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Urinary Iodine, Perchlorate, and Thiocyanate Concentrations in U.S. Lactating Women

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Background: Iodine is an essential micronutrient for thyroid hormone production. Adequate iodine intake and normal thyroid function are important during early development, and breastfed infants rely on maternal iodine excreted in breast milk for their iodine nutrition. The proportion of women in the United States of childbearing age with urinary iodine concentration (UIC) <50 μg/L has been increasing, and a subset of lactating women may have inadequate iodine intake. UIC may also be influenced by environmental exposure to perchlorate and thiocyanate, competitive inhibitors of iodine transport into thyroid, and lactating mammary glands. Data regarding UIC in U.S. lactating women are limited. To adequately assess the iodine sufficiency of lactating women and potential associations with environmental perchlorate and thiocyanate exposure, we conducted a multicenter, cross-sectional study of urinary iodine, perchlorate, and thiocyanate concentrations in healthy U.S. lactating women.

Methods: Lactating women ≥18 years of age were recruited from three U.S. geographic regions: California, Massachusetts, and Ohio/Illinois from November 2008 to June 2016. Demographic information and multivitamin supplements use were obtained. Iodine, perchlorate, and thiocyanate levels were measured from spot urine samples. Correlations between urinary iodine, perchlorate, and thiocyanate levels were determined using Spearman's rank correlation. Multivariable regression models were used to assess predictors of urinary iodine, perchlorate, and thiocyanate levels, and UIC <100 μg/L.

Results: A total of 376 subjects (≥125 from each geographic region) were included in the final analyses [mean (SD) age 31.1 (5.6) years, 37% white, 31% black, and 11% Hispanic]. Seventy-seven percent used multivitamin supplements, 5% reported active cigarette smoking, and 45% were exclusively breastfeeding. Median urinary iodine, perchlorate, and thiocyanate concentrations were 143 μg/L, 3.1 μg/L, and 514 μg/L, respectively. One-third of women had UIC <100 μg/L. Spot urinary iodine, perchlorate, and thiocyanate levels all significantly positively correlated to each other. No significant predictors of UIC, UIC <100 μg/L, or urinary perchlorate levels were identified. Smoking, race/ethnicity, and marital status were significant predictors of urinary thiocyanate levels.

Conclusion: Lactating women in three U.S. geographic regions are iodine sufficient with an overall median UIC of 143 μg/L. Given ubiquitous exposure to perchlorate and thiocyanate, adequate iodine nutrition should be emphasized, along with consideration to decrease these exposures in lactating women to protect developing infants.

Keywords: iodine nutrition, iodine in breastfeeding, lactation, iodine, perchlorate, thiocyanate

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Introduction

Iodine is an essential micronutrient necessary for thyroid hormone production. Adequate iodine intake and normal thyroid function are especially important during early development. Breastfed infants rely on maternal iodine excreted in breast milk for the production of thyroid hormones necessary for normal neurodevelopment (1,2). Therefore, dietary iodine requirements are higher for lactating women than they are for nonlactating adults. The U.S. Institute of Medicine's Recommended Dietary Allowance for iodine is 290 μg/day for lactating women, compared with 150 μg/day recommended for nonpregnant adults (3).

Since the 1920s, U.S. dietary iodine consumption has been considered adequate, initially due to the introduction of iodized salt. Population iodine sufficiency, based on a sample size of at least 125 individuals (4), is defined by the World Health Organization (WHO) as median urinary iodine concentrations (UIC) ≥100 μg/L in lactating adults (5). A recent systematic review of UIC in lactating women based on the presence of mandatory or voluntary iodine fortification program reported the mean or median UIC was >100 μg/L in more than 50% of countries with mandatory iodine fortification programs, in contrast to less than 33% of countries with voluntary iodine fortification programs (6). The U.S. has never had a mandatory iodine fortification program. Although the UIC of the general population is currently deemed adequate at 164 μg/L (7), the median UIC in U.S. adults decreased by over 50% from the early 1970s to the early 1990s, according to data from the National Health and Nutrition Examination Survey (NHANES) (8). Of particular concern is that the prevalence of UIC <50 μg/L among women of childbearing age increased by almost four-fold, from 4% to 15%, during this period. Among pregnant women in large U.S. national datasets during 2005–2010, only third-trimester women were iodine sufficient, while first- and second-trimester women had median urinary iodine concentrations that categorized them in the mildly iodine insufficient range (9). While the overall U.S. adult population remains iodine sufficient by WHO standards, a subset of lactating women may have inadequate dietary iodine intake (10).

