Perchlorate and Thiocyanate Exposure and Thyroid Function in First-Trimester Pregnant Women

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Context: Thyroid hormone, requiring adequate maternal iodine intake, is critical for fetal neurodevelopment. Perchlorate decreases thyroidal iodine uptake by competitively inhibiting the sodium/iodide symporter. It is unclear whether environmental perchlorate exposure adversely affects thyroid function in pregnant women. Thiocyanate, derived from foods and cigarette smoke, is a less potent competitive sodium/iodide symporter inhibitor than perchlorate.

Objective: Our objective was to determine whether environmental perchlorate and/or thiocyanate exposure is associated with alterations in thyroid function in pregnancy.

Design and Setting: We conducted a cross-sectional study at health centers in Cardiff, Wales, and Turin, Italy.

Patients: During 2002–2006, 22,000 women at less than 16 wk gestation were enrolled in the Controlled Antenatal Thyroid Screening Study. Subsets of 261 hypothyroid/hypothyroxinemic and 526 euthyroid women from Turin and 374 hypothyroid/hypothyroxinemic and 480 euthyroid women from Cardiff were selected based on availability of stored urine samples and thyroid function data.

Main Outcome Measures: Urinary iodine, thiocyanate, and perchlorate and serum TSH, free T4 (FT4), and thyroperoxidase antibody were measured.

Results: Urinary iodine was low: median 98 μg/liter in Cardiff and 52 μg/liter in Turin. Urine perchlorate was detectable in all women. The median (range) urinary perchlorate concentration was 5 μg/liter (0.04–168 μg/liter) in Turin and 2 μg/liter (0.02–368 μg/liter) in Cardiff. There were no associations between urine perchlorate concentrations and serum TSH or FT4 in the individual euthyroid or hypothyroid/hypothyroxinemic cohorts. In multivariable linear analyses, log perchlorate was not a predictor of serum FT4 or TSH.

Conclusions: Low-level perchlorate exposure is ubiquitous but did not affect thyroid function in this cohort of iodine-deficient pregnant women. (J Clin Endocrinol Metab 95: 3207–3215, 2010)
Perchlorate is a competitive inhibitor of the sodium/iodide symporter (NIS), which is located on the basolateral membrane of thyroid epithelial cells and mediates the active transport of iodine from the blood into the thyroid. In sufficiently high concentrations, perchlorate decreases transport of iodide into the thyroid, resulting in decreased thyroid hormone synthesis (1).

Perchlorate salts are used as oxidizers in solid propellants for rockets and missiles, fireworks, road flares, matches, and airbag inflation systems. Perchlorate is present in large concentrations in Chilean nitrate fertilizers. Low perchlorate levels may also be found in the environment due to natural processes (2). Perchlorate has been detected in the drinking water of communities around the United States (3) and has been detected in foods such as lettuce and wheat (4, 5), in cows’ milk (6), and in multivitamins (including prenatal multivitamins) (7). There has been recent concern that low-level perchlorate exposure might pose a health hazard by inducing or aggravating underlying thyroid dysfunction (8, 9).

Perchlorate exposure is ubiquitous in the U.S. population. Perchlorate was detected in all 2820 urine specimens from the 2001–2002 National Health and Nutrition Examination Survey (NHANES) (median 3.6 µg/liter) (10). Among the 35% of women age 12–85 yr with urinary iodine values less than 100 µg/liter in the NHANES 2001–2002 data set, urinary perchlorate concentrations were positively associated with serum TSH and inversely associated with serum T₄ values (11). Among women with urinary iodine values higher than 100 µg/liter, there was a positive association between urinary perchlorate and serum TSH but no association between urinary perchlorate concentrations and serum T₄ values. There were no associations between urinary perchlorate and thyroid function values in men, irrespective of urinary iodine values. This study has been criticized for its reliance on total T₄, rather than free T₄ (FT₄), measurements and because thyroperoxidase (TPO) antibody measurements were not obtained.

Thiocyanate is 15 times less potent than perchlorate as a NIS competitor (1). Cyanide in cigarette smoke is metabolized to thiocyanate. Thiocyanate is also a metabolite of cyanogenic glucosides present in plant foods (12). Newborns of mothers who smoke during pregnancy are more likely to have low serum T₄ levels, increased TSH levels, and thyroid enlargement (13, 14). We have recently found that among women in the first trimester of pregnancy, FT₄ index levels were lower in smokers than in nonsmokers (15). These effects are postulated to be related to thiocyanate exposure.

