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Temporal variation of total mercury levels in the hair of pregnant women from the Maternal-Infant Research on Environmental Chemicals (MIREC) study

Anna O. Lukina [a, *], Mandy Fisher [a], Cheryl Khoury [a, **], John Than [a], Mireille Guay [a], Jean-François Paradis [b], Tye E. Arbuckle [a], Melissa Legrand [c]

[a] Environmental Health Science & Research Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, ON, Canada
[b] Health Products and Food Laboratories, Regulatory Operations and Regions Branch, Health Canada, Longueuil, QC, Canada
[c] Family Physician, GMF Wakefield, 777 Riverside Dr., Wakefield, QC, Canada

HIGHLIGHTS

- Mercury exposure was evaluated in the pan-Canadian MIREC pregnancy cohort.
- T-Hg levels in scalp hair significantly decreased during pregnancy, from conception to delivery.
- T-Hg levels in hair were significantly correlated with T-Hg levels in blood.
- Median hair-to-blood ratios of T-Hg levels increased from 364 to 408 during pregnancy.
- Consumption of predatory fish weakly correlated with T-Hg levels in hair and blood.

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ABSTRACT

Prenatal exposure to total mercury (T-Hg) comes from both natural and anthropogenic sources. T-Hg can cross the blood-brain and placental barriers, and may be associated with future neurological and physiological dysfunctions. Scalp hair is an optimal and non-invasive indicator of chronic T-Hg exposure. As part of the Maternal-Infant Research on Environmental Chemicals (MIREC) Study, hair samples from 350 women were collected within weeks after giving birth, to determine temporal variations in T-Hg levels from preconception to delivery, and to compare these levels to corresponding levels measured in other matrices (maternal and umbilical cord blood, and infant's meconium). A maximum of 12 one-cm hair segments were cut starting at the scalp; segments closer to the scalp reflected recent exposure (within the last month). For proper comparison, the hair segments were matched with the collection dates for other matrices. GM hair T-Hg levels greatly decreased during pregnancy, from 0.26 μg g^{-1} (preconception or full-length hair) to 0.18 μg g^{-1} (at delivery or segments closer to the scalp). A similar decreasing trend was found for T-Hg in maternal blood: 1st trimester (0.60 μg L^{-1}) to 3rd trimester (0.47 μg L^{-1}). The median hair-to-blood ratios of T-Hg levels varied from 364 (1st trimester), to 408 (3rd trimester), to 229 (cord blood). Very low T-Hg levels were detected in meconium. Mercury levels in blood and hair correlated with consumption of large predatory fish.

1. Introduction

Mercury (Hg) is a volatile and odourless transition metal that is naturally present in the earth's crust. As a result of human activities, Hg is either released into the environment (e.g., coal combustion) or is incorporated into various products (e.g., medical and measuring devices, batteries, fluorescent light bulbs) (UNEP, 2017). Hg is a very persistent and mobile metal, and can travel over long

Abbreviations: (MIREC) Study, Maternal-Infant Research on Environmental Chemicals; T-Hg, total mercury; MeHg, methylmercury; BMI, pre-pregnancy body mass index; GM, geometric mean; CI, confidence intervals; ppm, parts per million; ppb, parts per billion; ppt, parts per trillion.

* Corresponding author. 8-111, 269 Laurier Avenue W., Ottawa, ON, K1A 0K9, Canada.
** Corresponding author. 8-122, 269 Laurier Avenue W., Ottawa, ON, K1A 0K9, Canada.
E-mail addresses: anna.lukina@canada.ca (A.O. Lukina), cheryl.khoury@canada.ca (C. Khoury).

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distances via ocean and air currents. It is known to bioaccumulate in wildlife and biomagnify in food webs to humans. Hg exists in many forms, but one particularly concerning form is methylmercury (MeHg). The toxicity of MeHg was first described in the mid-twentieth century in Japan and Iraq (Skerfving and Copplestone, 1976; WHO, 2017). Although MeHg is a major neurotoxicant affecting the central and peripheral nervous systems (Skerfving and Copplestone, 1976; WHO, 2017), it may also affect cardiovascular and digestive systems (Roy et al., 2017).

Methylmercury can be found in the tissues of large predatory marine (e.g., shark, swordfish, albacore/white tuna, escolar, marlin) and freshwater (e.g., pike, bass, walleye) fish (Health Canada, 2004). In Canada, it is recommended that pregnant women or women of reproductive age (20–39 years) limit large predatory fish consumption to 150 g/month, which is equivalent to approximately one cup (Health Canada, 2007a, 2007b, and 2009).

Pregnant women and their developing fetuses are considered particularly susceptible to MeHg, because it can pass the placental barrier and cross the blood-brain barrier of the fetus (Kajiwara et al., 1996). A number of studies have reported associations between prenatal exposure to MeHg or total mercury (T-Hg) and decreased fetal growth or early delivery (Myers et al., 2000; Xue et al., 2007; Ramón et al., 2009; Basu et al., 2014) with possible neurotoxic effects later in childhood, including effects on cerebral function (Grandjean et al., 1998), delays in brainstem auditory evoked responses (Murata et al., 2004), effects on deep tendon reflexes and poor muscle coordination, as well as reduced attention and short-term memory (Cordier et al., 2002). Previous studies have shown negative effects of MeHg on neurodevelopment in infants, especially boys (Grandjean et al., 1998, Myers et al., 2000; Cordier et al., 2002; Gao et al., 2007; Kim et al., 2018). Other studies have found no association between prenatal mercury exposure and adverse birth outcomes (Björnberg et al., 2005; Drouillet-Pinard et al., 2010; Castano et al., 2015; Miyashita et al., 2015). Given the divergence in the literature on prenatal effects of mercury exposure, one possible explanation is that there might be differences in exposures among geographically diverse populations (Karagas et al., 2012), specifically populations residing in coastal regions, who have easier access to food known to be rich in Hg compared to inland populations. A positive association between consumption of local food (swordfish and fresh tuna and/or seal and whale) and MeHg/T-Hg exposure has been seen in some coastal areas, including the Canadian Arctic (Muckle et al., 2001a, b; Plusquellec et al., 2010), the Mediterranean (Ramón et al., 2009; Llop et al., 2014; Tratnik et al., 2019), China (Gao et al., 2007), the Faroe Islands (Grandjean et al., 1998, 2003) and Greenland (Foldspang and Hansen, 1990).