Sources of iodine in the diet of U.S. adults have been difficult to identify because there are a wide variety of potential sources, there is a wide amount of variation in the iodine content of some common foods, and food iodine content is not listed on packaging. In addition, UIC thresholds have been identified for populations, but not for individual patients. For this reason, a public health approach to iodine supplementation in the United States has been advocated, particularly for women of childbearing age. The American Thyroid Association has recommended that all women receive dietary supplements containing 150 μg iodine daily during preconception, pregnancy, and lactation and that all prenatal vitamins contain 150 μg of iodine (11). This position is also supported by the Endocrine Society (12), the Teratology Society (13), and the American Academy of Pediatrics (14) but has not yet been widely adopted in current clinical practice. In the United States, iodine is not a required component of prenatal vitamins, and a study in 2009 revealed that only 51% of U.S.-marketed prenatal multivitamins contain iodine, and the iodine content is often lower than listed and highly variable (15). In early 2015, the Council for Responsible Nutrition, the U.S. trade group for supplement manufacturers, recommended that all manufacturers include at least 150 μg of iodine per daily dose of supplements intended for pregnant or lactating women (16). However, as this remains a voluntary measure, there was only a modest increase to 61% in the proportion of U.S. prenatal vitamins with iodine in a recent study (17). In a U.S. survey of 275 obstetricians and 199 midwives, providers answered that they at best ''rarely recommended'' iodine-containing prenatal multivitamins for women planning pregnancy (68% and 70%, respectively), for pregnant women (66% and 67%), or for lactating women (68% and 72%) (18).

Urinary iodine content may be influenced by factors other than maternal dietary iodine intake. The thyroidal effects of low-level environmental perchlorate and thiocyanate exposures have recently been controversial. In particular, perchlorate exposure has been adversely associated with thyroid dysfunction in some studies. Perchlorate is formed by natural processes and is a byproduct from airbag inflation systems, matches, fertilizers, road flares, solid rocket fuel, munitions, and fireworks (19). Perchlorate is highly soluble and can persist in groundwater for decades. In the U.S., perchlorate is ubiquitous and has been detected in food supplies including baby food, dairy products, eggs, fruits, grains, and vegetables; in crops such as tobacco; in vitamins (20–25); and in river water following a July fourth fireworks celebration (26). It is a competitive inhibitor of the sodium-iodide symporter (NIS), which actively transports iodine into thyroid and lactating mammary cells (27). When given in pharmacological doses, perchlorate decreases the active transport of iodine into the thyroid and possibly breast milk (27). Low-level environmental perchlorate exposure appears to be ubiquitous in the U.S. population. In the NHANES 2001–2002 survey, perchlorate was detected in all 2820 spot urine samples (median urine perchlorate concentration 3.6 μg/L) (28) and was a significant negative predictor of total thyroxine and a positive predictor of thyrotropin values in women, primarily those with UIC <100 μg/L (29). NIS expression is upregulated in the lactating breast and concentrates iodine from the circulation to a degree similar to the thyroid (30). Given perchlorate's high affinity for NIS, breastmilk is a direct source of perchlorate exposure in the breastfeeding infant.

Cigarette smoke contains cyanide that is metabolized to thiocyanate, which can also decrease the uptake of iodine into the thyroid and breastmilk by competitively inhibiting NIS, although thiocyanate is a less potent NIS competitor than perchlorate (31). One study in Denmark concluded that cigarette smoking decreases breastmilk iodine concentrations (32), and we demonstrated the same effect in a small cohort of Boston-area lactating women (33). Cigarette smoke exposure may thus exacerbate the effects of environmental perchlorate exposure on thyroid function. Thiocyanate is also naturally present in certain foods, such as cauliflower, broccoli, kale, bamboo shoots, and Brussels sprouts.