The developing fetus is likely to be most vulnerable to adverse thyroidal effects of perchlorate exposure because thyroidal iodine turnover is highest in fetal life and the fetus requires adequate thyroid hormone for normal neurodevelopment. Adverse neurocognitive outcomes have been observed in children of women with either elevated serum TSH values or isolated low serum FT₄ in pregnancy (16, 17). The objective of the present study was to determine whether thyroid function in pregnant women, particularly those with low iodine intake, is adversely affected by environmental perchlorate exposure and/or by thiocyanate exposure from cigarette smoke and dietary sources.

Subjects and Methods

Subjects

Subjects were a subset of the study cohort from the Controlled Antenatal Thyroid Screening Study (CATS) (18). This prospective study was designed to determine whether l-T₄ treatment for hypothyroid or hypothyroxinemic pregnant women during pregnancy improves child development. Starting in 2002, a total of 22,000 women with singleton pregnancies were enrolled at less than 16 wk gestation (mean gestational age 12.5 wk).

Women were randomized to immediate assay of thyroid function with l-T₄ treatment for elevated serum TSH (>97.5th percentile: >3.65 mIU/liter in Cardiff, Wales, and >3.18 mIU/liter for Turin, Italy) and/or low serum FT₄ (<2.5th percentile: <8.3 pg/ml for Cardiff and <7.36 pg/ml for Turin) vs. storage of blood samples for measurement of thyroid function only after completion of pregnancy.

Thyroid antibodies were measured on all hypothyroid or hypothyroxinemic women and in a randomly selected subset of 900 euthyroid CATS participants. Urinary iodine measurements were similarly performed on a randomly selected sample. Due to storage constraints, some urine specimens were randomly selected for pooling in batches of 10. For the present study, women were selected from the larger CATS study cohort based on the availability of stored individual urine samples and thyroid function and antibody data. The initial cohort examined for the present study included 376 women from Cardiff and 261 women from Turin, all of whom had had elevated serum TSH and/or low first-trimester serum FT₄ values. Two women were excluded from the initial Cardiff cohort for laboratory values consistent with central hypothyroidism (serum TSH values of 0.03 and 0.10 mIU/liter with FT₄ 8.0 pg/ml in both), yielding a total sample size of 374 for the hypothyroid/hypothyroxinemic Cardiff women. A second cohort included 526 euthyroid women from Turin and 480 euthyroid women from Cardiff. All women provided blood and urine samples at a single time point in the first trimester of pregnancy. All blood and urine samples were obtained for the present study before initiation of any l-T₄ therapy. The women studied were similar to the entire CATS study population with regard to mean maternal age (29.6 vs. 30.3 yr), mean gestational age at enrollment (87.6 vs. 85.3 d), and mean maternal weight (67.6 vs. 65.1 kg). The women studied, however, included fewer smokers (12.1 vs. 18.1%).

The research protocol was approved by the relevant institutional review boards, and all human participants provided written informed consent.
Laboratory methods

Urinary iodine and perchlorate measurements were obtained during the first trimester of pregnancy in all subjects. Samples were obtained from 2002–2006, and all aliquots were stored at −40°C until measurement.

Serum TSH in Cardiff was measured using immunochemiluminescence (Advia Centaur; Bayer Corp., Tarrytown, NY). The 95% range in the CATS population was 0.15–3.65 mIU/liter. Serum TSH in Turin was measured using an immunofluorescent method (Autodelfia; PerkinElmer Life and Analytical Sciences, Inc., Waltham, MA). The 95% range in the CATS population was 0.110–3.50 mIU/liter. Serum FT₄ in Cardiff was measured using immunochemiluminescence (Advia Centaur; Bayer). The 95% range in the CATS population was 8.4–14.6 pg/ml. Serum FT₄ in Turin was measured using an immunofluorescent method (Autodelfia; PerkinElmer). The 95% range in the CATS population was 7.15–11.34 pg/ml.

Serum TPO antibody titers for all samples were measured by immunooassay (Advia Centaur; Bayer Vital, Fernwald, Germany). Values higher than 32 IU/ml were considered positive.