The effects of mercury in the vulnerable populations described above continue to be of public health concern, with ongoing efforts to monitor exposures locally, nationally and internationally. To this end, the best biospecimens to estimate MeHg exposure are blood and scalp hair (Berglund et al., 2005). The biological half-life of MeHg in blood varies from 1 to 2 months, depending on peak exposure, the individual's sex, age, body mass index (BMI), and Hg concentration (Stern, 2005; Mergler et al., 2007; Yaginuma-Sakurai et al., 2012; Akerstrom et al., 2017). Alternatively, scalp hair reflects chronological exposure to MeHg (Nuttall, 2006; Mergler et al., 2007). In both blood and hair, nearly all Hg is in the form of MeHg; however, for simplicity and cost-effectiveness purposes, T-Hg is normally determined (Berglund et al., 2005; Yaginuma-Sakurai et al., 2012). Previous studies have shown that hair T-Hg correlates well with blood T-Hg (Budtz-Jørgensen et al., 2004; Yaginuma-Sakurai et al., 2012), and, to reflect overall exposure, the hair-to-blood ratio is often calculated.

Mercury exposure has been broadly studied; however, previous studies with pregnant women often focused on collecting segmented hair strands closer to the scalp (i.e., recent or short-term exposure) rather than collecting full-length hair (i.e., long-term exposure) (Xue et al., 2007; van Wijngaarden et al., 2014; Basu et al., 2014; Miyashita et al., 2015). Measuring T-Hg in full-length hair demonstrates how levels change during the course of pregnancy, especially during critical points in pregnancy when basic embryonic growth and development happens. Analysis of T-Hg in different maternal and infant matrices is not only important for biomonitoring studies of vulnerable populations, but also helps to describe T-Hg pharmacokinetics within the body over a longer period. The Maternal-Infant Research on Environmental Chemicals (MIREC) Study was designed to investigate potential associations between prenatal exposure to a variety of environmental chemicals, including T-Hg, and related health effects on pregnant women and their developing fetuses.

The first objective of this study was to characterize temporal variations of T-Hg levels in scalp hair for the full duration of pregnancy, from preconception to postpartum, using one-cm sequential hair segments from a representative sub-sample of the MIREC Study cohort. The second objective was to determine pregnancy specific hair-to-blood ratios of T-Hg levels.

2. Methodology

2.1. Study participants

The MIREC Study recruited approximately 2000 pregnant women from 10 sites across Canada between 2008 and 2011. The details of the MIREC cohort can be found elsewhere (Arbuckle et al., 2013). Briefly, all participants were recruited during the 1st trimester of pregnancy (6 to <14 weeks of gestation), were at least 18 years of age, and were planning to deliver at local hospitals. Women with histories of known fetal chromosomal abnormalities or major malformations during pregnancy, major chronic diseases, threatened abortion, or illicit drug use were excluded. Information on participants' physical and socio-demographic characteristics were collected from administered questionnaires. Information on fish consumption during pregnancy (specifically identifying fish likely to be higher in Hg levels) was collected. This study was reviewed and approved by the Health Canada Research Ethics Board, as well as the ethics committees at the MIREC study coordination centre (Ste-Justine hospital, Montreal, QC), and the participating hospitals and research centres across Canada.

2.2. Biological sample collection and analysis

Three hundred and fifty women from the MIREC Study were included in the T-Hg hair analysis, representing approximately 27% of those who provided a hair sample at delivery or postpartum visit (1282 women). Selection of hair samples for T-Hg analysis was based on a specific algorithm that allowed random selection of subsamples from each of the 10 participating sites across Canada. Scalp hair samples were collected at least 24 days post-delivery and around 25% of participants had their hair collected more than 75 days post-delivery. A 5-mm (approximate) bundle of hair was isolated and cut from the occipital region, as close to the scalp as possible, ensuring minimal effect on participants' aesthetics. The hair bundle was then placed in a polyethylene bag and fastened to the bag with staples near the scalp end of the hair bundle. Each participant's hair bundle was cut into sequential one-cm segments (presumed to represent ~ one month of hair growth; Nuttall, 2006) starting from the scalp, up to a maximum of 12 segments (total of 12 cm). For each participant, the hair segment that corresponded to

her delivery date was taken to be hair segment number one. The subsequent hair segments were then recorded and numbered two, three, etc., which retrospectively represent the pregnancy period and if hair was long enough, preconception as well.

Determination of T-Hg content in human hair was done in Health Canada's laboratory using a specific analytical method (QLA-MA-0050). This method is accredited by the Standards Council of Canada and complies with the requirements of RG-PT (Requirements & Guidance- Proficiency Testing for Laboratories (Testing and Medical)), ISO/IEC 17025:2005 and RG-TMDNRT (Requirements and Guidance for Accreditation of Laboratories Engaged in Test Method Development and Non-Routine Testing). Briefly, the digestion method included adding 1 mL of 1% cysteine and 2 mL of 45% sodium hydroxide solutions to the hair samples. Solutions were heated with a DigiPrep at 90 °C for 15 min with a slight agitation after the first 7 min. The digested samples were diluted to 50 mL using a 10 g L^{-1} sodium chloride solution. A 50-fold dilution was then performed using an aqueous solution containing 1% (v/v) of concentrated hydrochloric acid and 0.001% of potassium dichromate. Samples were analyzed using a cold vapour atomic fluorescence spectrophotometry (CVAFS).