There are limited data regarding median UICs among U.S. lactating women. We previously reported that the median UIC of 56 Boston-area lactating women was 114 μg/L (range 25–920 μg/L) (33), similar to that (104 μg/L; range 13–528 μg/L) of 97 Boston-area women in the immediate postpartum period (34). Others have shown that median urinary iodine levels fluctuate in the immediate postpartum period, ranging from 36–63 μg/L at 3–10 days after delivery (35).

However, there is a lack of studies of U.S. lactating women with a sample size large enough to make an inference regarding population level iodine sufficiency. We conducted a multicenter, cross-sectional observational study of urinary iodine, perchlorate, and thiocyanate concentrations in 376 healthy lactating U.S. mothers to adequately determine the iodine sufficiency of this particularly susceptible population and assess whether this may be associated with low-level environmental perchlorate and thiocyanate exposures.

Materials and Methods

A multicenter, cross-sectional study of dietary habits and UIC of 378 lactating women in the U.S. was conducted from November 2008 through June 2016 (in Massachusetts [MA] from November 2008 through September 2015; in California [CA] from March 2011 through June 2016; and in Ohio [OH] and Illinois [IL] from June 2011 through December 2015). Institutional Review Board approval for the study was obtained from the Boston University Medical Campus and Boston Medical Center (BMC), Boston, MA; University of California Los Angeles (UCLA) Medical Center, Los Angeles, CA; University of Southern California, Los Angeles, CA; Ohio State University (OSU) Medical Center, Columbus, OH; and NorthShore University Health System, Evanston, IL, where subject recruitment and urine sample collection occurred.

Study subjects and measures

Breastfeeding women at least 18 years of age were recruited from obstetric and pediatric clinics and through advertisements in the local community. Women who were postpartum for any length of time if delivered vaginally or who were at least two months postpartum if delivered by cesarean section at BMC were eligible because of the use of topical iodine-containing cleaners for Foley catheter insertion for cesarean section at BMC. Women who were at least three weeks postpartum at UCLA and OSU medical centers were eligible because of the routine use of topical iodine-containing cleaners at delivery at these sites. The differences in the duration after birth for eligibility for each site were partly due to changing information during the course of the study. Spanish-speaking women at OSU were eligible for recruitment. Otherwise, non-English speaking women and women with history of or current known thyroid disease, use of thyroid hormones or anti-thyroidal medications, or use of amiodarone within 24 months were excluded. Women who had undergone radiologic studies with intravenous iodine-containing contrast agents within three months were also excluded.

Subject demographic information, including age, race/ethnicity, marital status, education level, smoking behavior, present exposure to passive smoke, and any family history of thyroid disorders was obtained through a questionnaire. Use of iodine-containing prenatal or other multivitamin supplements (MVI) was also assessed. However, iodine content of MVI was not known for most subjects, and therefore, we could not differentiate iodine-containing and non-iodine-containing MVI. Spot urine samples were collected from all participants for measurements of iodine, perchlorate, and thiocyanate.

A total of 378 lactating women from three U.S. geographic locations were recruited: 126 from Boston, MA; 125 from Los Angeles, CA; and 127 combined from Columbus, OH and Evanston, IL. Two participants from IL were unable to provide urine samples following informed consent, and thus were excluded from analyses. Therefore, a total of 376 subjects (126 from MA; 125 from CA; and 125 from OH and IL) were included in the final analyses. Spot UIC cannot be used as an individual biomarker of iodine nutritional status due to its fluctuation from recent iodine intake, and median spot UIC in at least 125 subjects is used instead to assess population level iodine sufficiency (4).

