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ORIGINAL ARTICLE

Perchlorate and thiocyanate exposure and thyroid function in first-trimester pregnant women from Greece

Elizabeth N. Pearce*, Maria Alexiou†, Eftychia Koukkou†, Lewis E. Braverman*, Xuemei He*, Ioannis Iliast, Maria Alevizaki‡ and Kostas B. Markou§

*Section of Endocrinology, Diabetes and Nutrition, Boston University School of Medicine, Boston, MA, USA, †Department of Endocrinology, Diabetes and Metabolism, "Elena Venizelou" Hospital, ‡Department of Endocrinology, Metabolism and Diabetes, Evgenideion Hospital, Athens University School of Medicine, Athens and §Department of Internal Medicine, University of Patras School of Medicine, Patras, Greece

Abstract

Objective Thyroid hormone, requiring adequate maternal iodine intake, is critical for neurodevelopment *in utero*. Perchlorate and, less so, thiocyanate decrease uptake of iodine into the thyroid gland by competitively inhibiting the sodium/iodide symporter (NIS). It remains unclear whether environmental perchlorate exposure adversely affects thyroid function in first-trimester pregnant women.

Design Cross-sectional.

Patients 134 pregnant women from Athens, Greece, at mean ± SD 10·9 ± 2·3 weeks' gestation.

Measurements Urinary iodide, perchlorate, and thiocyanate and thyroid function tests were measured.

Results The median urinary iodide was 120 μg/l. Urinary perchlorate levels were detectable in all women: median (range) 4·1 (0·2–118·5) μg/l. Serum thyroperoxidase antibodies (TPO Ab) were detectable in 16% of women. Using Spearman's rank correlation analyses, there was no correlation between urinary perchlorate concentrations and serum TSH, although inverse correlations were seen between urine perchlorate and free T3 and free T4 values. In univariate analyses, urine thiocyanate was positively correlated with serum TSH, but was not associated with serum free T3 or free T4. Urine perchlorate was positively correlated with gestational age. In multivariate analyses adjusting for urinary iodide concentrations, urine thiocyanate, gestational age, maternal age and TPO Ab titres, urine perchlorate was not a significant predictor of thyroid function.

Conclusions Low-level perchlorate and thiocyanate exposure is ubiquitous, but, in adjusted analyses, is not associated with alterations in thyroid function tests among mildly iodine-deficient Greek women in the first trimester of pregnancy.

Correspondence: Elizabeth N. Pearce, 88 East Newton Street, Evans 201, Boston, MA 02118, USA. Tel.: 617 414 1348; Fax: 617 638 7221; E-mail: elizabeth.pearce@bmc.org

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Introduction

Thyroid hormone is essential for foetal neurodevelopment, especially during the first trimester. Even mild maternal hypothyroidism or hypothyroxinaemia during the first trimester has been reported to adversely affect pregnancy outcomes and neurocognitive outcomes in children.[1–4] Perchlorate, a competitive inhibitor of the sodium/iodide symporter (NIS), is widely present in the environment in the United States and elsewhere. Low levels of perchlorate are found in a variety of foodstuffs including cows' and human breast milk, drinking water, fruits and vegetables, and prenatal vitamins.[5–8] There is a concern that exposure to environmental perchlorate could decrease the transport of iodine into the thyroid and therefore could impair thyroid hormone synthesis.[9]

In the United States, low levels of perchlorate were detected in all 2,820 urine specimens from the 2001–2002 NHANES, with a median value of 3·6 μg/l.[10] Blount *et al.* reported that these low levels of perchlorate were positively associated with serum TSH and inversely associated with serum T_4 values among the 348 women in the NHANES sample with urinary iodine values <100 μg I/l.[11] No effect on thyroid function because of these low levels of perchlorate was observed in men.[11] We have recently reported no associations between urinary perchlorate concentrations and thyroid function among 1,002 first-trimester, iodine-deficient pregnant women residing in Cardiff, Wales and Turin, Italy.[12] We similarly found no associations between perchlorate exposure and thyroid function among 134 first-trimester pregnant women from Los Angeles, California, and 107 from Cordoba, Argentina.[13] The reasons for the discrepancy between our findings and those of Blount *et al.* remain unclear.