A calibration curve was prepared with the same diluent used for the samples and spiked with different volumes of a 1 ppb mercury solution to obtain 2.5, 5.0, 10, 25, 50 and 100 ppt standards. A human hair sample, containing a low amount of mercury, was analyzed and added to the calibration standards and control standards so that the hair matrix was present. The human hair sample was subtracted to the standards result before calculating each response. Linearity of the calibration curve was checked with the correlation coefficient being $r \geq 0.995$ and the calculated concentrations ±20% for standard 1 and ± 15% for the others. Quality assurance was ensured by injecting different controls. Control standards of 5 ppt were analyzed every 15 injections and at the end of the sequence to verify the instrument stability. A 5 ppt control standard was prepared and analyzed using a different supplier or lot number to verify the accuracy of the calibration curve. A validated reference material (NIES-13) was analyzed to verify the accuracy and precision of the analytical method. The analytical method was validated following Health Canada laboratory procedure (QLA-0086). The minimum T-Hg amount detectable in maternal hair was 0.07 μg g^{-1}. Those laboratory results that fell below the detection limit (LOD) were substituted with LOD/2.

The procedures for collection, handling, and chemical analysis of other mother-child matrices (maternal and cord blood, and meconium) procedures are described in detail elsewhere (Arbuckle et al., 2013, 2016).

2.3. Statistical analyses

A trend test was used to examine the monthly temporal variation in T-Hg body burden. Since the measurements of T-Hg levels in sequential one-cm hair segments from the same woman were not independent, the random coefficient model was used, where the response variable was log T-Hg level in hair and the explanatory variable was the hair segment number. The random regression line for each participant deviates about the overall population (fixed) regression line. The latter's slope and its statistical significance would answer the question of whether a trend existed.

Comparisons of T-Hg levels in maternal hair to levels in different mother-infant biological matrices were presented as ratios and Pearson's correlations. The segments of hair (pregnancy time windows) corresponding to the collection of 1st trimester (6–13 weeks of gestation) and 3rd trimester (32–34 weeks) whole blood, umbilical cord blood, and infant meconium were identified. It was assumed that the point closest to the scalp where the piece of hair was cut was formed 3 weeks (Nuttall, 2006; Legrand et al., 2010) prior to the hair collection date and that each subsequent one-cm segment represented approximately one month prior to the preceding one-cm segment. Thus, one-cm hair segments covered a range of dates and the one containing the collection date of the respective blood or meconium was the matching segment whose T-Hg level was used for the correlation and ratio calculations. For example, if a hair segment covered dates 1–31 of the month and 1st trimester blood collection happened on the 15th of that month, then the T-Hg in that hair segment was matched with the T-Hg detected in the 1st trimester blood sample. For proper comparisons of T-Hg levels among matrices, a universal unit (ppm) was used.

For determination of potential predictors of mercury exposure and for comparison with the larger MIREC cohort, the parametric one-way analysis of variance was used to determine whether geometric mean (GM) T-Hg levels were the same across categories for each physical or socio-demographic characteristic. The average T-Hg level in up to 12 segments of scalp hair was used for each participant. Since the normality assumption was not met, values of hair T-Hg levels were log-transformed. Pairwise comparisons among groups were conducted if overall significance at the 5% level ($\alpha = 0.05$) was found. Statistical analyses were conducted using SAS Enterprise Guide version 5.1 (SAS Institute Inc., Cary, North Carolina).

3. Results

3.1. Characteristics of study participants

Of the 350 pregnant women selected for this study, hair samples from 22 women could not be analyzed (i.e., insufficient amount for chemical analysis or laboratory error), resulting in a final sample size of 328 women and a total of 3687 one-cm hair segments. Of these 328 women, 267 (81%) had 12 hair segments, the maximum number collected. Physical and socio-demographic characteristics of study participants and their comparison to the larger MIREC cohort are summarized in Table 1. In our study, the majority of participants were 30 years or older, had never smoked, were born in Canada, were well educated, were either giving birth for the first time or had given birth once before, had an underweight-normal pre-pregnancy BMI, and had an annual household income > $50,000 CAD. In the present cohort, the infant sex ratio was nearly equal (1:1).

Our results suggest that maternal age, pre-pregnancy BMI, educational attainment, and whether a mother was born in Canada or foreign-born, were potential predictors of hair T-Hg (Table 1). These predictors were also identified in models of maternal blood T-Hg from the full MIREC cohort (Table 1).

3.2. Temporal variation in hair and blood T-Hg levels during pregnancy

The GM hair T-Hg level was 0.21 μg g^{-1} (95% CI: 0.19–0.24 μg g^{-1}) (Table 2). Overall, mean T-Hg levels in hair across all participants decreased over time from preconception (GM = 0.26 μg g^{-1}; 95% CI: 0.21–0.32 μg g-1) to delivery (GM = 0.18 μg g^{-1}; 95% CI: 0.16–0.20 μg g-1) (Fig. 1). This trend was tested by using the random coefficient model, which showed a significant positive slope ($\beta = 0.030$, $p < 0.0001$) for the fixed effect of the hair segment number, suggesting that T-Hg levels in hair were increasing the larger the hair segment number, meaning that T-Hg levels were decreasing throughout pregnancy (Fig. 1). There was a decrease in T-Hg levels detected in maternal blood from the 1st trimester (GM = 0.60 μg L^{-1}; 95% CI: 0.54–0.68 μg L-1) compared to levels in maternal blood from the 3rd trimester

Table 1
Descriptive statistics of our study participants (N = 328, smaller cohort) and T-Hg levels (μg g^{-1}) in maternal hair in comparison to larger MIREC cohort (N = 1983) and maternal T-Hg levels (μg L^{-1}) in blood of 1st and 3rd trimesters combined (N = 3611) (Arbuckle et al., 2016).

