

## Urinary Perchlorate Excretion Does Not Predict Thyroid Function Among Pregnant Women

### Dear Editor:

A recent analysis of NHANES 2001–2002 data by Blount *et al.* (1) reported an association between altered thyroid function (increased TSH, decreased total T4) and increasing urinary perchlorate ( $\text{ClO}_4^-$ ) concentration among females (age 12 and older, of whom <4% were pregnant). The association with increased TSH was found regardless of urinary iodide ( $\text{I}^-$ ) concentration, and the association with decreased total T4 was found only among those females with urinary  $\text{I}^-$  concentration <100  $\mu\text{g}/\text{L}$ . Subsequent analysis of women of reproductive age from this same dataset using creatinine-adjusted urinary  $\text{I}^-$  concentration found no association between total T4 and urinary  $\text{ClO}_4^-$  concentrations in the population with low urinary  $\text{I}^-$  concentrations (2). Similarly, a recent study from Europe found no correlation between urinary  $\text{ClO}_4^-$  concentration and thyroid function (TSH or free T4 [fT4]) among pregnant women with urinary  $\text{I}^-$  concentrations <100  $\mu\text{g}/\text{L}$  (3). We show in the following analysis of a previously reported cohort of pregnant women in Chile (4) that the data do not support the association reported by Blount *et al.* (1), but are consistent with the recent findings by both Pearce *et al.* (2) and Lamm *et al.* (3).

In 2005 we reported the thyroid function data of pregnant women from three cities in Northern Chile that had differing levels of  $\text{ClO}_4^-$  in their drinking water (4). This cohort of pregnant women in Chile had a median urinary iodine concentration of 262  $\mu\text{g}/\text{L}$  with 3.6% less than 50  $\mu\text{g}/\text{L}$ . By comparison, pregnant women in the United States (5) had median urinary iodine concentrations of 327 and 141  $\mu\text{g}/\text{L}$  with 1.0% and 6.9% less than 50  $\mu\text{g}/\text{L}$  (NHANES I and III, respectively). Our Chilean dataset and the European dataset (2) contained measurements of fT4 and TSH, whereas the NHANES dataset from the United States (1,3) contained measurements of total T4 and TSH. In that study we did not find an effect of city of residence on thyroid function, but we did not specifically look for an interaction between thyroid function and individual urinary  $\text{I}^-$  or  $\text{ClO}_4^-$  concentrations, nor did we separately evaluate the women with urinary  $\text{I}^-$  concentration <100  $\mu\text{g}/\text{L}$ . We present those analyses now.

To explore the Chilean dataset further for these possible associations, we combined the data from all three cities and then restricted the dataset to women who were pregnant (first and/or second prenatal visits) and for whom urinary concentration data for  $\text{ClO}_4^-$ ,  $\text{I}^-$ , and creatinine were complete, and for whom an associated serum fT4 or TSH measurement was recorded. For fT4, there are 202 measurements on 149 individuals, and for TSH, there are 220 measurements on 155 individuals. The distribution of dependent and independent variables in this entire dataset is presented in

Table 1. Seven percent of these women smoked a median of 20 cigarettes per week.

This dataset was evaluated using regression analysis to determine if there are any significant associations between thyroid function measurements (fT4 or TSH) and urinary  $\text{ClO}_4^-$  concentration, urinary  $\text{I}^-$  concentration, and/or an interaction term between urine  $\text{ClO}_4^-$  and urine  $\text{I}^-$  (urine  $\text{ClO}_4^- \times$  urine  $\text{I}^-$ , noncreatinine adjusted). Potential confounding variables assessed were maternal age, weeks gestation, and cigarettes smoked. Urinary  $\text{I}^-$  and  $\text{ClO}_4^-$  concentrations were evaluated both on a concentration basis ( $\mu\text{g}/\text{L}$ ) and on a creatinine-adjusted basis ( $\mu\text{g}/\text{g-creat}$ ). fT4 and  $\ln(\text{TSH})$  were used in the analyses as well as an inverse square root transformation of fT4 in order to achieve normality of the residuals ( $p$ -value from Shapiro–Wilks test >0.05). No transformation of TSH resulted in normality of the residuals. In no case did the smoking, maternal age, or urinary  $\text{ClO}_4^-$  concentration variables reach statistical significance. Reduced parameter sets were evaluated (nonsignificant variables eliminated) when one or more independent variables were significant. The  $\beta$ -coefficients and  $p$ -values from these regressions are presented in Table 2.

The regression coefficients for gestational age (weeks gestation) were significant for all the fT4 analyses but not for the TSH analyses. The regression coefficients for urine  $\text{I}^-$  were significant for fT4 (decreasing fT4 with increasing urine  $\text{I}^-$ ). Interestingly, the regression coefficient for urine  $\text{I}^-$  expressed as  $\mu/\text{g-creat}$  was negatively associated with  $\ln(\text{TSH})$  (i.e., in the same, rather than opposite, direction as for fT4). None of the regression coefficients for fT4 or  $\ln(\text{TSH})$  for urine  $\text{ClO}_4^-$  (whether expressed as  $\mu/\text{L}$  or  $\mu/\text{g-creat}$ ) were significant, which was the primary question being asked. An interaction term was significant in only one analysis, and in that analysis, the coefficient for urine  $\text{ClO}_4^-$  was not significant.