Laboratory methods

Urine samples were frozen upon collection and stored at −80°C until measurement. Samples from sites outside of Boston were shipped on dry ice to Boston University Iodine Research Laboratory for measurements. Levels of spot urinary iodine, perchlorate, and thiocyanate were measured by ion-chromatography mass spectrometry. The limit of detection for iodine is 0.5 μg/L, and the interassay coefficient of variation for iodine measurement in our laboratory is 2.2–7.6%. The limit of detection for perchlorate is 0.05 μg/L, and the interassay coefficient of variation for perchlorate measurement in our laboratory ranges from 2.2% to 5.9%. The limit of detection for thiocyanate is 0.05 μg/L, and the interassay coefficient of variation for thiocyanate measurement in our laboratory is <5%.

Statistical analyses

Descriptive statistics are reported as mean ± standard deviation or median (range). Kruskal-Wallis tests and ANOVA were used to compare characteristics among the three geographical sites for categorical variables and continuous variables, respectively. Spearman's rank correlation was used to determine univariate associations between urinary perchlorate, iodine, and thiocyanate. The univariate associations between urinary perchlorate, iodine, and thiocyanate levels were further assessed for only those with urinary iodine concentration (UIC) less than 100 μg/L, the WHO-recommended cutoff for population level iodine sufficiency in lactating women (5). Wilcoxon rank sum tests were used to determine univariate associations between MVI use and urinary iodine levels and between smoking and urinary thiocyanate levels.

Multivariable linear regression models were used to assess predictors of urinary iodine, urinary perchlorate, and urinary thiocyanate levels. Multivariable logistic regression models were used to assess predictors of UIC <100 μg/L. The covariates included in all multivariable analyses were selected based on potential biological or clinical significance related to outcome, and included race/ethnicity, mother's age, marital status, highest education level, MVI use, smoking, and use of formula supplementation for baby. Mother's age was entered as a continuous variable in years. The following were entered as categorical variables; race/ethnicity (white, black, Latino, Asian, Native American, and others), marital status (never married, married, divorced, widowed, other), highest education level (high school or below, vocation/trade school, two-year college, four-year college, grad school or higher), MVI use (yes, no), smoking (yes, no). Use of formula supplementation for baby was categorized in two different ways: a dichotomous variable of yes/no or a categorical variable of none/<12 ounces/day/≥12 ounces/day. For assessment of predictors of urinary perchlorate level, urinary thiocyanate level was included as a covariate. For assessment of predictors of urinary thiocyanate level, urinary perchlorate level was included as a covariate.

All statistical analyses were performed using SAS version 9.3 (SAS institute, Cary, NC). Results were considered statistically significant if the two-tailed *p*-value was <0.05.

Results

A total of 376 subjects (125 from CA, 126 from MA, and 125 from OH/IL) were included in the analyses. Demographic subject characteristics are presented in Table 1. The distribution of lactating women who were smoking was significantly different among regions, likely because of the difference between CA and OH/IL (2 and 9 subjects, respectively), although the overall proportion of women who were active cigarette smokers was small. Use of MVI or supplemental baby formula use when assessed as yes/no was not significantly different among sites.

The laboratory measurements of spot urinary iodine, perchlorate, and thiocyanate levels, as well as the proportions of women with UIC less than 100 μg/L, are presented in Table 2. Overall median UIC was 143 μg/L (range 6–2140 μg/L), and median UICs were not significantly different between geographic regions ($p = 0.18$). The median UIC in all three regions

