

## ORIGINAL ARTICLE

# Iodine deficiency in pregnant women in Austria

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**BACKGROUND/OBJECTIVES:** In Austria, iodine deficiency has been considered to be eliminated owing to table salt fortification with iodine, but whether this also applies to pregnant women is unclear. Even mild iodine deficiency during gestation may lead to neurocognitive sequelae in the offspring.

**SUBJECTS/METHODS:** This is a cross-sectional investigation of urinary iodine excretion in 246 pregnant women (first trimester  $n=2$ , second trimester  $n=53$ , third trimester  $n=191$ , gestational diabetes mellitus  $n=115$ , no gestational diabetes mellitus  $n=131$ ). The iodine content of morning spot urine samples was determined using inductively coupled plasma mass spectrometry.

**RESULTS:** Pregnant women in the Vienna area had a median urinary iodine concentration (UIC) of 87  $\mu\text{g/l}$ . Only 13.8% of the cohort were in the recommended range of 150–249  $\mu\text{g/l}$ , whereas 21.5% had a UIC of 0–49  $\mu\text{g/l}$ , 40.2% had a UIC of 50–99  $\mu\text{g/l}$  and 19.5% had a UIC of 100–149  $\mu\text{g/l}$ . In all, 4.9% had a UIC over 250  $\mu\text{g/l}$ . A total of 137 women of foreign origin had a significantly higher iodine excretion compared with Austrian-born women. Maternal or gestational age had no influence on UIC. Although 79 women on iodine supplementation had a significantly higher iodine concentration compared with women without iodine supplementation (97.3 vs 80.1  $\mu\text{g/l}$ ,  $P=0.006$ ), their UIC was below the recommended range, indicating that doses of 100–150  $\mu\text{g}$  per day are not sufficient to normalize iodine excretion. Sodium and iodine concentrations in the urine were tightly correlated ( $R=0.539$ ,  $n=61$ ), suggesting that low intake of iodized salt might contribute to insufficient iodine supply.

**CONCLUSIONS:** This study shows that pregnant women in the Vienna area have a potentially clinically significant iodine deficiency and that currently recommended doses of iodine supplementation may not be sufficient.

*European Journal of Clinical Nutrition* (2015) 69, 349–354; doi:10.1038/ejcn.2014.253; published online 10 December 2014

## INTRODUCTION

Iodine as a component of thyroid hormones is essential for several metabolic functions and for normal prenatal and postnatal growth and development.<sup>1–3</sup> Thus, lack of iodine causes iodine deficiency disorders.<sup>2–4</sup>

In women, ensuing hypothyroidism may cause anovulation and infertility, as well as fetal death and stillbirth. During pregnancy, iodine requirements increase  $\geq 50\%$  owing to a higher production of T4, fetal needs and renal loss.<sup>2</sup> Thus, adequate maternal intake of iodine is essential for the supply of the fetus with both T4 and iodine.<sup>1,3,5</sup> Even mild iodine deficiency may lead to a preferential T3 secretion at the expense of T4 secretion owing to auto-regulatory thyroid stimulating hormone-independent mechanisms. This maternal T3 cannot compensate for the decreased amount of T4 available to the fetal brain,<sup>1,2</sup> which, as rat models suggest, is only locally converted to T3.<sup>6,7</sup> The effects of insufficient iodine and/or T4 supply to the fetus and neonate may be decreased birth weight, high neonatal and infant mortality and disturbed development of the brain.<sup>2,3</sup> The consequences of iodine deprivation depend on the time, duration and the severity of the resulting hypothyroidism.<sup>3</sup> Mental retardation ranges from reduced intellectual ability, poor school performance and decreased work capacity to cretinism (severe mental retardation and associated defects, for example, deaf mutism, spasticity and stunted growth).<sup>3</sup> Even mildly to moderately impaired iodine supply may lead to intelligence quotient and motor development deficits,<sup>2,7</sup> as shown in two recent observational studies.<sup>8,9</sup>

Nearly all iodine is excreted renally. Thus, the urinary iodine concentration (UIC) of spot urine samples is the recommended

method to assess recent iodine supply of populations.<sup>2–4</sup> Hynes *et al.*<sup>8</sup> demonstrated reduced capability in spelling, grammar and English-literacy performance in 9-year-old children of mothers whose UIC was below 150  $\mu\text{g/l}$  during pregnancy. Bath *et al.*<sup>9</sup> showed a dose-dependent risk of scoring in the lowest quartile for verbal intelligence quotient and reading accuracy and comprehension in 8- and 9-year-old children of women with mild iodine deficiency (median UIC 91.1  $\mu\text{g/l}$ ). Possible confounders, such as the previous iodine status of the children, have to be taken into consideration.<sup>10</sup>