Characteristics	N	%	[T-Hg] in hair[a]			N	%	[T-Hg] in maternal blood[b]		
			p-value	Pairwise[c]	GM (95% CI)			p-value	Pairwise[c]	GM (95% CI)
Maternal age (years)			<0.0001					<0.0001		
<25	14	4.3		A	0.12 (0.07, 0.20)	244	6.8		A	0.27 (0.21, 0.33)
25–29	88	26.8		A	0.17 (0.14, 0.21)	848	23.5		B	0.41 (0.36, 0.46)
30–34	128	39.0		A	0.20 (0.17, 0.24)	1290	35.7		C	0.55 (0.50, 0.61)
35+	98	29.9		B	0.31 (0.26, 0.38)	1229	34.0		D	0.79 (0.71, 0.87)
Smoking status at first visit (<14 weeks)			0.3997					**<0.0001**		
Never	214	65.2			0.22 (0.19, 0.25)	2205	61.1		A	0.41 (0.35, 0.48)
Former	93	28.4			0.22 (0.18, 0.27)	974	27.0		B	0.61 (0.55, 0.68)
Current/Quit during pregnancy	21	6.4			0.16 (0.11, 0.25)	427	11.8		B	0.56 (0.52, 0.60)
Country of birth			**0.0013**					**<0.0001**		
Foreign-born	54	16.5		A	0.32 (0.25, 0.41)	677	18.7		A	0.91 (0.82, 1.00)
Canadian-born	274	83.5		B	0.20 (0.18, 0.22)	2934	81.3		B	0.49 (0.47, 0.52)
Maternal education			**<0.0001**					**<0.0001**		
High school or less	14	4.3		A	0.13 (0.08, 0.22)	309	8.6		A	0.31 (0.26, 0.38)
College courses or diploma	73	22.3		A	0.14 (0.11, 0.17)	1031	28.6		B	0.45 (0.41, 0.50)
University degree	241	73.5		B	0.25 (0.22, 0.29)	2267	62.9		C	0.65 (0.61, 0.70)
Parity[d]			0.6786					0.3286		
0	149	45.4			0.22 (0.19, 0.26)	1604	44.5			0.57 (0.52, 0.62)
1	135	41.2			0.20 (0.17, 0.24)	1447	40.1			0.55 (0.50, 0.59)
2+	44	13.4			0.23 (0.17, 0.31)	557	15.4			0.52 (0.45, 0.59)
Infant sex			0.5729							
Male	168	51.2			0.22 (0.19, 0.26)					
Female	160	48.8			0.21 (0.18, 0.24)					
Pre-pregnancy BMI (kg m^{-2})			**<0.001**					**<0.001**		
Underweight-Normal (<25.00)	206	66.2		A	0.26 (0.23, 0.29)	2141	63.9		A	0.62 (0.57, 0.66)
Overweight (25.00–29.99)	60	19.3		B	0.17 (0.13, 0.22)	720	21.5		B	0.53 (0.47, 0.59)
Obese (>29.99)	45	14.5		B	0.14 (0.10, 0.18)	487	14.5		C	0.40 (0.34, 0.46)
Season of sampling			0.6892					**<0.0001**		
Fall	79	24.1			0.21 (0.17, 0.26)	995	27.6		A	0.56 (0.52, 0.60)
Winter	81	24.7			0.21 (0.17, 0.26)	826	22.9		AB	0.51 (0.47, 0.56)
Spring	94	28.7			0.20 (0.16, 0.25)	947	26.2		AB	0.53 (0.49, 0.57)
Summer	74	22.6			0.24 (0.19, 0.30)	843	23.3		AC	0.60 (0.56, 0.65)
Annual household income			0.0824					**<0.0001**		
≤50,000	43	13.1			0.21 (0.16, 0.29)	618	17.9		A	0.42 (0.37, 0.48)
50,001–100,000	137	41.8			0.19 (0.16, 0.22)	1433	41.5		B	0.51 (0.47, 0.55)
>100,000	136	41.5			0.25 (0.21, 0.30)	1398	40.5		C	0.68 (0.62, 0.74)
No response	12	3.7			0.17 (0.10, 0.30)					
Marital status			0.7849							
Married or common-law	318	97.0			0.21 (0.19, 0.24)	–				–
Other	10	3.0			0.23 (0.13, 0.43)	–				–

[a] Our current study.
[b] Arbuckle et al., (2016).
[c] When the null hypothesis, that all categories of a physical/socio-demographic characteristic had the same mean log T-Hg level, was rejected ($p < 0.05$), then the pairwise comparisons were conducted. Groups sharing same letter indicate levels that are statistically similar, whereas groups with different letters are significantly different.
[d] Number of previous viable pregnancies.

(GM = 0.47 μg L^{-1}; 95% CI: 0.41–0.52 μg L-1) (Table 2).

3.3. Correlations and ratios among matrices and fish consumption

The rates of detection of T-Hg in maternal and infant matrices were high, except for meconium samples, 72% of which fell below the detection limit (Table 2); hence, meconium was omitted from further comparisons. T-Hg levels in hair were highly correlated with T-Hg levels in blood (both 1st and 3rd trimesters maternal blood and umbilical cord blood) with correlation coefficients of 0.78 or greater (Fig. 2). The GM T-Hg in cord blood (0.72 μg L^{-1}) was 1.5 times higher than the GM T-Hg in 3rd trimester maternal blood

Table 2
T-Hg levels in mother-infant biological matrices (maternal hair and blood, umbilical cord blood and meconium).