Table 1. Subject Characteristics Among Three U.S. Geographic Regions

	All (N=*376*)	*CA* (N=*125*)	*MA* (N=*126*)	*OH/IL* (N=*125*)	*Comparison* (p-*value*)
	n (%)				
Race/ethnicity					<0.001
Non-Hispanic white	137 (37%)	43 (34%)	23 (18%)	71 (29%)	
Non-Hispanic black	114 (31%)	13 (10%)	80 (63%)	21 (18%)	
Hispanic	39 (11%)	18 (14%)	7 (6%)	14 (12%)	
Asian	60 (16%)	45 (36%)	9 (7%)	6 (5%)	
Native American	6 (2%)	1 (1%)	5 (4%)	0	
Other	15 (4%)	5 (4%)	2 (2%)	8 (7%)	
Birthplace					<0.001
US	221 (59%)	72 (58%)	53 (42%)	96 (78%)	
Other	153 (41%)	53 (42%)	73 (58%)	27 (22%)	
Marital status					<0.001
Never married	89 (24%)	13 (11%)	48 (38%)	28 (23%)	
Married	237 (64%)	74 (60%)	75 (60%)	88 (72%)	
Divorced	36 (10%)	32 (26%)	2 (2%)	2 (2%)	
Widowed	2 (1%)	1 (1%)	0	1 (1%)	
Other	8 (2%)	3 (2%)	1 (1%)	4 (3%)	
Highest education					<0.001
High school or below	62 (17%)	8 (7%)	24 (19%)	30 (24%)	
Vocation/trade school	71 (19%)	26 (21%)	39 (31%)	6 (5%)	
2-yr college	42 (11%)	7 (6%)	17 (13%)	18 (15%)	
4-yr college	82 (22%)	22 (18%)	23 (18%)	37 (30%)	
Grad or higher	114 (31%)	59 (48%)	23 (18%)	32 (26%)	
MVI use					0.53
Yes	285 (77%)	99 (80%)	93 (74%)	93 (76%)	
No	87 (23%)	25 (20%)	33 (26%)	29 (24%)	
Smoking					0.03
Yes	19 (5%)	2 (2%)	6 (5%)	11 (9%)	
No	354 (95%)	122 (98%)	120 (95%)	112 (91%)	
Use of supplemental baby formula by category					0.04
None	168 (45%)	59 (48%)	48 (38%)	61 (50%)	
<12 ounces/day	159 (43%)	56 (45%)	53 (42%)	50 (41%)	
≥12 ounces/day	43 (12%)	9 (7%)	24 (19%)	10 (8%)	
Dichotomous supplemental baby formula use					0.03
Yes	202 (45%)	65 (52%)	77 (62%)	60 (50%)	
No	168 (55%)	59 (48%)	48 (38%)	61 (50%)	
	Mean (SD) or Median (range)				
Mother's age (years)	31.1 (5.6)	32.7 (5.0)	29.5 (5.8)	31.1 (5.6)	<0.001
GA at birth (weeks)	38.6 (2.5)	38.9 (2.4)	39.3 (1.2)	37.6 (3.3)	<0.001
Baby age at enrollment (days)	45.5 (6–1868)	49.5 (12–1868)	43.5 (10–672)	44.5 (6–428)	<0.001

CA, subjects recruited in California; IL, subjects recruited in Illinois; GA, gestational age; MA, subjects recruited in Massachusetts; MVI, multivitamin supplements; OH, subjects recruited in Ohio; SD, standard deviation.

Table 2. Laboratory Measurements and Comparison of Distribution by Region

	All (n = *376*)	*CA* (n = *125*)	*MA* (n = *126*)	*OH/IL* (n = *125*)	*Comparison* (p-*value*)
	Median (range)				
Urinary iodine concentration (μg/L)	143 (6–2140)	159 (16.9–720)	131 (10.6–595)	154 (6–2140)	0.18
Urinary perchlorate concentration (μg/L)	3.1 (0.2–94.5)	2.8 (0.2–94.5)	3.2 (0.2–22.4)	3.5 (0.2–31.7)	0.70
Urinary thiocyanate concentration (μg/L)	514 (12.3–4250)	565 (43.2–2020)	450.8 (31.1–2755)	525.5 (12.3–4250)	0.16
	N (%)				
UIC <100 μg/L	125 (33%)	37 (30%)	44 (35%)	44 (35%)	0.54

UIC, urinary iodine concentration.

were adequate (159 μg/L in CA, 131 μg/L in MA, and 154 μg/L in OH/IL), per the World Health Organization recommendation of UIC ≥100 μg/L in lactating women (5). There were no significant differences of the median urinary iodine, perchlorate, or thiocyanate levels between regions. There were also no significant differences in proportion of women with UIC <100 μg/L between regions.

