Increasing the iodine concentration in the Swiss iodized salt program markedly improved iodine status in pregnant women and children: a 5-y prospective national study

Michael B Zimmermann, Isabelle Aeberli, Toni Torresani, and Hans Bürgi

ABSTRACT
Background: Many industrialized countries struggle to maintain adequate iodine intake because of changes in dietary habits and the food supply. In Switzerland, because of declining iodine intakes in children and pregnant women, the iodine concentration in table salt was increased from 15 to 20 mg/kg.
Objective: We evaluated Swiss iodine nutrition after the 1999 increase in the salt iodine concentration.
Design: In 1999 and 2004, a 3-stage probability proportionate-to-size cluster sampling was done to obtain a representative national sample of primary schoolchildren and pregnant women. Urine and household salt were collected for iodine measurement. The frequency of elevated thyrotropin concentrations found in the newborn screening program was evaluated before and after the increase.
Results: In 1999, median urinary iodine (UI) concentrations among children (n = 610) and pregnant women (n = 511) were 115 μg/L (range: 5–413 μg/L) and 138 μg/L (range: 5–181 μg/L), respectively, which indicated marginal iodine status. In 2004, median UI concentrations among children (n = 386) and pregnant women (n = 279) were 141 μg/L (range: 0–516 μg/L) and 249 μg/L (range: 8–995 μg/L), respectively (P < 0.01). Newborn thyrotropin concentrations >5 mU/L decreased from 2.9% in 1992–1998 (n = 259 035) to 1.7% in 1999–2004 (n = 218 665) (P < 0.0001).
Conclusions: A 25% increase in iodine concentration in iodized table salt markedly improved iodine status in Switzerland, which showed the value of monitoring and adjusting iodine concentrations in national salt programs. The frequency of newborn thyrotropin concentrations >5 mU/L appears to be a sensitive indicator of iodine nutrition during pregnancy.

KEY WORDS Salt, iodine, monitoring, Switzerland, children, newborns, thyrotropin, pregnancy

INTRODUCTION

Because dietary iodine supply in many countries depends on several shifting commercial, agricultural, and societal factors, regular monitoring of iodine nutrition is necessary. Industrialized countries with long-standing salt iodization programs, including the United States, Netherlands, New Zealand, France, and Australia, have reported declining or low concentrations of urinary iodine (UI) among their populations (1–5). The World Health Organization (WHO) has emphasized the importance of periodic monitoring and adjustment of salt iodide concentrations, but few developed or developing countries have established regular and systematic programs (6, 7). Although the WHO has suggested that the frequency of moderately elevated thyrotropin concentrations in newborn screening programs can be used to assess the severity of iodine deficiency in a population, the cutoff values for defining severity are uncertain (6, 7).

Since 1952, iodized salt has been available nationwide in Switzerland. The concentration of iodine in table salt was increased from 3.75 mg/kg to 7.5 mg/kg in 1962 and then to 15 mg/kg in 1980 (8, 9). During the 1980s, iodine status in Switzerland was adequate (8, 9). However, in the 1990s, studies began to suggest marginal iodine deficiency among schoolchildren and pregnant women (10–13). In 1994, among pregnant women in Lausanne, the mean UI concentration was 83–100 μg/g creatinine (12), and, in 1997, the median UI concentration in primary schoolchildren from Zürich and the Engadine valley was 96 μg/L (13). In response, the Swiss federal government increased the concentration of iodine in table salt to 20 mg/kg in 1998. Considering retail and household turnover of salt, it is thought that, by the end of 1999, most of the salt being consumed in Swiss households was iodized at the new concentration.

However, it was not certain what effect this increase would have on iodine nutrition in Switzerland. Approximately 95% of household salt and 70% of salt for industrial food production in Switzerland is iodized, although iodized salt use is voluntary, and manufacturers and retailers must offer both iodized and non-iodized salt (8). Most dietary intake of salt in industrialized countries comes from processed foods (14), and a significant proportion of salt consumed in processed foods in Switzerland is...
iodized at low concentrations (5–10 mg/kg) or noniodized (8, 10). Export-oriented Swiss food producers are reluctant to use iodized salt because it may limit their markets, and an increasing number of imported processed foods contain noniodized salt. In addition, current guidelines from the Ministry of Health recommend that Swiss adults reduce their intake of salt. In this report, we compare data from the national study done in 1999, at the time of the increase, with findings 5 y later, in 2004.