Biological matrix	n	LOD[a]	% < LOD	GM (95% CI)	Percentiles			
					25th	50th	75th	95th
hair (average) (μg g^{-1})	328	0.07	2.1	0.21 (0.19, 0.24)	0.13	0.26	0.44	0.81
hair (1st trimester) (μg g^{-1})	298	0.07	17.1	0.22 (0.19, 0.24)	0.12	0.26	0.48	0.83
hair (3rd trimester) (μg g^{-1})	306	0.07	19.3	0.18 (0.16, 0.20)	0.09	0.23	0.37	0.74
1st trimester blood (μg L^{-1})	323	0.12	9.9	0.60 (0.54, 0.68)	0.36	0.68	1.18	2.81
3rd trimester blood (μg L^{-1})	312	0.12	11.5	0.47 (0.41, 0.52)	0.26	0.54	0.94	2.01
umbilical cord blood (pg L^{-1})	268	0.40	17.5	0.72 (0.64, 0.81)	0.32	0.82	1.48	3.01
meconium (pg g^{-1})	300	0.01	72.3	N/A	<LOD	<LOD	0.011	0.027

Note: low detection rate in meconium precluded calculation of geometric mean (GM).
[a] -LOD is Limit of Detection (minimum amount of contaminant chemically detected).

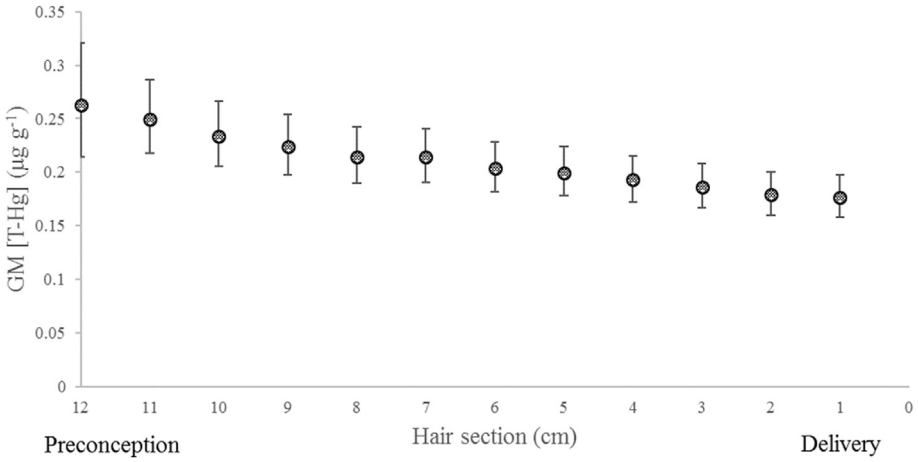

Fig. 1. GM T-Hg levels across study participants (the hair sections were aligned from the same collection time across all women in this study) from preconception period (hair section # 12) to delivery (hair section # 1). The error bars represent 95% confidence intervals (CIs) for the GM T-Hg levels for each hair section. The same information in tabular form is presented in Supplemental Materials.

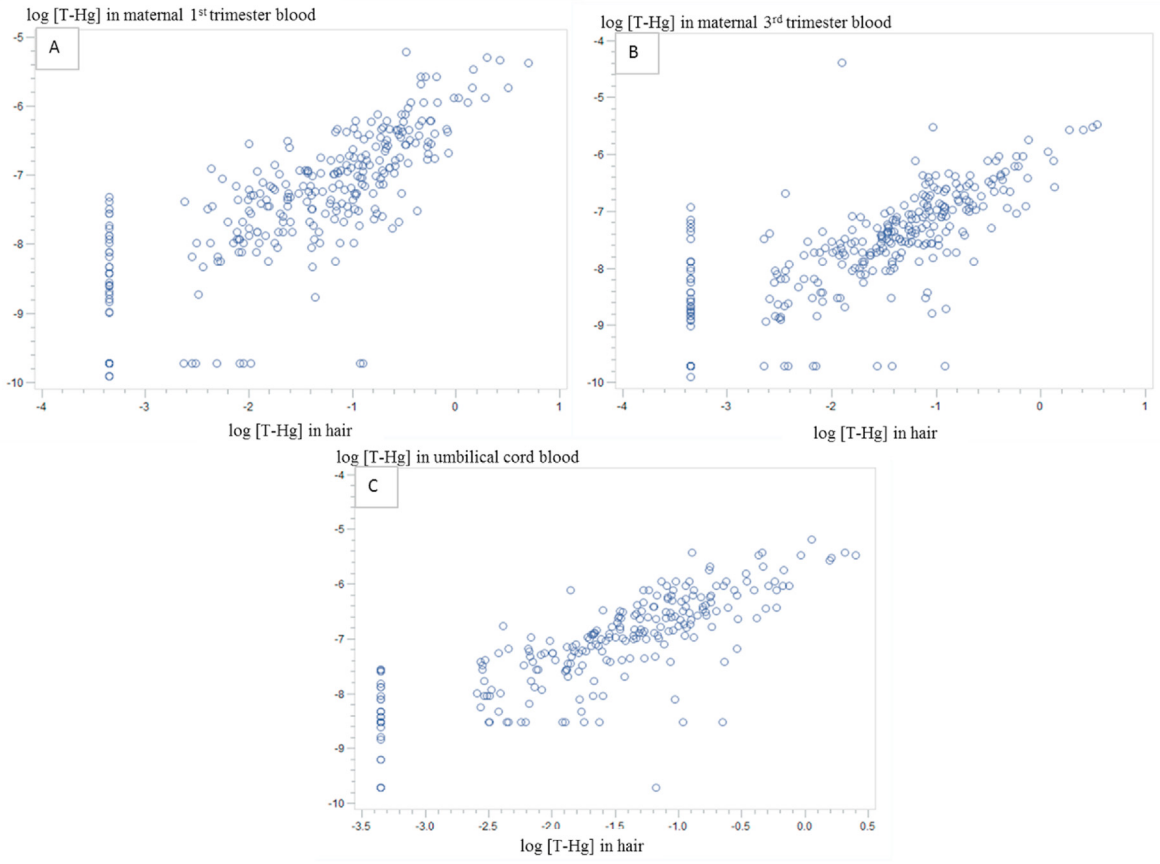

Fig. 2. Correlations of T-Hg levels between biological matrices: A) hair-to-1st trimester maternal blood ($r = 0.80$, $p < 0.0001$), B) hair-to-3rd trimester maternal blood ($r = 0.78$, $p < 0.0001$), C) hair-to-umbilical cord blood ($r = 0.84$, $p < 0.0001$).