Urinary iodine concentrations for the first, hypothyroid/hypothyroxinemic, cohort of women from both Cardiff and Turin were measured at the UCD Conway Institute in Dublin, Ireland, using the ammonium persulfate method (19). Urinary iodide concentrations for the women from the second (euthyroid) cohort from both Cardiff and Turin were measured using ion chromatography-mass spectrometry at Boston University, Boston, MA. A randomly selected group of 20 urine samples (10 each from the hypothyroid/hypothyroxinemic Cardiff and Turin cohorts; range of values 29–325 μg/liter using the ammonium persulfate method used in Dublin) were again measured in Boston by mass spectrometry and were slightly lower (median difference 13 μg/liter lower; P = 0.003 using the signed rank test). This is an expected finding because the ammonium persulfate method measures iodine, whereas the mass spectrometry method captures only inorganic iodide. Urinary iodide could not be reliably measured for some euthyroid women from Cardiff because some samples had been contaminated with iodine by the use of Combur Test D* urine test strips (Roche Diagnostics Ltd., Burgess Hill, UK) before storage (20, 21).

Urinary cotinine values for the second, euthyroid, cohort were measured by ELISA (Calbiotech, Spring Valley, CA). Values higher than 500 ng/ml were considered to be consistent with cigarette smoking. Urine thiocyanate concentrations for the second cohort of women were measured at Boston University using ion chromatography-mass spectrometry. The limit of detection is 0.5 μg/liter. The interassay coefficient of variation for this assay in our laboratory ranges from 0.9–8.3%.

All urine perchlorate measurements were performed at Boston University using ion chromatography-mass spectrometry (22). The limit of detection is 0.05 μg/liter. The interassay coefficient of variation ranges from 2.2–5.9% in our laboratory.

Statistical analysis

Because laboratory testing was carried out using different methods at the different study sites and in the different cohorts, the primary analyses were carried out separately for each of the two cohorts at each study site. A combined analysis of the second (euthyroid) cohorts from Cardiff and Turin was also performed in which thyroid function values were transformed into multiples of the median (MoM) values (23) separately for each center (so that for each analyte, the median MoM value is 1 in each center), as is commonly done for biochemical markers in antenatal screening for Down’s syndrome (24). This allows for systematic differences between the two laboratory methods.

Individual Spearman rank correlation analyses were used to separately examine the associations between urine perchlorate concentrations and serum FT₄ and TSH in each cohort and in the combined euthyroid cohorts. We performed these analyses on the total data sets and for those subjects with urinary iodine concentrations less than 100 μg/liter to determine whether the effects of perchlorate exposure on thyroid function tests are limited to individuals with low dietary iodine intake, as was seen in the NHANES data set (11). Similar analyses were carried out to examine correlations between thyroid function and urine thiocyanate concentrations. Wilcoxon rank sum tests were used to determine whether serum TSH and FT₄ values differed in smokers vs. nonsmokers. Multivariable analyses could not be carried out in the individual cohorts due to relatively small sample sizes.

In the combined second (euthyroid) cohort data set, we used multiple linear regression analyses to assess the associations between urine perchlorate and thyroid function tests (MoM TSH and MoM FT₄), considered separately, adjusted for urine iodide concentration, TPO antibody positivity, and other urine thiocyanate concentration or smoking status. We selected covariates for these models that might be associated with thyroid function. We suspected that women with TPO antibodies might have some underlying thyroid compromise and therefore be less able to maintain normal thyroid function in the setting of perchlorate exposure. Urinary thiocyanate was included because thiocyanate and perchlorate are known to have additive NIS-inhibitory effects (1). In separate models, smoking status, based on urine cotinine levels, was included instead of thiocyanate. Urinary iodide concentrations were included in the FT₄ model because women with low dietary iodine intake might be more susceptible to thyroidal effects of perchlorate (although a spot urine iodine is an imperfect reflection of an individual’s dietary iodine status). Urinary iodide concentrations were not a significant predictor in the TSH model, and in fact, the overall model was not significant with urinary iodide included, so urinary iodide was removed from the TSH model. For the multiple regression analyses, non-normal data were transformed. For the multiple regression analyses, iodide, perchlorate, and thiocyanate concentrations were log-transformed so that these data adequately followed a Gaussian distribution. TSH and FT₄ MoM values approximately followed a Gaussian distribution using a square root transformation and 1 divided by the square root transformation, respectively. Because of concern regarding iodine contamination of the Cardiff samples, 96 individuals with urine iodide concentrations higher than 500 μg/liter were excluded from the multivariable analyses. This cutoff point was selected based on a comparison of urinary iodide distributions in the Cardiff euthyroid sample to the other three samples; after removal of the outliers over 500, the distribution of the euthyroid Cardiff sample approximated those of the other three groups.