We now report the results of urinary perchlorate and iodine values and thyroid function tests in first-trimester pregnant women residing in Athens, Greece.

Methods

Subjects

One hundred and thirty-four first-trimester pregnant women were recruited at the outpatient clinic of the Endocrine Department of the Elena Venizelou Hospital, in the Athens, Greece area, between 2008 and 2010. Women with known thyroid dysfunction, including those on levothyroxine therapy, those recently exposed to radiographic contrast media and those ingesting medications known to contain iodine, were excluded. All of the women were nonsmokers. Spot urine samples and blood samples were obtained during the clinic visit. All specimens were stored at $-20\ ^{\circ}C$ until measurement. Blood was drawn at the same visit. The local ethics committee at the Hospital approved the study, and informed consent was obtained from all participants.

Laboratory Methods

Iodide, perchlorate and thiocyanate content of urine samples was measured at the Boston University School of Medicine using ion chromatography/mass spectrometry.[14] TSH, free thyroxine (FT4), free triiodothyronine (FT3) and thyroperoxidase (TPO) antibodies were measured using electrochemiluminescence (Cobas e 411, Roche). All samples were measured in duplicate. The nonpregnant laboratory reference ranges were as follows: TSH, 0·33–4·59 mIU/l; FT4, 12·10–19·56 pmol/l; and FT3 2·46–3·89 pmol/l. TPO antibody values >34 kIU/l were considered positive.

Statistical Analyses

Individual Spearman's rank correlation analyses were used to separately examine the correlations between urine perchlorate concentrations and serum TSH, FT4 and FT3. Similar analyses were carried out to examine correlations between urine thiocyanate concentrations and thyroid function. We performed these analyses on the total data sets and for those subjects with urinary iodide concentrations <100 μg/l to determine whether the effects of perchlorate exposure on thyroid function tests were limited to individuals with low dietary iodine intake, as was seen in the NHANES data set.[11]

We used multiple linear regression analyses to assess the associations between urine perchlorate and thyroid function tests, considered separately, adjusted for urine thiocyanate concentration, urine iodide concentration, TPO antibody titres, gestational age and maternal age. These covariates were selected because of the likelihood that they might affect thyroid function. We suspected that women with TPO antibodies and/or increased maternal age might have some underlying thyroid compromise and therefore be less able to maintain normal thyroid function in the setting of perchlorate exposure. Urinary iodide concentrations were included because women with low dietary iodine intake might be more susceptible to the adverse thyroidal effects of perchlorate (although a spot urine iodide is an imperfect reflection of an individual's dietary iodine status). Gestational age was included to account for expected physiological changes in thyroid hormone levels during the first trimester. For the multiple regression analyses, the variables TSH, FT4, thiocyanate and perchlorate were distributed non-normally and were natural-log-transformed so that they adequately followed a Gaussian distribution. Statistical tests were considered significant if the two-tailed P-value was <0·05.

Results

Sample Characteristics

The mean age of the 138 women studied was 29·8 ± 4·8 years, and their mean gestational age at the time of sampling was 10·9 ± 2·3 weeks. Thyroid function tests are shown in Table 1. TPO antibodies were positive in 16% of the pregnant women. The median urinary iodide concentration was 120 μg/l. Fifty women had urinary iodide values less than 100 μg/l. The median urine perchlorate value was 4·1 μg/l (range, 0·2–118·5), and the median urine thiocyanate concentration was 413 (0·6–1635).

Effects of Perchlorate and Thiocyanate on Thyroid Function

Using Spearman's rank correlation analyses, there was no correlation between urinary perchlorate concentrations and serum TSH (Table 2). FT4 and FT3 values were inversely associated with urine perchlorate concentrations in the total sample, although significant relationships were not observed when the sample was restricted to the subset of 50 women with urinary iodine values less than 100 μg/l. Urine thiocyanate was positively correlated with serum TSH (r = 0·22; $P = 0·008$) but was not correlated with either FT4 ($r = -0·16$; $P = 0·06$) or FT3 ($r = 0·02$; $P = 0·8$).