(32–34 weeks of gestation) (Table 2). The maternal median hair-to-blood T-Hg ratio was 364 (25th-75th percentile: 252–543), 408 (25th-75th percentile: 295–582), and 229 (25th-75th percentile: 174–311) for the 1st and 3rd trimesters of pregnancy, and for umbilical cord blood, respectively (see Table 3).

Many pregnant women consumed large predatory fish species with varying frequency during pregnancy (Table 4). Weaker, but positive correlations were found between consumption of those predatory species known to accumulate higher Hg in their tissues and T-Hg levels in hair ($r = 0.25$, $p < 0.0001$ for 1st trimester and $r = 0.27$, $p < 0.0001$ for 3rd trimester) and T-Hg levels in blood ($r = 0.31$, $p < 0.0001$ for 1st trimester and $r = 0.16$, $p = 0.0056$ for 3rd trimester) (Table 4). Overall, throughout pregnancy, around 56% of women consumed tuna, either packaged in a can or pouch,

Table 3
Comparison of hair-to-blood T-Hg ratios between participants in our study and other studies of pregnant women and women of reproductive age (20–39 years).

Study population (N)	gm hair T-Hg (μg g^{-1})	hair T-Hg 25th-75th percentile	Hair (μg g^{-1})-to-blood (mg L^{-1}) ratio	Location	Reference
Pregnant women					
328	0.21	(0.13, 0.44)	Hair-to-1st trimester blood: 364 Hair-to-3rd trimester blood: 408 Hair-to-cord blood: 229	Canada (several cities in southern Canada)	This study
818 (Slovenia = 584, Croatia = 234)	0.35 [h]	(0.02, 8.71)[g]	Hair-to-cord blood: 188	Central Europe (Slovenia and Croatia)	Trdin et al. (2019)
31	0.25 (exposed group)	(0.19, 0.39)[e]	Hair-to-3rd trimester blood: 135	Slovenia	Kobal et al. (2017)
	0.21 (control group)	(0.13, 0.34)[e]	Hair-to-3rd trimester blood: 215		
54	1.22	(0.88, 1.79)	Hair-to-1st trimester blood: 307	Japan	Sakamoto et al. (2015)
115	1.62	(1.18, 2.20)	Hair-to-3rd trimester blood: 350 Hair-to-cord blood: 166	Japan	Sakamoto et al. (2007)
176	0.85	(0.40, 2.20)[e]	Hair-to-1st trimester blood: 190	Quebec, Canada (southwest region)	Morrissette et al. (2004)
	0.48	(nd, 2.00)[e]	Hair-to-2nd trimester blood: 203		
	0.56	(nd, 1.20)[e]	Hair-to-3rd trimester blood: 213		
175	3.5	(2.2, 6.1)	Hair-to-1st trimester blood: 337[a]	Quebec, Canada (northern)	Muckle et al. (2001b)
	3.6	(2.3, 6.6)	Hair-to-2nd trimester blood: 346[a]		
	3.7	(2.4, 6.0)	Hair-to-3rd trimester blood: 356[a]		
Women of reproductive age					
1084 participants (536 women and 548 men)	0.27	(0.25, 0.29)[e]	Hair-to-blood: 241	Slovenia	Tratnik et al. (2019)
1730 women	0.17	(0.15, 0.18)	Hair-to-blood: 191	Quebec, Canada (northern)	Ripley et al. (2018)
80 participants (38 female and 42 male)	0.10[f]	N/P	Hair-to-blood: 306[f]	Iran (Persian Gulf Coast)	Okati and Esmaili-Sari (2018)
1333 participants (795 women and 538 men from 9 different communities)	1.22 [f] (women only)	(5.0, 7.2) [e]	Hair-to-blood: 3-2845[d]	Quebec, Canada (Northern)	Liberda et al. (2014)
Women of reproductive age					
27 participants (13 women and 14 men)	2.3 [f]	(1.1, 6.5) [g]	Hair-to-blood: 351	Japan	Yaginuma-Sakurai et al. (2012)
106 participants (women of Japanese descent)	1.6 [f]	(1.3, 1.8) [e]	Hair-to-blood: 305[b]	Washington State, USA (Puget Sound area)	Tsuchiya et al. (2012), 2009
28 participants (23 women and 5 men)	0.76[f]	(0.08, 2.0)	Hair-to-blood: 345[c]	Sweden	Berglund et al. (2005)
Cohort of singleton births	4.22 (full length 6–9 cm, n = 1019)	(2.52, 7.66)	Maternal hair (full length 6–9 cm, n = 993)-to-cord blood: 190	Faroe Islands	Budtz-Jørgensen et al. (2004)
	4.46 (proximal 2 cm, n = 683)	(2.85, 7.90)	Maternal hair (proximal 2 cm, n = 666)-to-cord blood: 201		

Abbreviations used: n, sample number; GM, geometric mean; nd, non-detectable; N/P, not provided.
[a] calculated values based on reported GMs.
[b] an average from 3 clinical visits.
[c] calculated from Table 3 in paper (whole blood converted to mg L^{-1}).
[d] range of measured hair ratios from 9 different communities.
[e] 5th to 95th percentile range.
[f] mean.
[g] range.
[h] median.