SUBJECTS AND METHODS

In 1999 and 2004, we used a 3-stage probability proportionate-to-size cluster sampling to obtain a representative national sample of primary schoolchildren and pregnant women. Proportionate-to-size cluster sampling is the recommended method for monitoring national salt iodization programs (7). Census data were used to provide a systematic sampling of urban and rural communities on the basis of the cumulative population. In stage 1 of the sampling, primary schools and obstetric clinics were recruited with the use of stratified random selection. If a school or clinic declined participation, a replacement was randomly selected from the same stratum. The ratio of pregnant women in Switzerland who receive their prenatal care in hospitals to those who receive their prenatal care in private clinics is ≈1:2 (Swiss Society for Obstetrics and Gynecology, written communication, 1999), and this ratio was used to sample prenatal care clinics. In stage 2, classrooms were randomly selected from each school. Finally, all children whose parents provided consent were enrolled from the classroom, and the clinic physician sequentially enrolled the desired number of pregnant women. In 1999, ≈30 children and pregnant women were sampled from 20 clusters (15); in 2004, ≈20 children and pregnant women were sampled from 20 and 15 clusters, respectively.

At the schools, the age of the children was obtained from the school record, and weight and height were measured (16). For the pregnant women, age, week of gestation, type of salt used in the home, and use of vitamin-mineral supplements were recorded by the clinic staff. Spot urine samples were collected from children and pregnant women. In 1999, 30-g salt samples were collected from households in the Zürich metropolitan area. In 2004, every fourth child from the school lists participating in the study brought a 30-g salt sample from home. In 1999, data were collected from April through December; in 2004, data were collected from April through September. Data on newborn thyrotropin concentrations were obtained from the newborn screening program for eastern Switzerland at the University Children’s Hospital in Zürich. In this program, whole-blood samples obtained on day 3 or 4 (72–96 h) after birth are spotted and dried on filter paper (grade 903; Schleicher & Schuell, Dassel, Germany) and sent to a central laboratory for analysis. Because the iodine supply is uniform across Switzerland and a standardized collection protocol is used for newborn screening throughout the country, these thyrotropin data are likely to be nationally representative.

Written informed consent was obtained from the parents of the children and from the pregnant women. Ethical approval for the study was obtained from the Swiss Federal Institute of Technology in Zürich.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Age, sex ratio, and urinary iodine concentrations in primary schoolchildren in Swiss national surveys done before (1999) and after (2004) an increase in the iodine concentration in table salt from 15 to 20 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study</td>
</tr>
<tr>
<td></td>
<td>1999 (n = 610)</td>
</tr>
<tr>
<td></td>
<td>2004 (n = 386)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>9.5 ± 1.9</td>
</tr>
<tr>
<td>Male:female</td>
<td>307:303</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>139 ± 14</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>34.8 ± 10.2</td>
</tr>
<tr>
<td>Urinary iodine concentration (µg/L)</td>
<td>115 (5–413)</td>
</tr>
<tr>
<td>Prevalence of urinary iodine &lt;100 µg/L (%)</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>9.9 ± 1.8</td>
</tr>
<tr>
<td></td>
<td>184:202</td>
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<tr>
<td></td>
<td>141 ± 12</td>
</tr>
<tr>
<td></td>
<td>35.7 ± 9.6</td>
</tr>
<tr>
<td></td>
<td>141 (0–516)</td>
</tr>
</tbody>
</table>

1 Mean ± SD (all such values).
2 Median; range in parentheses (all such values).
3 Significantly different from 1999, \( P < 0.01 \) (t test).
4 Significantly different from 1999, \( P < 0.01 \) (chi-square test).

Data analysis

Salt and urine samples were stored at −20 °C until they were analyzed. UI concentration was measured at the Human Nutrition Laboratory in Zürich by using a modification of the Sandell-Kolthoff reaction (17). By this method, the CV for UI concentration in our laboratory is 10.0% at 47.4 ± 0.6 µg/L and 12.7% at 79.5 ± 0.8 µg/L. Salt iodine concentration was measured by colorimetric titration (7). Dried blood spots on filter paper were analyzed for newborn thyrotropin with the use of an immunoassay (18). Normal reference values are <15 mU/L whole blood.

Statistical analysis

We used SPLUS-2000 (Insightful Corporation, Seattle, WA), PRISM (version 3; GraphPad, San Diego, CA), and EXCEL (XP 2002; Microsoft, Seattle, WA) software for data processing and statistics. Normally distributed data were expressed as means ± SDs; nonnormally distributed data were expressed as medians (ranges). Unpaired \( t \) tests and chi-square tests were used for comparisons of normally distributed data. UI and thyrotropin concentrations were not normally distributed and were log transformed for comparisons. \( P \) values < 0.05 were considered significant.