All subgroup comparisons were preplanned. Statistical tests were considered significant if the two-tailed P value was <0.05. Data processing and statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC). Power calculations were performed using PASS software (NCSS, Kaysville, UT).
Results

Iodine and perchlorate

Median urinary iodine values were low in all groups: 98 μg/liter in the hypothyroid/hypothyroxinemic women from Cardiff, approximately 117 μg/liter in the euthyroid Cardiff women, 55 μg/liter in the hypothyroid/hypothyroxinemic women from Turin, and 50 μg/liter in the euthyroid Turin women (Table 1). Urine perchlorate was detectable in all women (Table 1).

TPO antibody positivity

In the first, hypothyroid/hypothyroxinemic, cohort, 32% of women from Cardiff and 26% of women from Turin were TPO antibody positive, a relatively high prevalence consistent with the known increased prevalence of hypothyroidism in individuals with positive thyroid antibodies. In the euthyroid cohort, 11% of women from Cardiff and 15% of women from Turin were TPO antibody positive (Table 1).

Cotinine and thiocyanate

In the euthyroid cohort 11% of women from Cardiff and 8% of women from Turin were smokers, based on urine cotinine values higher than 500 ng/ml. Thiocyanate values are provided in Table 1. There was a significant positive correlation between thiocyanate and cotinine concentrations (r = 0.46; P < 0.0001).

Relationship between thiocyanate exposure and thyroid function

Using correlation analyses, in the euthyroid Cardiff cohort, there was no association between urine thiocyanate concentration and serum TSH (r = −0.02; P = 0.7) or serum FT₄ (r = −0.07; P = 0.1). In the euthyroid Turin cohort, there was no association between urine thiocyanate concentration and serum TSH (r = 0.05; P = 0.3), but there was a small but significant inverse correlation between urine thiocyanate and serum FT₄ (r = −0.1; P = 0.03). In the combined second cohort data set, there was no association between urine thiocyanate concentration and serum TSH (r = 0.02; P = 0.5), but there was a very slight but significant inverse correlation between urine thiocyanate concentration and serum FT₄ (r = −0.07; P = 0.02).

Relationship between smoking status and thyroid function

Defining smoking status based on urine cotinine concentrations, median serum TSH did not differ between smokers (1.19 mIU/liter) and nonsmokers (1.18 mIU/liter) in the euthyroid Cardiff (P = 0.3) or Turin (1.08 mIU/liter in nonsmokers vs. 1.30 mIU/liter in smokers; P = 0.09).
cohort. In the euthyroid Cardiff cohort, median serum FT$_4$ was 11.3 pg/ml in nonsmokers and 10.8 pg/ml in smokers ($P = 0.05$). In the euthyroid Turin cohort, the median serum FT$_4$ was 9.4 pg/ml in nonsmokers and 9.0 pg/ml in smokers ($P = 0.02$).

**Relationships between perchlorate exposure and thyroid function**

In the first, hypothyroid or hypothyroxinemic, cohort there were no associations between urinary perchlorate levels and first-trimester serum TSH or FT$_4$ values in Cardiff or in Turin (Table 2). There were no associations between urinary perchlorate levels and thyroid function tests among the 191 women (51%) with urinary iodine values less than 100 g/liter or Turin (analysis not shown). There were similarly no associations between urinary perchlorate levels and thyroid function tests among the 171 women (36%; a proportion likely artificially low due to iodine contamination of some of the samples that could have excluded some women with a truly low urinary iodine concentration) with urinary iodide values less than 100 µg/liter in Cardiff or the 433 women (82%) with urinary iodide values less than 100 µg/liter in Turin. Median TSH and FT$_4$ values did not differ between individuals in the highest and lowest urinary perchlorate deciles in Cardiff or Turin (analysis not shown).

In the combined data set from the euthyroid Cardiff and Turin cohorts (using MoM-adjusted thyroid function values), there was no association between urinary perchlorate levels and first-trimester serum TSH ($r = 0.04$; $P = 0.4$) or FT$_4$ levels ($r = -0.03$; $P = 0.2$). There were similarly no associations between urinary perchlorate levels and thyroid function tests among the 604 women (60%) with urinary iodide values less than 100 µg/liter ($r = -0.03$ and $P = 0.4$ for TSH and $r = -0.04$ and $P = 0.4$ for FT$_4$).