Correlations between spot urinary iodine, perchlorate, and thiocyanate levels in all subjects, and in subjects with UIC <100 μg/L are presented in Table 3. Spot urinary iodine, perchlorate, and thiocyanate levels were all significantly positively correlated with each other. MVI use and spot UIC were not significantly correlated ($p = 0.095$). Smoking and thiocyanate level was significantly positively correlated ($p < 0.001$). Among those with UIC <100 μg/L, only perchlorate and iodine levels and thiocyanate and iodine levels were significantly correlated to each other.

The multivariable models predicting UIC were not statistically significant ($p = 0.32$, $R^2 = 0.054$ when supplemental baby formula use was assessed as a dichotomous variable and $p = 0.24$, $R^2 = 0.061$ when supplemental baby formula use was assessed as a categorical variable). The multivariable model predicting UIC <100 μg/L was not statistically significant when supplemental baby formula use was assessed as a dichotomous variable ($p = 0.060$, $R^2 = 0.075$). However, the multivariable model predicting UIC <100 μg/L was statistically significant when supplemental baby formula use was assessed as a categorical variable ($p = 0.012$, $R^2 = 0.094$), with race/ethnicity as the only significant predictor ($p = 0.02$). In the *post hoc* subgroup analyses, Asian race/ethnicity was significantly associated with 0.75 times lower risk of UIC <100 μg/L compared with white race/ethnicity (log estimate –0.287, $p = <0.001$). The multivariable models predicting spot urine perchlorate levels were not statistically significant ($p = 0.30$, $R^2 = 0.058$ when supplemental baby formula use was assessed as a dichotomous variable and $p = 0.30$, $R^2 = 0.061$ when supplemental baby formula use was assessed as a categorical variable). The multivariable models predicting spot urine thiocyanate levels were statistically significant (Tables 4, 5). When supplemental baby formula use was assessed as a dichotomous variable, the model was statistically significant, with $p < 0.001$ and $R^2 = 0.22$. Among the covariates assessed, race/ethnicity, marital status, and smoking were statistically significant predictors (*p*-values of 0.013, 0.025, and <0.001, respectively). In the *post hoc* subgroup analyses,

Table 3. Correlations Between Spot Urinary Iodine, Perchlorate, and Thiocyanate Concentrations

All subjects			
	Iodine	*Perchlorate*	*Thiocyanate*
Iodine	——	Correlation coefficient = 0.284 $p < 0.001$	Correlation coefficient = 0.364 $p < 0.001$
Perchlorate	Correlation coefficient = 0.284 $p < 0.001$	——	Correlation coefficient = 0.186 $p < 0.001$
Thiocyanate	Correlation coefficient = 0.364 $p < 0.001$	Correlation coefficient = 0.186 $p < 0.001$	——
Subjects with UIC <100μg/L only			
	Iodine	*Perchlorate*	*Thiocyanate*
Iodine	——	Correlation coefficient = 0.257 $p = 0.004$	Correlation coefficient = 0.447 $p < 0.001$
Perchlorate	Correlation coefficient = 0.257 $p = 0.004$	——	Correlation coefficient = 0.138 $p = 0.12$
Thiocyanate	Correlation coefficient = 0.447 $p < 0.001$	Correlation coefficient = 0.138 $p = 0.12$	——

Table 4. Multivariable Regression Analysis Predicting Spot Urine Thiocyanate Levels Using Supplemental Baby Formula as a Categorical Variable ($p < 0.0001$, $R^2 = 0.22$)

Covariates	*Estimate (SE)*	p-*Value*
Intercept	1609.5 (175.7)	<0.0001
Race/ethnicity		0.013
Black	−213.7 (65.1)	0.001
Hispanic	−129.9 (86.8)	0.14
Asian	−20.5 (77.3)	0.79
Native American	−279.0 (188.2)	0.14
Other	−227.1 (118.5)	0.06
Mother's age	0.37 (4.76)	0.94
Marital status		0.03
Married	−200.0 (64.6)	0.002
Divorced	−119.7 (102.0)	0.24
Widowed	−387.2 (438.9)	0.38
Other	−333.5 (180.0)	0.06
Highest education level		0.98
Vocation/trade school	−45.0 (82.2)	0.58
2-year college	−44.6 (93.6)	0.63
4-year college	−32.6 (84.8)	0.70
Graduate school or higher	−23.5 (83.9)	0.78
MVI use – no	90.6 (57.2)	0.12
Smoking – no	−806.8 (144.7)	<0.0001
Supplemental baby formula use		1.00
<12 ounces/day	−2.5 (53.8)	0.96
≥12 ounces/day	0.69 (82.1)	0.99
Spot urine perchlorate level	5.7 (3.7)	0.12