This analysis is consistent with our previous conclusions with respect to the effect of weeks gestation on fT4 and indicates the lack of an association of urinary  $\text{ClO}_4^-$  concentration with either fT4 or TSH among pregnant women with urinary  $\text{I}^-$  concentrations generally above 100  $\mu\text{g}/\text{L}$ . Throughout the range of urinary  $\text{ClO}_4^-$  and  $\text{I}^-$  concentrations observed in this dataset, there is no consistent indication of an interaction between  $\text{ClO}_4^-$  and  $\text{I}^-$  on either fT4 or TSH. These results for TSH are inconsistent with those reported previously among American females (1).

Both for fT4 and TSH, there are only 17 measurements on 16 individuals for whom urinary  $\text{I}^-$  concentration is <100  $\mu\text{g}/\text{L}$ . Separate analysis of this smaller subset of the data demonstrated that fT4 is not lower and TSH is not higher than for the remaining measurements in which urinary

TABLE 1. DISTRIBUTION OF VARIABLES IN COMBINED DATASET

|                 | Age<br>(years) | Weeks<br>gestation | fT4<br>(ng/dL) | TSH<br>( $\mu$ IU/mL) | Urine I <sup>-</sup><br>( $\mu$ g/L) | Urine ClO <sub>4</sub> <sup>-</sup><br>( $\mu$ g/L) |
|-----------------|----------------|--------------------|----------------|-----------------------|--------------------------------------|---|
| 10th Percentile | 17             | 9                  | 0.8            | 1.0                   | 119                                  | 7   |
| Median          | 25             | 16.5               | 0.9            | 2.2                   | 277                                  | 34  |
| 90th Percentile | 35             | 34                 | 1.1            | 5.0                   | 574                                  | 160   |
| Mean            | 25             | 20                 | 0.95           | 2.7                   | 307                                  | 73  |
| SD              | 7              | 9                  | 0.14           | 1.7                   | 182                                  | 116   |

fT4: free T4; I<sup>-</sup>: iodide; ClO<sub>4</sub><sup>-</sup>: perchlorate.

TABLE 2.  $\beta$ -COEFFICIENTS AND *P*-VALUES FROM REGRESSION OR REDUCED PARAMETER REGRESSION ANALYSES (REPEATED MEASURES INCLUDED IN THE ANALYSES)

| Dependent<br>variable | Independent<br>variable                                   | Urine I <sup>-</sup> and urine ClO <sub>4</sub> <sup>-</sup> concentration metrics |         |                        |         |
|-----------------------|---|--|---------|------------------------|---------|
|                       |   | $\mu$ /L   |         | $\mu$ /g-Creat         |         |
|                       |   | $\beta$ -Coefficient   | p-Value | $\beta$ -Coefficient   | p-Value |
| fT4                   | Weeks gestation   | $-5.03 \times 10^{-3}$   | <0.0001 | $-4.81 \times 10^{-3}$ | <0.0001 |
|                       | Urine I <sup>-</sup>                                      | $-1.37 \times 10^{-3}$   | 0.009   | $-1.60 \times 10^{-4}$ | 0.011   |
|                       | Urine ClO <sub>4</sub> <sup>-</sup>                       | –  | NS      | –                      | NS      |
|                       | I <sup>-</sup> -ClO <sub>4</sub> <sup>-</sup> interaction | –  | NS      | –                      | NS      |
| 1/Sqrt(fT4)           | Weeks gestation   | $2.69 \times 10^{-3}$  | <0.0001 | $2.55 \times 10^{-3}$  | <0.0001 |
|                       | Urine I <sup>-</sup>                                      | $8.56 \times 10^{-4}$  | 0.0028  | $8.30 \times 10^{-5}$  | 0.014   |
|                       | Urine ClO <sub>4</sub> <sup>-</sup>                       | –  | NS      | –                      | NS      |
|                       | I <sup>-</sup> -ClO <sub>4</sub> <sup>-</sup> interaction | –  | NS      | $6.26 \times 10^{-7}$  | <0.0001 |
| ln(TSH)               | Weeks gestation   | –  | NS      | –                      | NS      |
|                       | Urine I <sup>-</sup>                                      | –  | NS      | $-7.30 \times 10^{-4}$ | 0.025   |
|                       | Urine ClO <sub>4</sub> <sup>-</sup>                       | –  | NS      | –                      | NS      |
|                       | I <sup>-</sup> -ClO <sub>4</sub> <sup>-</sup> interaction | –  | NS      | –                      | NS      |

I<sup>-</sup>: iodide; ClO<sub>4</sub><sup>-</sup>: perchlorate; fT4: free T4; NS: not significant.

I<sup>-</sup> concentrations are  $\geq 100 \mu\text{g/L}$  (*t*-test). Additionally, in this subgroup, urinary ClO<sub>4</sub><sup>-</sup> concentration did not correlate significantly with fT4, transformed fT4, or ln(TSH), whether or not urine I<sup>-</sup> or weeks gestation were included in the regressions and whether or not urinary I<sup>-</sup> and ClO<sub>4</sub><sup>-</sup> concentrations were creatinine adjusted. Although the number of observations for which urinary I<sup>-</sup> concentrations were <100  $\mu\text{g}$  is small, the data are not supportive of the findings of decreasing total T4 levels and increasing TSH levels with increasing urinary ClO<sub>4</sub><sup>-</sup> concentration previously reported among American females with urinary I<sup>-</sup> concentrations <100  $\mu\text{g}$  (1).

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