Sufficient iodine supply of pregnant women and their offspring can prevent all these adverse consequences<sup>7</sup> and may even reduce the infant mortality rate.<sup>2</sup> Consequently, the WHO, the American Thyroid Association and the Endocrine Society recommend a daily intake of iodine of 250  $\mu\text{g}$  for pregnant and breastfeeding women.<sup>4,11,12</sup> Very often, this requirement is not met. Ideally, in order to replenish the intrathyroidal stores, iodine supplementation should start before conception.<sup>7,10–12</sup> Foods rich in iodine are saltwater fish, dairy products and eggs (which contain 30  $\mu\text{g}$  of iodine per piece, mostly in the yolk<sup>10,13</sup>). The median iodine content in milk from dairy farms around Vienna (22.6  $\mu\text{g}/100\text{ g}$ , range 8.9–65.5  $\mu\text{g}/100\text{ g}$ ) corresponds to the values published by the National Institute of Health<sup>14</sup> and does not vary between regions.<sup>15</sup> As salt is considered an ideal vehicle for iodine, the WHO, the United Nations Children's Fund and the International Council for the Control of Iodine Deficiency Disorders recommend that iodine be added at a level of 20–40  $\text{mg}$  per  $\text{kg}$  salt.<sup>4</sup>

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Received 12 February 2014; revised 9 September 2014; accepted 19 September 2014; published online 10 December 2014

According to the WHO, pregnant and lactating women do not need iodine supplementation in regions in which a salt iodization program, which covers at least 90% of households, has been sustained for at least 2 years and where the median UIC indicates iodine sufficiency.<sup>4</sup>

Twenty years after the implementation of universal statutory salt iodization of 10 mg of potassium iodide per kg table salt in Austria in 1963,<sup>16</sup> persistent iodine deficiency was found,<sup>17</sup> and in 1990 salt iodization was raised to 20 mg/kg.<sup>16</sup> A study conducted in 1993 in school-age children confirmed that iodine intake had normalized.<sup>18</sup> Since then, the iodine supply in Austria has been considered sufficient,<sup>19</sup> although reports existed to the contrary.<sup>20–22</sup> Iodine sufficiency of school-age children is a good indicator for general iodine sufficiency. This, however, may not apply to pregnant and lactating women,<sup>10</sup> as shown in several studies.<sup>23–25</sup> As the actual iodine supply of pregnant women in Austria is unknown, we considered it necessary to investigate this population group.

## MATERIALS AND METHODS

This is a cross-sectional survey of UICs among 246 pregnant women from the Vienna area.

### Subjects

A total of 246 pregnant women were recruited consecutively from the outpatient clinics of Diabetes of the Division of Endocrinology and Metabolism between August 2009 and June 2010, and of the Department of Obstetrics and Fetal Maternal Medicine of the General Hospital of Vienna, between July 2010 and March 2011.

Exclusion criteria were any present or past thyroid disease, current thyroid hormone medication, any severe disease that might affect the iodine metabolism, medication containing iodine, except for vitamin and trace element supplements, severe anemia and impaired kidney function, as well as being underage.

Pregnant women attending our outpatient clinics gave their written consent to an interview regarding eating habits (particularly consumption of dairy products, eggs and saltwater fish) and iodine supplementation, and to give a morning spot urine sample to be tested for iodine and sodium concentration. Demographic data are shown in Table 1.

### Determination of urinary iodine and sodium concentrations

The urine samples were stored at  $-20^{\circ}$  until analysis. Samples divided into an a- and a b-sample were pipetted into polytetrafluoroethylene digestion vessels together with digestion solution containing 71 g  $KClO_3$  and 286 ml 65%  $HNO_3$ , made up to 1 l with ultrapure deionized water.  $KClO_3$  pro analysis, Art. 4944, and  $HNO_3$  65% suprapure, Art. 1.00441.1000, were both from Merck KGaA, Darmstadt, Germany.

