dedina, J., Matousek, T., Stýblo, M., 2007. Examination of the effects of arsenic on glucose homeostasis in cell culture and animal studies: development of a mouse model for arsenic-induced diabetes. Toxicol. Appl. Pharmacol. 222 (3), 305–314. 17336358. https://doi.org/10.1016/j.taap.2007.01.010.
Peng, S., Liu, L., Zhang, X., Heinrich, J., Zhang, J., Schramm, K., et al., 2015. A nested case-control study indicating heavy metal residues in meconium associate with maternal gestational diabetes mellitus risk. Environ. Health 14 (Feb 28), 19. https://doi.org/10.1186/s12940-015-0004-0. (PMID: 25888735).
Quansah, R., Armah, F.A., Essumang, D.K., Luginaah, I., Clarke, E., 2015. Association of arsenic with adverse pregnancy outcomes/infant mortality: a systematic review and meta-analysis. Environ. Health Perspect. 123 (5), 412–421. https://doi.org/10.1289/ehp.1307894. (PMID: 25626053).
Retnakaran, R., Shah, B.R., 2015. Fetal sex and the natural history of maternal risk of diabetes during and after pregnancy. J. Clin. Endocrinol. Metab. 100 (7), 2574–2580. https://doi.org/10.1210/jc.2015-1763.
Richardson, D.B., Kaufman, J.S., 2009. Estimation of the relative excess risk due to interaction and associated confidence bounds. Am. J. Epidemiol. 169 (6), 756–760. https://doi.org/10.1093/aje/kwn411. (PMID: 19211620).
Saravanabhavan, G., Werry, K., Walker, M., Haines, D., Malowany, M., Khoury, C., 2017. Human biomonitoring reference values for metals and trace elements in blood and urine derived from the Canadian Health Measures Survey 2007–2013. Int. J. Hyg. Environ. Health 220, 189–200. https://doi.org/10.1016/j.ijheh.2016.10.006.
Shapiro, G.D., Dodds, L., Arbuckle, T.E., Ashley-Martin, J., Fraser, W., Fisher, M., et al., 2015. Exposure to phthalates, bisphenol A and metals in pregnancy and the association with impaired glucose tolerance and gestational diabetes mellitus: The MIREC study. Environ. Int. 83 (Oct), 63–71. https://doi.org/10.1016/j.envint.2015.05.016. (PMID: 26101084).
Thomas, S., Arbuckle, T.E., Fisher, M., Fraser, W.D., Ettinger, A., King, W., 2015. Metals exposure and risk of small-for-gestational age birth in a Canadian birth cohort: the MIREC study. Environ. Res. 140 (Jul), 430–439. https://doi.org/10.1016/j.envres.2015.04.018. (PMID: 25967284).
Toriola, A., Vaarasmaki, M., Lehtinen, M., Zeleniuch-Jacquotte, A., Lundin, E., Rodgers, K.-G., Lasko, H.-A., 2011. Determinants of maternal sex steroids during the first half of pregnancy. Obstet. Gynecol. 118 (5), 1029–1036. https://doi.org/10.1097/AOG.0b013e3182342b7f. (PMID: 22015870).
Tseng, C., 2004. The potential biological mechanisms of arsenic-induced diabetes mellitus. Toxicol. Appl. Pharmacol. 197, 67–83. https://doi.org/10.1016/j.taap.2004.02.009.
Walton, F.S., Harmon, A.W., Paul, D.S., Drobna, Z., Patel, Y.M., Styblo, M., 2004. Inhibition of insulin-dependent glucose uptake by trivalent arsenicals: possible mechanism of arsenic-induced diabetes. Toxicol. Appl. Pharmacol. 198 (3), 424–433. https://doi.org/10.1016/j.taap.2003.10.026. (PMID: 15276423).
Wang, W., Xie, Z., Lin, Y., Zhang, D., 2014. Association of inorganic arsenic exposure with type 2 diabetes mellitus: a meta-analysis. J. Epidemiol. Community Health 68 (2), 176–184. https://doi.org/10.1136/jech-2013-203114. (PMID: 24133074).
Watanabe, T., Hirano, S., 2013. Metabolism of arsenic and its toxicological relevance. Arch. Toxicol. 87 (6), 969–979. https://doi.org/10.1007/s00204-012-0904-5. (PMID: 22811022).
Xia, X., Liang, C., Sheng, J., Yan, S., Huang, K., Li, Z., 2018. Association between serum arsenic levels and gestational diabetes mellitus: a population-based birth cohort study. Environ. Pollut. 235 (Apr), 850–856. https://doi.org/10.1016/j.envpol.2018.01.016. (PMID: 29348076).
Zou, G.Y., 2008. On the estimation of additive interaction by use of the four-by-two table and beyond. Am. J. Epidemiol. 168 (2), 212–224. 18511428. https://doi.org/10.1093/aje/kwn104.