Table 4
Number of women who consumed large predatory fish species (those species possibly containing higher Hg levels) meals on a monthly basis during pregnancy. Correlations between large predatory fish consumptions and T-Hg levels in 1) hair and 2) maternal blood during pregnancy (1st and 3rd trimesters) are included.

Collection time	Large predatory fish sp. consumption[a]		# large predatory fish meals/month			Correlations of fish consumption to hair and maternal blood		
	No (%)	Yes (%)	>0–2 (%)	>2–4 (%)	>4 (%)	N	R	p-value
1st trimester (N = 327)	124 (37.9)	203 (62.1)	140 (69.0)	18 (8.9)	45 (22.2)	295	1) 0.25	**<0.0001**
							0.31	**<0.0001**
3rd trimester (N = 320)	133 (41.6)	187 (58.4)	125 (66.8)	16 (8.6)	46 (24.6)	306	0.27	**<0.0001**
							0.16	**0.0056**

[a] List of predatory species containing possibly higher Hg levels was taken from Health Canada (2007a), 2007b, and 2009.

although the type of tuna was unknown (data not shown). During early pregnancy, 1.2% preferred bass, 3.4% - pickerel, 1.5% - marlin, 1.5% - swordfish, 0.9% - orange roughy, and 0.6% consumed meals containing shark. During the 3rd trimester, 2.5% consumed pickerel, 0.6% ate swordfish and 0.3% preferred shark. The majority of women who did consume large predatory species possibly containing high Hg levels consumed at most two meals per month (Table 4).

4. Discussion

In our study, the GM (0.21 μg g^{-1}) and the 95th percentile (0.81 μg g^{-1}) of T-Hg level in hair were lower than the US EPA health-based reference level (1 μg g^{-1}) (USEPA, 2000) and the WHO health-based reference level (2 μg g^{-1}) (WHO, 1990). The GM T-Hg level in maternal (1st and 3rd trimesters) and cord blood were below the provisional Health Canada blood guidance value of 8 μg L^{-1} calculated for vulnerable populations (pregnant women, women of reproductive age and young children) (Legrand et al., 2010).

This study of temporal variation of T-Hg body burden from preconception to delivery in a subset of a national-level cohort, supports the findings of a smaller regional study of pregnant women in Quebec, Canada (Morissette et al., 2004). A decreasing temporal T-Hg trend in maternal hair was observed in both studies, along with higher T-Hg levels in cord blood than in maternal blood. In a study of 54 healthy Japanese pregnant women, Sakamoto et al. (2015) also found a decreasing trend of T-Hg in hair and much higher T-Hg levels in cord blood than in maternal blood. Kim et al. (2008) observed an overall decreasing temporal trend of T-Hg in maternal hair over 15 months, although older mothers tended to have higher levels, which was also observed in our study for those women older than 35 years of age. Similarly, higher MeHg levels in blood were significantly associated with increasing maternal age, but overall levels decreased over the course of pregnancy and up to 15 months postpartum among 148 women, due to natural excretion of mercury (Vahter et al., 2000). In a study of 142 Korean pregnant women, Kim et al. (2015) found significant decreases in GM T-Hg levels in blood during 2nd trimester and at delivery.

Correlations between hair and blood T-Hg levels were strong in the current study. As such, for monitoring of mercury exposure in vulnerable populations, hair is viewed as an appropriate alternative to more invasive blood sampling, as it very accurately reflects the concentration in blood. Hair segments closer to the scalp reflect the most recent exposures, and those segments farther from the scalp are representative of previous blood mercury levels (Srogi, 2007). Collection, transportation and storage of hair is much easier than for blood (Liberda et al., 2014). Determination of mercury in hair is also simpler than in blood since ~70–90% of MeHg easily binds to the organic cysteine protein (Chen et al., 2002).

In general, the average Hg level in scalp hair is approximately 250 times higher than that in blood; however, individual ratios may vary widely, with an acceptable range of 140–370 (JECFA, 2004; WHO, 1990). In our study, the median hair-to-blood ratios among all participants varied from 364 (25th-75th percentile: 252–543) in 1st trimester to 408 (25th-75th percentile: 295–582) in 3rd trimester and 229 (25th-75th percentile: 174–311) postpartum. In a study of individuals from Indigenous communities in northern Quebec, Canada the T-Hg hair-to-blood ratio ranged from 3 to 2845, with higher ratios found among men (Liberda et al., 2014). Okati and Esmaili-Sari (2018) also reported variations in hair-to-blood ratios spanning 182 to 546 (mean: 335), with higher ratios among those individuals consuming more than two fish meals/week. Consumption of large fish species resulted in a mean hair-to-blood T-Hg ratio of 351 (min-max: 263–478) among 27 participants (Yaginuma-Sakurai et al., 2012). Besides diet, gender and sex, age also plays a key role in hair-to-blood ratios, as seen in a study by Budtz-Jørgensen et al. (2004), where 14-year old children had a ratio closer to the WHO-defined ratio of 250 (WHO, 1990), while younger children had a much higher ratio. Trdin et al. (2019) found that older pregnant women had much higher mercury levels in blood. Similarly, in a study with 229 pregnant women from Florida, USA, women who were 30+ years of age had higher T-Hg levels in scalp hair (Schaefer et al., 2019). In this subsample of the MIREC cohort, the majority of women (69%) were 30 years of age or above, which may partly explain the higher hair-to-blood ratios that were observed.