**Multivariable analyses**

In a multivariable analysis adjusted for TPO antibody positivity, log urine perchlorate and thiocyanate concentrations were not predictors of serum TSH (Table 4). The only significant predictor in this model was TPO positivity, which was associated with higher serum TSH levels. In a similar multivariable analysis adjusted for urine iodide and TPO antibody positivity, log perchlorate was not a predictor of serum FT$_4$ (Table 5). In this model, both log urine iodide and urine thiocyanate concentrations were positively associated with serum FT$_4$. Results did not

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**TABLE 2.** Correlations between urine perchlorate concentrations and serum thyroid function values

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Urine perchlorate and serum TSH</th>
<th>Urine perchlorate and serum FT$_4$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r$</td>
<td>$P$</td>
</tr>
<tr>
<td>Cardiff</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroid/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroxinemic</td>
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<td>0.5</td>
</tr>
<tr>
<td>Total (n = 374)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UIC &lt;100 µg/liter (n = 191)</td>
<td>0.06</td>
<td>0.4</td>
</tr>
<tr>
<td>Euthyroid</td>
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<td></td>
</tr>
<tr>
<td>Total (n = 480)</td>
<td>-0.04</td>
<td>0.4</td>
</tr>
<tr>
<td>UIC &lt;100 µg/liter (n = 171)</td>
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<td>0.6</td>
</tr>
<tr>
<td>Turin</td>
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<td></td>
</tr>
<tr>
<td>Hypothyroid/</td>
<td></td>
<td></td>
</tr>
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<td>Hypothyroxinemic</td>
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<tr>
<td>Total (n = 261)</td>
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<td></td>
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<tr>
<td>UIC &lt;100 µg/liter (n = 204)</td>
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<tr>
<td>Euthyroid</td>
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<td></td>
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<tr>
<td>Total (n = 526)</td>
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<td>0.3</td>
</tr>
<tr>
<td>UIC &lt;100 µg/liter (n = 433)</td>
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<td>0.3</td>
</tr>
<tr>
<td>Combined euthyroid</td>
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<td></td>
</tr>
<tr>
<td>Cardiff and Turin</td>
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<td></td>
</tr>
<tr>
<td>Total (n = 1006)</td>
<td>-0.04</td>
<td>0.2</td>
</tr>
<tr>
<td>UIC &lt;100 µg/liter (n = 604)</td>
<td>-0.03</td>
<td>0.4</td>
</tr>
</tbody>
</table>

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**TABLE 3.** Correlations between urine thiocyanate concentrations and serum thyroid function values

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Urine thiocyanate and serum TSH</th>
<th>Urine thiocyanate and serum FT$_4$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r$</td>
<td>$P$</td>
</tr>
<tr>
<td>Euthyroid Cardiff</td>
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<td></td>
</tr>
<tr>
<td>Total (n = 480)</td>
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<td>0.7</td>
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<tr>
<td>UIC &lt;100 µg/liter (n = 171)</td>
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<td>0.7</td>
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<tr>
<td>Euthyroid Turin</td>
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<td>Total (n = 526)</td>
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<td>0.3</td>
</tr>
<tr>
<td>UIC &lt;100 µg/liter (n = 433)</td>
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<td>0.5</td>
</tr>
<tr>
<td>Combined Euthyroid Cardiff and Turin</td>
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<td></td>
</tr>
<tr>
<td>Total (n = 1006)</td>
<td>0.02</td>
<td>0.5</td>
</tr>
<tr>
<td>UIC &lt;100 µg/liter (n = 604)</td>
<td>0.04</td>
<td>0.3</td>
</tr>
</tbody>
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TABLE 4. Multivariable regression model predicting the square root of serum TSH

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Coefficient</th>
<th>SE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.9110</td>
<td>0.0703</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Log urine perchlorate</td>
<td>-0.0176</td>
<td>0.0106</td>
<td>0.1</td>
</tr>
<tr>
<td>Log urine thiocyanate</td>
<td>0.0139</td>
<td>0.0117</td>
<td>0.2</td>
</tr>
<tr>
<td>TPO positivity</td>
<td>0.0695</td>
<td>0.0230</td>
<td>0.02</td>
</tr>
</tbody>
</table>

change when smoking status, rather than thiocyanate concentration, was included as a covariate.