The digestion vessels were heated in a microwave digestion system (Microwave Laboratory Systems mls 1200 mega high performance microwave digestion unit, MLS GmbH, Leutkirch, Germany), using the following time/power program: 1 min 250 W/2 min 0 W/5 min 250 W/5 min 400 W/5 min 500 W/20 min ventilation.<sup>26</sup>

Each resulting a- and b-sample was divided into three subsamples after cooling, and iodate solutions (made of  $KIO_3$ /potassium iodate pro analysis, Art. 5053, Merck KGaA, Darmstadt, Germany and ultrapure deionized water) at concentrations of 200  $\mu$ g/l and 400  $\mu$ g/l, respectively, were added to two of the subsamples for standard addition, resulting in concentrations of 2 and 4  $\mu$ g/l, respectively. The resulting sample solutions were measured at an inductively coupled plasma mass spectrometer (Perkin Elmer Sciex ICP mass spectrometer Elan DRC II, Concord, ON, Canada) for the isotope <sup>127</sup>I.

The iodine concentrations of the original a- and b-samples were calculated by standard addition (each inductively coupled plasma mass spectrometer result divided by the slope of the straight line resulting from the measurements of the three subsamples); the blank, which was digested and measured once per digestion and/or measuring day, was subtracted; and the means of the results for the corresponding a- and b-samples were calculated. According to the recent WHO/ICCIDD expert group recommendations,<sup>4</sup> iodine intake was categorized into groups corresponding to UIC (Table 1).

In 61 samples, the sodium concentration was determined by inductively coupled plasma optical emission spectrometry (Perkin Elmer Optima 3000 XL, Norwalk, CT, USA) at the emission line at 589.592 nm, from the digests prepared for the analysis of iodine.

### Estimation of iodine intake

An adaptation of the questionnaire of the German work group of iodine deficiency ([www.jodmangel.de/service/pdf/fragebogen-jodaufnahme.pdf](http://www.jodmangel.de/service/pdf/fragebogen-jodaufnahme.pdf)) was used to estimate the iodine ingested via milk, cheese, saltwater fish and eggs. The women were asked how much milk they consumed on average per day and how many eggs and servings of cheese and saltwater fish they consumed on average per week. The use of iodized salt was not surveyed, as virtually all salt sold in Austria is iodized.

### Statistics

The statistics were computed with IBM SPSS Statistics 20 (IBM Corp., Armonk, NY, USA). Whenever two groups were compared (gestational age, gestational diabetes mellitus, iodine supplementation), Mann–Whitney *U*-tests were applied. For comparison of three groups (ethnicity, age groups), Kruskal–Wallis tests were used, and if the result was statistically significant (ethnicity) pairwise Mann–Whitney *U*-tests were applied. To determine the influence of milk (five groups: no milk consumption; an average consumption of 1–249 ml per day; 250–499 ml per day; 500–749 ml per day; and 750 ml or more per day) and saltwater fish consumption (four groups: no saltwater fish consumption; less than one meal containing saltwater fish per week on average; one saltwater fish meal per week; more than one saltwater fish meal per week), the Spearman correlation coefficient was calculated. To determine the correlation of iodine excretion and sodium excretion, the Kendall–Tau correlation coefficient was calculated. In all calculations, a *P*-value  $< 0.05$  was considered significant. A Bonferroni correction for multiple testing was done and considered in addition to the uncorrected *P*-values.

### Study approval

This noninterventive prospective cross-sectional study protocol was approved by the Ethics Committee of the Medical University of Vienna.

## RESULTS

### Urinary iodine concentration

The overall median UIC in the cohort was 87.0  $\mu$ g/l (range 2.3–649.2  $\mu$ g/l), indicating mildly insufficient iodine intake (Tables 1 and 2). Only 13.8% of the individuals were in the desired range of 150–249  $\mu$ g/l, and 2.8% had a UIC of 250–499  $\mu$ g/l, indicating adequate or more than adequate iodine supply, respectively, in only 16.6% of the cohort. In 81.2%, the UIC was lower than 150  $\mu$ g/l (21.5% 0–49  $\mu$ g/l, 40.2% 50–99  $\mu$ g/l, 19.5% 100–149  $\mu$ g/l). In all, 4.9% of the individuals had a UIC over 250  $\mu$ g/l (2.8% 250–499  $\mu$ g/l, 2%  $\geq 500$   $\mu$ g/l).