RESULTS

Data from the children in 1999 and 2004 are shown in Table 1. The median UI concentration in 2004 was 23% higher than that in 1999 (\( P < 0.01 \)). As shown in Figure 1, the proportion of children with a UI concentration >100 µg/L (the cutoff for iodine sufficiency (6)) increased from 60% to 86%, whereas the proportion with a UI concentration >300 µg/L, which indicates iodine excess (6), increased from 2% to 4%. Significant sex or age differences in median UI concentration were not observed in either year among children (data not shown). Data from the pregnant women in 1999 and 2004 are shown in Table 2. The median UI concentration in 2004 was 80% higher than that in 1999 (\( P < 0.001 \)). The UI concentration in pregnancy that corresponds to the current recommendations for iodine intake in pregnancy (200–220 µg/d) is estimated to be ≈140 µg/d (19).
As shown in Figure 2, the proportion of women with a UI concentration >140 µg/L increased from 48% to 77%, whereas the proportion of those with a UI concentration >500 µg/L increased from 6% to 8%. In 1999, 70% of the pregnant women were taking a prenatal multivitamin-mineral supplement, but only 13% were taking a supplement containing iodine [150 µg iodide as potassium iodide (KI)]. In 2004, although 62% of the women were taking a prenatal supplement, only 9% were taking a supplement containing iodine (150 µg iodide as KI). In both years, a significant ($P < 0.05$) difference was observed in median UI concentration between women taking an iodide-containing supplement and women not taking an iodide-containing supplement. In 1999, women taking an iodine-containing supplement had a higher median UI concentration than did women not taking a supplement, but in 2004, the pattern was reversed (Table 2). In 1999 and 2004, 82–86% of pregnant women reported using iodized salt at home.

As shown in Table 3, a comparison of the period before the increase in salt iodine (1992–1998) with the period afterward (1999–2004) found that the frequency of newborn thyrotropin concentrations >5 mU/L decreased from 2.9% to 1.7% ($P < 0.0001$). From 1992 to 2004, no significant difference was observed in the mean thyrotropin concentrations when samples obtained on day 3 (1.60 mU/L) were compared with samples obtained on day 4 (1.59 mU/L) ($P = 0.27$). However, the frequency of thyrotropin concentrations >5 mU/L was slightly but significantly ($P < 0.0001$) higher on day 3 (2.4%) than on day 4 (2.2%).

In 1999 and 2004, 13% and 15% of household salt samples, respectively, contained <10 mg I/kg. Among the samples of iodized household salt, the mean salt iodine concentration in 1999 ($n = 91$) and 2004 ($n = 72$) was 13.7 ± 1.9 and 18.3 ± 3.0 mg/kg, respectively ($P < 0.01$).

### DISCUSSION

In this study, schoolchildren, pregnant women, and newborns were used as target groups for iodine monitoring. Schoolchildren are recommended for monitoring iodine nutrition in a population because of their easy availability as subjects and their vulnerability to the adverse effects of iodine deficiency (6, 7). An indicator of optimal iodine nutrition in a population is a median UI concentration of 100–200 µg/L in school-age children (6). During pregnancy, adequate iodine is essential for optimal neurologic development of the fetus (6), and the recommended monitoring indicator is thyrotropin concentrations in newborns (7). Older recommendations from WHO suggest that a <3% frequency of newborn thyrotropin values >5 mU/L indicates iodine deficiency vs. 0.1% in a population with optimal iodine nutrition (6, 7).

### TABLE 2

<table>
<thead>
<tr>
<th>Study year</th>
<th>1999 ($n = 511$)</th>
<th>2004 ($n = 279$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>29.5 ± 4.8</td>
<td>29.1 ± 4.6</td>
</tr>
<tr>
<td>2nd:3rd trimester</td>
<td>206:290</td>
<td>129:139</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>28 ± 8</td>
<td>27 ± 8</td>
</tr>
<tr>
<td>Urinary iodine (µg/L)</td>
<td>138 (5–1881)</td>
<td>249 (8–995)</td>
</tr>
<tr>
<td>Urinary iodine (µg/L)</td>
<td>194 (31–990)</td>
<td>177 (26–861)</td>
</tr>
<tr>
<td>In women taking a supplement containing 150 µg iodide</td>
<td>130 (5–1881)</td>
<td>257 (8–995)</td>
</tr>
<tr>
<td>Prevalence of urinary iodine &lt;140 µg/L (%)</td>
<td>52</td>
<td>23</td>
</tr>
</tbody>
</table>

$^{1}$ ± SD (all such values).

$^{2}$ Median; range in parentheses (all such values).