White race/ethnicity, never married marital status, highest education level of high school or less, MVI use, smoking, and no baby formula use were used as the reference groups.

Table 5. Multivariable Regression Analysis Predicting Spot Urine Thiocyanate Levels Using Supplemental Baby Formula as a Dichotomous Variable ($p < 0.0001$, $R^2 = 0.22$)

Covariates	*Estimate (SE)*	p-*Value*
Intercept	1608.1 (169.6)	<0.0001
Race/ethnicity		0.013
Black	−213.7 (65.0)	0.001
Hispanic	−130.0 (86.6)	0.13
Asian	−20.9 (76.5)	0.78
Native American	−277.7 (185.0)	0.13
Other	−227.5 (117.9)	0.05
Mother's age	−0.003 (0.004)	0.94
Marital status		0.03
Married	−200.2 (64.3)	0.002
Divorced	−119.6 (101.8)	0.24
Widowed	−387.8 (438.0)	0.38
Other	−333.1 (179.5)	0.06
Highest education level		0.98
Vocation/trade school	−45.0 (82.1)	0.58
2-year college	−44.4 (93.3)	0.63
4-year college	−32.5 (84.6)	0.70
Graduate school or higher	−23.3 (83.7)	0.78
MVI use – no	90.6 (57.1)	0.11
Smoking – no	−807.1 (114.3)	<0.0001
Supplement baby formula use – no	1.86 (51.5)	0.97
Spot urine perchlorate level	5.7 (3.7)	0.12

White race/ethnicity, never married marital status, highest education level of high school or less, MVI use, smoking, and no baby formula use were used as the reference groups.

black race/ethnicity was significantly associated with lower thiocyanate level by 213.68 μg/L compared with white race/ethnicity (p- = 0.001), married status was associated with lower thiocyanate level by 200.19 μg/L compared with never married status ($p = 0.002$), and not smoking was associated with lower thiocyanate level by 807.08 μg/L compared with smoking ($p < 0.001$). When supplemental baby formula use was assessed as a categorical variable, the model was statistically significant with a $p < 0.001$ and $R^2 = 0.22$. Among the covariates assessed, race/ethnicity, marital status, and smoking status were statistically significant (p-values of 0.013, 0.026, and <0.001, respectively). In the *post hoc* subgroup analyses, black race/ethnicity was significantly associated with lower thiocyanate level by 213.70 μg/L compared with white race/ethnicity ($p = 0.001$), married status was associated with lower thiocyanate level by 199.98 μg/L compared with never married status ($p = 0.002$), and not smoking was associated with lower thiocyanate level by 806.77 μg/L compared with smoking ($p = <0.001$).

Discussion

The data presented here show that U.S. lactating women from three distinct geographic regions are iodine sufficient, with an overall median UIC of 143 μg/L, above the WHO recommended threshold for iodine sufficiency in lactating women of 100 μg/L. The proportion of women with UIC <100 μg/L were similar among all regions, ranging from 30% to 35%. This is similar to the proportion of U.S. pregnant women with a UIC <100 μg/L in NHANES data (7). Although two-thirds of women were taking a MVI, there was no correlation between MVI use and UIC, although most women were unsure whether their MVI contained iodine. A recent study of U.S. prenatal multivitamin supplements showed only 61% contained iodine according to the product labeling (17).