### Ethnicity

To look for possible genetic or cultural effects (nutrition), the cohort was divided into three groups according to the nationalities ((1) women of Austrian origin,  $n = 109$ ; (2) women of non-Austrian origin who had been living in Austria for 3 years or less at the time of their participation in the study,  $n = 24$ ; (3) women of non-Austrian origin who had been living in Austria for more than 3 years at the time of their participation,  $n = 113$ ; Table 1).

The UIC differed significantly between groups ( $P = 0.018$ ), with women of Austrian origin having a lower UIC than women of non-Austrian origin who had been living in Austria for 3 years or less ( $P = 0.022$ ) and those who had been living in Austria for more than 3 years ( $P = 0.023$ ). The UIC of women of non-Austrian origin who had been living in Austria for 3 years or less did not differ from those who had been living in Austria for more than 3 years ( $P = 0.315$ ).

**Table 1.** Demographics, groups, median urinary iodine concentration (UIC)

Total			
<i>N</i>	246		
Age (years): median (range)	32 (19–48)		
Week of pregnancy: median (range)	30 (11–39)		
median UIC (µg/l; range)	87.0 (2.3–649.2)		
Ethnicity groups <sup>a</sup>			
	Austrian	Non-Austrian, in Austria 0–3 a	Non-Austrian, in Austria > 3a
<i>N</i>	109	24	113
UIC (µg/l) median (range)	77.5 (2.3–649.2)	104.6 (21.4–472.5)	92.4 (5.6–628.0)
Age groups <sup>b</sup>			
	19–29 years	30–39 years	40–48 years
<i>N</i>	81	141	24
UIC (µg/l) median (range)	94.0 (2.3–628.0)	82.9 (5.6–649.2)	80.6 (9.9–590.3)
Gestational age <sup>c</sup>			
	First trimester	Second trimester	Third trimester
<i>N</i>	2	53	191
UIC (µg/l) median (range)	124.9 (74.4–175.4)	95.1 (2.3–628.0)	83.5 (5.6–649.2)
First+second trimester			
<i>N</i>	55		
UIC (µg/l) median (range)	95.1 (2.3–628.0)		
Gestational diabetes <sup>d</sup>			
	Gestational diabetes mellitus	No gestational diabetes mellitus	
<i>N</i>	115	131	
UIC (µg/l) median (range)	89.5 (9.9–649.2)	82.9 (2.3–628.0)	
Iodine supplementation <sup>e</sup>			
	Iodine supplementation	No iodine supplementation	
<i>N</i>	79	167	
UIC (µg/l) median (range)	97.3 (5.6–649.2)	80.1 (2.3–628.0)	

<sup>a</sup>Austrian vs non-Austrian, in Austria 0–3 a:  $P=0.022$ ; Austrian vs non-Austrian, in Austria > 3a:  $P=0.023$ ; non-Austrian, in Austria 0–3 a vs non-Austrian, in Austria > 3a:  $P=0.315$ . <sup>b</sup>all three groups compared:  $P=0.45$ . <sup>c</sup>First+second vs third trimester:  $P=0.173$ . <sup>d</sup> $P=0.502$ . <sup>e</sup> $P=0.006$ .

**Table 2.** WHO classification of UIC, percentage of women in each group and influence of iodine supplementation

Median UIC (µg/l)	WHO classification	Median UIC (µg/l) subgroups	% Of women in each WHO group (total)	% Of women on iodine supplementation in each WHO group	% Of women without iodine supplementation in each WHO group
0–149	insufficient	0–49	21.5	19.0	22.8
		50–99	40.2		
		100–149	19.5		
150–249	Adequate	13.8	16.6	21.5	10.2
250–499	More than adequate	2.8	2.0	3.8	2.4
≥ 500	Excessive	2.0	2.0	3.8	1.2

Abbreviation: UIC, urinary iodine concentration.

#### Age

The women were divided into three groups regarding their age: (1) 19–29 years, (2) 30–39 years and (3) 40–48 years. UIC did not differ between the three age groups ( $P=0.45$ ; Table 1).

#### Gestational age

As there were only 2 women in the 1st trimester group, a comparison between the first+second trimesters vs the third was made, which showed no significant differences in UIC ( $P=0.173$ ; Table 1).