Statistical power

Given the lack of association of urine perchlorate concentrations with first-trimester serum TSH and FT₄ values, we estimated our statistical power to detect associations (25); at an α of 0.05, we had 80% power to detect correlation coefficients of ±0.1433 in the hypothyroid/hypothyroxinemic women from Turin, ±0.1274 in the euthyroid Cardiff women, ±0.1723 in the hypothyroid/hypothyroxinemic women from Turin, ±0.1218 in the euthyroid Turin women, and ±0.0882 in the combined euthyroid cohort.

Discussion

Our study demonstrates that although low-level perchlorate exposure is ubiquitous, it is not associated with alterations in serum TSH or FT₄ among iodine-deficient women in the first trimester of pregnancy in adjusted or unadjusted analyses.

Because of increased thyroid hormone production, increased renal iodine losses, and fetal iodine requirements in pregnancy, dietary iodine requirements are higher in pregnancy than they are for nonpregnant adults (26). Decreases in maternal T₄ associated with even mild iodine deficiency may have adverse effects on the cognitive function of offspring (19, 27, 28). Mild iodine deficiency may also be associated with attention deficit and hyperactivity disorders in offspring (29). The World Health Organization recommends 250 μg iodine ingestion daily for pregnant women, higher than the 150 μg/d recommended for nonpregnant individuals (19). According to World Health Organization guidelines, median iodine concentrations of 150–249 μg/liter in pregnant women are consistent with adequate iodine intake (19); by this benchmark, the populations of women from Turin and Cardiff were clearly iodine deficient. In the United Kingdom, only about 5% of households use iodized salt (30). Italian legislation passed in 2005, after many of these urine samples had been collected, requires retailers to sell only iodized salt unless consumers specifically request otherwise (31); this measure should help to increase dietary iodine intake in pregnant women in Turin.

This study also demonstrates the ubiquitous nature of low-level perchlorate exposure, even in regions not known to have been affected by industrial perchlorate contamination. Levels of exposure in these European cohorts (geometric mean 3.62 μg/liter for the combined euthyroid women from Cardiff and Turin) were similar to the geometric mean urinary perchlorate concentration of 3.6 μg/liter previously reported for the United States (10).

Several previous prospective studies have examined the effects of perchlorate on thyroid function in nonpregnant U.S. individuals. We have previously found that the administration of 3 or 10 mg perchlorate to normal volunteers throughout the day for 14 d did not affect serum TSH or thyroid hormone concentrations, although the higher perchlorate dose decreased the 24-h thyroid ¹²³I uptake (32, 33). Greer et al. (34) gave doses ranging from 0.5–35 mg perchlorate daily to normal volunteers for 14 d and found no change in serum TSH, T₄, and T₃ concentrations; there was a slight decrease in the thyroid ¹²³I uptake at the 1.4-mg and higher doses but not at the 0.5-mg dose. A longer-term 6-month study in normal volunteers at daily doses of 0.5 or 3.0 mg perchlorate daily resulted in no changes in serum TSH, thyroglobulin, T₄, FT₄ index, total T₃, and the thyroid ¹²³I uptake with urine perchlorate concentrations of 248 and 1941 μg/liter, although the study was underpowered (35). Finally, in a study of long-term (mean 3 yr) exposed workers in a perchlorate production plant who excreted up to 40 mg perchlorate daily, no effect on serum thyroid function tests or abnormalities on thyroid ultrasound were observed compared with nonexposed individuals (36).

The lack of association between low-level environmental perchlorate exposure, as assessed by urinary perchlorate concentrations, and first-trimester thyroid function in the present study is reassuring. The iodine deficiency of the women in the present study might have made them par-

TABLE 5. Multivariable regression model predicting one divided by the square root of serum FT₄