$^{3}$ Significantly different from 1999, $P < 0.001$ (t test).

$^{4}$ $n = 64$.

$^{5}$ In each year, significantly different from women not taking an iodide supplement, $P < 0.05$ (t test).

$^{6}$ $n = 25$.

$^{7}$ $n = 447$.

$^{8}$ $n = 254$.

$^{9}$ Significantly different from 1999, $P < 0.01$ (chi-square test).

### TABLE 3

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Newborn whole blood thyrotropin (mU/L)</td>
<td>1.2 (0.8, 1.9)</td>
<td>1.2 (0.8, 1.8)</td>
</tr>
<tr>
<td>Prevalence of newborn thyrotropin &gt;5 mU/L (%)</td>
<td>2.9</td>
<td>1.7</td>
</tr>
</tbody>
</table>

$^{1}$ Median; interquartile range in parentheses (all such values).

$^{2}$ Significantly different from 1999, $P < 0.0001$ (chi-square test).
sufficiency (7). Although no criteria are established for median UI concentration during pregnancy, the UI concentration in pregnancy that corresponds to current recommendations for iodine intake in pregnancy has been estimated to be ≈140 μg/d (19). In 1999, on the basis of these 3 indicators, iodine intake in Switzerland was marginal.

The 25% increase in the content of Swiss iodized salt markedly improved iodine intakes in schoolchildren and pregnant women. The median UI concentration has increased 23% in schoolchildren and 80% in pregnant women. The reason for the larger increase in the median UI concentration in pregnancy is unclear. It was not due to an increase in iodine-containing supplements taken during pregnancy (19): the proportion of women taking a supplement containing 150 μg iodine was 13% in 1999 and 9% in 2004. Moreover, in 2004, women receiving an iodine-containing supplement had a significantly lower median UI concentration than women not supplementing with iodine. However, the number of women taking an iodine-containing supplement was small (n = 25), which made comparisons difficult. The food additive erythrosine is rich in iodine and is commonly used as a coloring agent in pharmaceuticals (20). However, it is not used in the prenatal supplements taken by Swiss women. Because the 2 studies (1999 and 2004) were conducted at the same time of year, seasonal variation is an unlikely confounder. Because urine samples were collected in the summer months, UI was at a low concentration in its seasonal variation; iodine intake tends to be higher during winter months in Switzerland because of higher concentrations of iodine in cow milk from feed additives used during the winter (21).

Thyrotropin screening in newborns has been used to assess the severity of iodine deficiency in populations (22–27). In iodine-sufficient populations in Australia and Canada, the prevalence of elevated thyrotropin concentrations (>5 mU/L, with the use of a sensitive monoclonal antibody assay) in blood filter paper specimens collected ≥3 days after birth was between 3% and 5% (23). However, multiple factors other than maternal iodine status can influence measurements of thyrotropin concentrations in newborns, including timing of specimen collection, maternal or newborn exposure to iodine-containing antiseptics, and the thyrotropin assay and collection paper used (26). Because of these uncertainties, the cutoffs for defining severity of iodine deficiency on the basis of newborn thyrotropin concentrations originally proposed by the WHO (7) were not included in the most recent recommendations (6). Our data, obtained with the use of a sensitive thyrotropin assay on samples collected 3–4 d after birth, generally support the original WHO recommendation that a <3% frequency of thyrotropin values >5 mU/L indicates iodine deficiency in a population (7).

The findings of this study indicate that iodine nutrition in children and pregnant women in Switzerland has improved from marginal to clearly sufficient. This improvement illustrates the value of periodic monitoring and adjustment of iodine concentrations in national iodized salt programs. The 1999 and 2004 national surveys are the first of a series that will monitor iodine status in the Swiss population every 5 y. Swiss legislation is flexible in that it specifies a range of 20–30 mg/kg for salt iodization. On the basis of new scientific evidence, a federal decree can change the concentration without the need for a lengthy parliamentary process (28). This approach could serve as a model for other countries that are struggling to maintain adequate iodine intake in the face of shifting dietary habits and changes in the food supply.

We thank the children and women who participated in the study, the medical staff of the obstetric centers, and the teachers. We thank S. Trachsel (Pratteln, Switzerland), N. Hurrell, and S. Geisselhardt (Zürich, Switzerland) for help with the data analyses and I. Molinari (Zürich, Switzerland) for help with the statistical analyses.

Each of the authors contributed to the study design. MBZ and IA collected the data; MBZ and TT supervised the laboratory analyses and performed the statistical analysis; and all authors contributed to the writing and editing of the paper. None of the authors had a personal or financial conflict of interest.

REFERENCES