#### Influence of gestational diabetes

Diabetic ( $n=115$ , median UIC 89.5 µg/l, range 9.9–649.2 µg/l) and nondiabetic women ( $n=131$ , median UIC 82.9 µg/l, range 2.3–628.0 µg/l) had similar iodine supply, as judged from their UIC ( $P=0.502$ ; Table 1).

#### Iodine supplementation

In all, 67.5% of the women had been taking vitamin and trace element supplements for pregnant women daily for at least a

month at the time of their participation, but only 32.1% took supplements containing iodine (Table 1). Of those women, 83.5% took 150 µg of iodine per day, 13.9% took 100 µg and 2.5% took 200 µg. Women on iodine supplementation had a significantly higher median UIC (97.3 µg/l) compared with those not on iodine supplementation (80.1 µg/l;  $P=0.006$ ). Nevertheless, the medians in both groups were below the value that indicates optimum iodine supply according to the WHO.

#### Iodine supplementation and adequacy

Of women not using iodine supplements, only 10.2% had a UIC within the recommended range of 150–249 µg/l, whereas it was lower than 150 µg/l in 86.3% of the women (Table 2). Iodine supplementation was beneficial, increasing the percentage of women with a UIC within the recommended range of 150–249 µg/l to 21.5% and reducing the percentage of women with a UIC lower than 150 µg/l to 70.9%.

#### Influence of milk and saltwater fish consumption

Furthermore, the women were divided into groups according to their daily milk consumption. There was no correlation between UIC and the amount of milk consumed by the women (Spearman's correlation coefficient = 0.016,  $P=0.802$ ).

The women were also divided into groups regarding their weekly consumption of saltwater fish. There was no correlation between UIC and the number of fish meals that the women consumed (Spearman's correlation coefficient = 0.17,  $P=0.787$ ).

#### Influence of salt intake

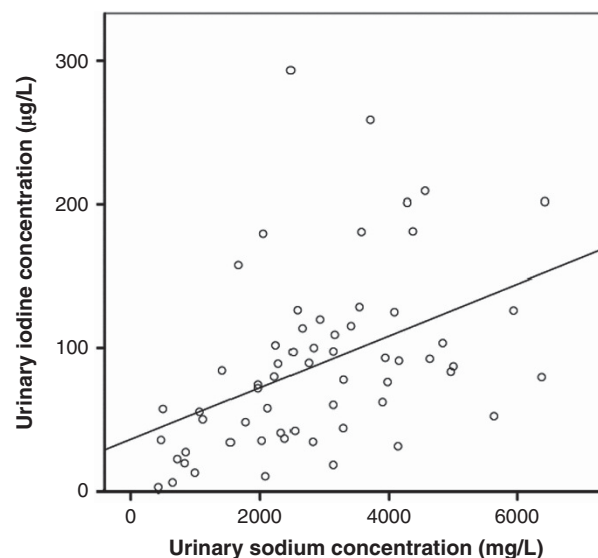
In 61 of the urine samples, the sodium concentration was measured. Iodine excretion and sodium excretion correlated well (Kendall–Tau correlation coefficient = 0.539,  $P < 0.001$ ; Figure 1).

## DISCUSSION

Despite earlier reports of sufficient iodine supply in the Austrian population,<sup>8</sup> but in accordance with recent evidence,<sup>20–22</sup> overall median UIC levels were below the range recommended by WHO in a representative cohort of pregnant women in the Vienna region.<sup>27</sup>

In all, 67.5% of the women took supplements (a lower rate than that observed in an Austrian survey in 2003),<sup>28</sup> and only half of those (32.1%) were prescribed supplements containing iodine. This percentage is lower than that in Australia (60%),<sup>29</sup> but it is similar to a Norwegian study<sup>30</sup> and much higher compared with a large US survey (22.3%).<sup>31</sup> Nevertheless, the majority of pregnant or lactating women (and possibly their doctors) in the Australian study were unaware of the importance of adequate iodine intake, the consequences of iodine deficiency and the ways to prevent it.<sup>29</sup>

Only iodine supplementation, mainly of 150 µg per day, and salt intake, but not milk or saltwater fish consumption, led to a significant increase in the median UIC. In a study of Bostonian nonpregnant volunteers, UIC was significantly associated with saltwater fish and yogurt intake, but not with iodine supplements, milk, cheese and eggs.<sup>32</sup> This difference may be because of the predominant importance of iodized salt for the iodine supply in Austria, and possible local fortifications or differences in consumption of yogurt and milk, or simply owing to the small sample size. Similar to earlier iodine supplementation studies from Denmark<sup>33</sup> and Germany,<sup>34</sup> even in women substituting iodine the median UIC was below the WHO-recommended range. In the Norwegian study, milk appeared to be the main dietary source of iodine, contributing 64% of the iodine in women who did not supplement iodine, whereas seafood only contributed 15%.<sup>30</sup> Dairy consumption, but not salt consumption, was also positively