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Coefficient</th>
<th>SE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
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<td>&lt;0.0001</td>
</tr>
<tr>
<td>Log urine perchlorate</td>
<td>-0.0019</td>
<td>0.0020</td>
<td>0.3</td>
</tr>
<tr>
<td>Log urine thiocyanate</td>
<td>0.00483</td>
<td>0.0023</td>
<td>0.03</td>
</tr>
<tr>
<td>TPO positivity</td>
<td>0.00288</td>
<td>0.0057</td>
<td>0.6</td>
</tr>
<tr>
<td>Log urine iodide</td>
<td>0.00435</td>
<td>0.0019</td>
<td>0.02</td>
</tr>
</tbody>
</table>
particularly vulnerable to any adverse thyroidal effects of perchlorate exposure. Our results agree with those of an ecological study from Chile that found that thyroid hormone and TSH levels in pregnant women and their neonates did not vary among three towns with drinking water perchlorate concentrations of 0.5, 6, and 114 µg/liter (37). However, pregnant women in all three Chilean towns had far higher urinary iodine concentrations (median 269 µg/liter) than those found in Europe, which may have made them less susceptible to perchlorate’s effects. In Israel, neonatal T₄ levels did not differ in infants of women who consumed drinking water with high (42–94 µg/liter) or very high (≥340 µg/liter) perchlorate concentrations during pregnancy, but maternal thyroid function was not assessed (38). Another study reported higher newborn serum TSH concentrations in an Arizona town with 6 µg/liter perchlorate in drinking water compared with another town with no detected drinking water perchlorate levels (39). However, a reanalysis showed that these results were due to different demographics and altitudes rather than perchlorate exposure (40).

We noted a slight but significant inverse correlation between urine thiocyanate exposure and serum FT₄ concentrations only in the Turin cohort. This is similar to adverse thyroidal effects of smoking in pregnancy described in previous studies (13–15). However, in multivariable analyses, after adjustment for urine perchlorate and iodide concentrations as well as TPO antibody status, the log of urine thiocyanate was positively associated with serum FT₄, with no effect on serum TSH. Cigarette smoke is likely to have been a major source of the thiocyanate exposure, although thiocyanate is also found in the diet. Vanderver et al. (41) reported that among women of childbearing age in NHANES III, increased smoking rates were associated with increased rates of hypothyroxinemia, but only among women with the highest urinary iodine concentrations. Steinmaus et al. (42) have demonstrated that among women with urine iodine concentrations less than 100 µg/liter in NHANES 2001–2002, there was a more marked inverse association between perchlorate exposure and serum T₄ levels in smokers, a finding not replicated in the present study. Nevertheless, these data provide another reason to counsel pregnant women against smoking.

The present study is limited by its cross-sectional design, which allowed us to assess for associations but not causality. Although our study used data from a selected sample, we do not believe that the individuals included in the present study differed systematically from the larger CATS study cohort except for the relative oversampling of women with mild hypothyroidism or hypothyroxinemia and the inclusion of relatively fewer smokers. The use of different TSH and FT₄ laboratory assays for different cohorts was not optimal and required statistical adjustment before pooling of thyroid function data. The accuracy of analog FT₄ measurements during pregnancy has been questioned (43). We do not believe that use of FT₄ values rather than a FT₄ index threatens the validity of the present study because our analyses rely on the comparison of FT₄ (within assays, or corrected across assays in the case of the MoM data) values with each other rather than the absolute FT₄ values. We would also note that the studies conducted by Pop et al. (16), which have led to concerns about effects of isolated maternal hypothyroxinemia on fetal neurodevelopment, defined hypothyroxinemia based on analog FT₄ methods. Although urine iodine was assessed using different measurement techniques, the iodine/iodide values measured by the different methods are not directly compared or pooled. Finally, although we did not detect an association between thyroid function and perchlorate exposure, many other environmental chemicals have been implicated as potential thyroidal disruptors (44, 45), and it is possible that there are cumulative effects of multiple exposures that were not assessed in the present study.

We conclude that low-level perchlorate exposure is ubiquitous but is not associated with alterations in thyroid function among iodine-deficient women in the first trimester of pregnancy. Our results do not support the findings reported in the United States that similar levels of perchlorate exposure increase serum TSH and lower serum T₄ in mainly nonpregnant women with urine iodine concentrations less than 100 µg/liter (11). Our study is the largest sample to date (n = 1002) of women with low urinary iodine values, all of whom were pregnant, and should have been adequately powered to detect effect sizes similar to those reported by Blount et al. (11), whose study included only 348 women with urinary iodine values less than 100 µg/liter. Further studies are needed to determine the reasons for these differences.

The Environmental Protection Agency and various state agencies are currently considering whether the perchlorate content of drinking water should be regulated. Regulatory determinations to date have been based on relatively limited human data. We believe that additional studies are needed to examine the effects of environmental perchlorate exposure in vulnerable populations.

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