U.S. lactating women are overall iodine sufficient. However, approximately one-third of our subjects have spot UICs <100 μg/L. The median perchlorate level in our sample was slightly higher than the mean perchlorate level in U.S. adults over 20 years of age in 2013–2014 reported by the Center for Disease Control and Prevention (CDC) (3.1 μg/L vs. 2.53 μg/L) (36). The median thiocyanate level in our sample was almost one-half of the mean thiocyanate level in U.S. adults over 20 years of age in 2013–2014 reported by the CDC (514 μg/L vs. 1060 μg/L) (36). This is likely because of the small number of smokers in our sample, and our mean is more in line with the mean thiocyanate level of 773 μg/L (0.773 mg/L) found in nonsmoking adults in 2013–2014 by the CDC.

Spot urine iodine, perchlorate, and thiocyanate concentrations were all significantly positively correlated with each other, likely due to co-contamination from common exposure routes. Interestingly, the correlation between thiocyanate and iodine became stronger when assessed in the subset of lactating women with UIC <100 μg/L. There may be underlying behavioral differences affecting the correlations between

UIC and urinary thiocyanate levels. For example, one subject had a very high UIC of 2140 μg/L and a high urinary thiocyanate level of 2230 μg/L, suggesting a possible unifying environmental exposure or possibly due to concentration of urine.

There were no significant predictors for UIC, although race/ethnicity was a significant predictor of UIC $<100\ \mu$g/L in one multivariable analysis. There were no significant predictors of urinary perchlorate levels. Smoking was one of the significant predictors of urinary thiocyanate levels in our multivariable analyses, as expected. As perchlorate and thiocyanate are inhibitors of NIS, they were not included in the multivariable models predicting UIC or low UIC. Normal UICs do not exclude the possibility that perchlorate or thiocyanate may still impair iodine uptake into the thyroid gland leading to thyroid dysfunction (29), or into lactating mammary glands leading to inadequate iodine nutrition for breastfed infants (32,33). In the presence of underlying iodine deficiency with low thyroidal iodine storage, the effects of perchlorate or thiocyanate exposure on thyroid function or breastmilk iodine content may be greater. Given the findings of an increasing proportion of women of reproductive age with UIC $<50\ \mu$g/L (7) and high proportions of pregnant or lactating women with UIC $<100\ \mu$g/L as seen in the NHANES data (7) and in the present study, U.S. pregnant or lactating women and breastfed infants remain particularly vulnerable to the adverse effects of low-level environmental perchlorate and thiocyanate exposures.

Limitations of this study include a lack of information regarding dietary habits and thyroidal iodine saturation status. A spot UIC does not reflect thyroidal iodine status since the thyroid may have adequate iodine storage even though UIC is low. However, obtaining a nuclear scan to assess thyroidal iodine uptake would have been extremely difficult, as our subjects were all lactating mothers. Therefore, we used UIC to assess population-level iodine sufficiency using the threshold recommended by the WHO. Another limitation of this study is lack of measurement of urinary creatinine levels as a marker of urine dilution. However, UIC without correction with urinary creatinine level is deemed to be sufficient in assessing population-level iodine status by the WHO and we measured iodine, perchlorate, and thiocyanate from the same urine sample to minimize potential confounding by dilution. Strengths include the sample size and the ethnic diversity of our study population, with 37% non-Hispanic whites, 31% non-Hispanic blacks, and 11% Hispanic.

In summary, this study provides novel data assessing the current status of iodine nutrition among U.S. lactating women, in direct line with one of the charges by the recent American Thyroid Association guidelines for the diagnosis and management of thyroid disease in pregnancy and the postpartum period (10). These findings show that population-level iodine sufficiency was demonstrated from three distinct U.S. geographic regions, and iodine nutrition among U.S. lactating women is comparable across these regions. Median urinary perchlorate and thiocyanate concentrations were similar among the three sites. Although the U.S. Environmental Protection Agency announced in February 2011 that perchlorate regulation of drinking water will be considered (37), such measures have not yet been implemented, and discussions to do so continue to be in progress (38). Given ubiquitous exposure to low-level environmental perchlorate and thiocyanate in our sample population, adequate iodine nutrition should be emphasized in lactating women to provide optimal iodine nutrition for their breastfed infants.

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Author Disclosure Statement

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