Table 1. Sample Characteristics*

Test	(n = 134)
TSH (μU/ml)	1·2 (0·005–9·1)
FT4 (pmol/l)	15·4 ± 5·1 15·1 (9·5–69·6)
FT3 (pmol/l)	4·6 ± 0·7 4·48 (3·3–8·5)
TPO antibody titre (U/ml)	6·1 (400·8)
Urine perchlorate (μg/l)	6·5 ± 11·2 4·1 (0·2–118·5)
Urine thiocyanate (μg/l)	440 ± 318 413 (0·6–1635)
Urine iodine (μg/l)	135 ± 77 120 (28–538)
Gestational age (weeks)	10·9 ± 2·3 11 (5–14)
Maternal age (years)	29·8 ± 4·8 30 (18–40)

*Values are mean ± standard deviation, where appropriate, and median (range).

Table 2. Correlations between urine perchlorate and thiocyanate concentrations and serum thyroid function values

	Urine perchlorate and serum TSH		Urine perchlorate and serum FT4		Urine perchlorate and serum FT3	
	r	*P*	*r*	*P*	*r*	*P*
Total (n = 133)	0·07	0·4	−0·19	0·03	−0·19	0·03
UIC < 100 μg/l (n = 50)	0·19	0·2	−0·23	0·09	−0·21	0·1
	Urine thiocyanate and serum TSH		Urine thiocyanate and serum FT4		Urine thiocyanate and serum FT3	
Total (n = 133)	0·2	0·008	−0·16	0·06	0·02	0·8
UIC < 100 μg/l (n = 50)	0·19	0·2	−0·11	0·5	0·02	0·9

In Spearman's rank correlation analysis of the other variables, urine perchlorate concentrations were significantly positively correlated only with gestational age (r = 0·18; P = 0·04). Urinary thiocyanate concentrations were not correlated with gestational age (r = 0·02; P = 0·8). There were no correlations between urine iodine concentrations and thyroid function (for TSH, r = −0·04, P = 0·7; for FT4, r = 0·14, P = 0·1; and for free FT3, r = −0·06, P = 0·5).

In multivariate analyses adjusting for urine thiocyanate concentrations, urine iodide concentrations, TPO Ab titre, gestational age and maternal age, urine perchlorate was not a significant predictor of thyroid function (Table 3). TPO antibody titre was positively associated with log serum TSH and inversely associated with serum FT4. Gestational age was inversely associated with serum FT4 and FT3. Maternal age was inversely associated with serum FT3. Results of multivariate analyses considering TPO antibodies as a dichotomous variable were similar (data not shown). No interactions were observed between urine perchlorate and TPO antibody positivity or between urine perchlorate exposure and thiocyanate in models predicting thyroid function.

Given the lack of association of urine perchlorate concentrations with first-trimester serum TSH values, we estimated our statistical power to detect associations. At an α of 0·05, we had 80% power to detect correlation coefficients of ±0·24.

Discussion

The present study in first-trimester pregnant women residing in and near Athens, Greece, largely confirms our recent finding in pregnant women residing in Wales, Italy, Argentina and California that perchlorate exposure did not affect thyroid function.[12,13] The environmental exposure to perchlorate in the present study was similar to that previously reported from the United States[10] and Europe[12] using the same methodology.

Urine perchlorate and gestational age each correlated inversely with FT4 and FT3 in univariate analyses, but the relationships between urine perchlorate and thyroid hormones were no longer observed following adjustment of models for gestational age. Gestational age was inversely associated with FT4 and FT3, likely reflecting the effect of decreasing stimulation of thyroidal TSH receptors by human chorionic gonadotrophin following the 10th week of gestation. In this sample, gestational age appears to be a confounder of the apparent relationship between urine perchlorate concentrations and both serum FT4 and FT3, although it is unclear why a greater gestational age was associated with increased perchlorate exposure. This relationship between gestational age and urine perchlorate was not observed in our previous study of pregnant women from California and Argentina.[13] It is unlikely that the correlation observed between gestational age and urinary perchlorate was attributable to increased glomerular filtration rates with more advanced pregnancies, as no relationship between urine thiocyanate exposure and gestational age was observed. The correlation between gestational age