Including fish in the diet is highly encouraged due to its high content of fatty acids, vitamins and essential nutrients; however, pregnant women should limit consumption of some large marine and freshwater fish as such species may contain higher Hg levels in their tissues/organs (Health Canada, 2007a, 2007b and 2009). In our study, weaker but positive correlations between fish consumption and each of hair and blood T-Hg levels were observed. Many women consumed either canned or pouched tuna (unknown type) during pregnancy. Although some women consumed large fish, including swordfish, pickerel, shark, marlin, orange roughy and bass during pregnancy, the majority of women limited themselves to at most two meals/month of such species during 1st (69%) and 3rd (67%) trimesters. Morrissette et al. (2004) found that consumption of market fish (fresh, canned and frozen) contributed to higher T-Hg levels in hair and blood of pregnant women. Schaefer et al. (2019) also found that higher T-Hg levels in scalp hair of pregnant women were associated with store-bought fish and seafood when consumed once a week or more. Reduction in consumption of local large fish have contributed to decreased hair mercury levels as seen in a long-term biomonitoring study of Cree First Nations from Northern Quebec (Ripley et al., 2018).

Beside fish consumption, there are also other factors that may affect T-Hg accumulation and temporal variations, including place of residence (Airey, 1983), genetic variations of gluthathione (GSH), an antioxidant important in MeHg metabolism (Llop et al., 2014; Wahlberg et al., 2018), mercury half-life, metabolism and elimination rate, hemodilution, and *trans*-placental transfer (Hytten, 1985; Kajiwara et al., 1996; Vahter et al., 2000; Akerstrom et al., 2017). During normal healthy pregnancy, plasma volume increases resulting in lower hematocrit and hemoglobin levels (Hytten, 1985; Stern and Smith, 2003); hence, lower T-Hg levels in maternal blood with further accumulation in cord blood, as seen in our study and in Arbuckle et al. (2016). Previous studies have shown that Hg may pass the placental barrier (Ramirez et al., 2000; Morrissette et al., 2004; Sakamoto et al., 2015) via active amino acid carriers (Kajiwara et al., 1996). The majority of MeHg from diet is absorbed into the gastrointestinal tract and distributed to various organs and tissues via bloodstream on average in four days (WHO, 1990; Akerstrom et al., 2017). Due to MeHg lipophilicity, Hg is not only able to pass the placenta but also the blood-brain barrier and some cellular membranes with lipid compositions (Halbach, 1985). The target organ for MeHg elimination is the liver (about 70% MeHg accumulation) with further excretion via bile and feces (Canuel et al., 2006), yet some small amounts of Hg can be found in urine via renal excretion (Berglund et al., 2005). The half-life of MeHg in blood is around 50–70 days, but it is even shorter for lactating women (WHO, 1990).

The majority of women in our study were living with their partner, were older, had higher educational levels and higher annual household incomes, and never smoked; accordingly, this study group may not reflect women in the general Canadian population. Indeed, GM T-Hg levels in maternal blood during the 1st and 3rd trimesters in this sub-sample of the MIREC cohort (0.60 μg L^{-1} and 0.47 μg L^{-1}, respectively) were comparatively lower than for women of reproductive age (0.65 μg L^{-1}) from the Canadian Health Measures Survey cycle 5 (CHMS, 2016–2017, Health Canada, 2019). Of the entire cohort, about 80% of the women donated full-length hair of 12 cm in total. During chemical analysis, it is often difficult to impossible to differentiate between mercury sources (accumulation during hair growth and deposition from anthropogenic emissions) (Nuttall, 2006); however, as the majority of mercury body burden comes from diet and only a small

proportion may come from direct deposition onto the hair via gaps and fissures on the hair surface, we did not perform any pre-treatments prior to chemical analysis. Lastly, heavy hair treatments (i.e., artificial hair waving), and especially usage of thioglycolate-containing products may reduce overall levels of T-Hg in hair (Yamamoto and Suzuki, 1978; Dakeishi et al., 2005); however, very few women in our study used perm solution products during pregnancy with only 1.2% and 0.9% during 1st trimester and 3rd trimester, respectively (data not shown). Therefore, minimal effect of those hair products on mercury content in hair was expected.

Based on the larger MIREC cohort (Arbuckle et al., 2016), maternal place of birth outside Canada may be a driving factor for the difference in mercury body burden. Similarly, this was observed in our study with foreign-born women having slightly higher T-Hg levels in hair compared to that of Canadian-born women. However, due to the small sample size (only 16% of all women in our study were foreign-born), we could not further analyse by country. Schaefer et al. (2019) found that women with Asian descent tended to have higher T-Hg levels in their scalp hair compared to women from other races (i.e., Caucasian, Latina and African/American). Other studies have shown that bodily accumulation and elimination of mercury may be associated with race and ethnicity (Canuel et al., 2006; Javorsky et al., 2014). This could be an area of future research involving vulnerable populations.

To date, few epidemiological studies of vulnerable populations such as pregnant women have looked at temporal trends in hair T-Hg, especially at the national level. Analysis of mercury in sequential hair segments allows the reconstruction of preconception to prenatal exposure, depending on the woman's length of hair. This in turn allows hair T-Hg levels to be compared with measurements of T-Hg in other matrices that were concurrently collected (1st and 3rd trimesters maternal blood, umbilical cord blood, or meconium). We found a decreasing temporal T-Hg trend in maternal hair and blood throughout pregnancy. Hair T-Hg was strongly correlated with blood T-Hg levels in both 1st and 3rd trimesters of pregnancy and cord blood collected at delivery. The median hair-to-blood ratios varied from 364 to 408 during pregnancy to 229 postpartum. Consistent with other studies, we found that T-Hg levels in hair and blood were associated with fish consumption, especially consumption of those species known to accumulate mercury in their tissues.

Credit author statement

Anna O. Lukina: Writing −Original draft preparation and final version of manuscript, Visualization, Validation; Mandy Fisher: Project administration, Writing - review & editing; Cheryl Khoury; Writing - review & editing, Supervision; John Than: Formal analysis, Data curation, Writing-review & editing; Mireille Guay: Software, Formal analysis; Jean-François Paradis: Resources; Tye E. Arbuckle: Project administration, Funding acquisition, Supervision, Writing-review & editing; Melissa Legrand: Conceptualization, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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