Table 3. Multivariable regression model predicting the (a) natural log of serum TSH, (b) log serum free T4 and (c) serum free T3

Independent variable	Coefficient	Standard error	*P*-value
(a)			
Intercept	0·40	0·97	0·7
Log urine perchlorate (μg/l)	0·02	0·12	0·8
Log urine thiocyanate (μg/l)	0·14	0·010	0·2
Urine iodide (μg/l)	−0·002	0·001	0·2
TPO titre (kIU/l)	0·006	0·002	0·001
Gestational age (days)	−0·006	0·006	0·4
Maternal age (years)	−0·24	0·02	0·3
(b)			
Intercept	0·55	0·17	0·001
Log urine perchlorate (μg/l)	−0·007	0·021	0·8
Log urine thiocyanate (μg/l)	−0·02	0·02	0·2
Urine iodide (μg/l)	0·0003	0·0002	0·2
TPO titre (kIU/l)	−0·006	0·0003	0·03
Gestational age (days)	−0·003	0·001	0·002
Maternal age (years)	0·0001	0·004	1·0
(c)			
Intercept	6·5	0·58	<0·001
Log urine perchlorate (μg/l)	−0·036	0·074	0·6
Log urine thiocyanate (μg/l)	−0·006	0·058	0·9
Urine iodide (μg/l)	−0·0007	0·0008	0·4
TPO titre (kIU/l)	−0·002	0·001	0·1
Gestational age (days)	−0·009	0·004	0·02
Maternal age (years)	−0·035	0·013	0·01

and urine perchlorate may simply have been a statistical fluke, but this issue deserves further study.

In univariate analyses, urine thiocyanate concentrations were positively correlated with serum TSH, although there were no significant correlations between urine thiocyanate and serum FT4 or FT3. Associations between urine thiocyanate concentrations and thyroid function were not observed in adjusted analyses. We did not detect interactions between urine thiocyanate and urine perchlorate in the prediction of thyroid function, as reported previously by Steinmaus and colleagues.[15]

Because of the importance of adequate thyroid hormone for foetal neurodevelopment in early gestation, exposure to quantities of perchlorate sufficient to decrease maternal thyroid function during the first trimester of pregnancy could have adverse foetal effects. It is therefore reassuring that low-level perchlorate exposure in first-trimester pregnant women was not associated with adverse effects on thyroid function in this and previous studies.[12,13] However, infant and childhood development in relation to maternal thyroid function and exposure to perchlorate and other potential thyroid disruptors await further study.

It is difficult to reconcile the present largely negative findings and those from our previous studies in Wales, Italy, Argentina and California, with the adverse effects of environmental perchlorate on thyroid function reported previously by Blount *et al.*[11] The study by Blount and colleagues was not limited to pregnant women or women of reproductive age. In the present and previous studies, TPO antibodies are associated with significantly higher serum TSH and significantly lower FT4 concentrations in first-trimester pregnant women. In the 2001–2002 NHANES study, TPO antibodies and FT4 were not measured; TPO positivity and differences in thyroxine-binding globulin could be potential confounding factors. Ongoing NHANES is addressing these issues.

The World Health Organization has defined optimal iodine nutrition in pregnant women as a median urinary iodine concentration of 150–249 μg/l[16]; by this standard, the Greek women studied were mildly iodine deficient. The adverse effects of perchlorate on thyroid function in the NHANES study were primarily seen in women, but not men, with urine iodine values less than 100 μg/l.

In conclusion, adjusted analyses demonstrated no effect of environmental perchlorate on thyroid function in these first-trimester pregnant women residing in Athens and demonstrating mild iodine deficiency. Nonetheless, optimal iodine nutrition during pregnancy should be encouraged to ensure normal thyroid function in pregnant women, their foetuses and their breast-fed infants.

Disclosure of conflicts of interest

The authors have no conflicting interests to declare.

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