**Figure 1.** Correlation of sodium concentration (abscissa, mg/l) and UIC (µg/l) in the 61 subjects.

correlated with UIC in US women of childbearing age,<sup>35</sup> and also in the UK, a country without salt iodization program, dairy products are the main source of iodine.<sup>36</sup>

A study in Saudi Arabia described a significantly decreased UIC in patients with type 2 diabetes mellitus compared with a healthy control group.<sup>37</sup> We therefore recruited pregnant women with and without gestational diabetes. In our study, there was no significant difference in UIC between women with and without gestational diabetes, leading to the conclusion that neither gestational diabetes mellitus nor the respective (nutritional) therapy affects iodine supply in pregnant women. The very short diabetes history of gestational diabetes may explain the lack of any influence on iodine metabolism.

We also found no difference between the second and third trimesters of pregnancy, which corresponds to the findings of several studies.<sup>38–40</sup>

Interestingly, the group of women of non-Austrian origin who had been living in Austria for 3 years or less had the highest median UIC. It was lowest in women of Austrian origin. Although the group of women of non-Austrian origin was very heterogeneous and consisted of 137 women from 37 nations (roughly corresponding to the distribution of women giving childbirth in Austria), these findings suggest that eating habits of non-Austrian women contribute to a better iodine supply than that of Austrian women, an effect that wanes after a few years. We cannot explain this difference, which might be related to a higher intake of salt (at which our data on sodium excretion might hint, although 24-hour urine specimen rather than spot samples are necessary to answer that question) and of food rich in iodine (seaweed, saltwater fish and so on). After correcting for multiple testing, the correlation of sodium spot urine excretion and UIC was the only statistical test that remained highly significant.

In a similar study in Austria's neighbor country Italy, the opposite effect of migration was seen. Although the median UIC in this cohort (83 µg/l) was similar to that in our Viennese study (87 µg/l), Italians had a significantly greater median UIC (100 µg/l) than non-Italians (45 µg/l in African and 46 µg/l in Eastern European women).<sup>41</sup>

In Austria, only iodized salt is permitted to be sold to both consumers and the food industry. Noniodized salt can only be acquired at specific request.<sup>16</sup> As a major part of salt consumed in industrialized countries comes from industrially processed food,<sup>10</sup> it is impossible to deduce the total intake of salt from a food

questionnaire and to estimate how much iodine is taken up via iodized salt. Sager *et al.*<sup>42</sup> recently determined the iodine content of 40 ready-made meals commercially available in Austria and found the highest concentration in meals consisting mainly of fish (fish fingers, mean 1.78 mg/kg), followed by meals containing milk or cheese (mean 0.64 mg/kg), meals consisting of pasta or rice and meals consisting of meat (both means 0.28 mg/kg).

The initial recommendation by the WHO to fortify salt with 20–40 mg/kg iodine was based on the assumption of an average salt intake of 10 g per day.<sup>43</sup> Owing to detrimental effects of high salt consumption, the WHO recently advised that daily salt intake should not exceed 5 g (2000 mg Na/day),<sup>44</sup> and the American Heart Association even aims at a general target of 3.8 g of salt (1500 mg Na/day).<sup>45</sup> If these recommendations are followed without concomitant increases in the concentration of salt iodization, iodine sufficiency is likely to fall.

Studies have found iodine deficiency due to salt restriction predominantly in women.<sup>46,47</sup> A decline of UIC was observed in German schoolchildren between 2003 and 2010, and the impact of sodium excretion (corresponding to salt intake) on UIC decreased. This paralleled a growing reluctance of the food industry to use iodized salt in Germany, where salt iodization is voluntary at a level of 15–25 mg/kg.<sup>48</sup> If salt were iodized at a higher level, a lower salt intake would have less severe consequences. Indeed, findings from the Republic of South Africa, where salt is iodized with 35–65 mg/kg, show that UIC is independent of salt intake.<sup>49</sup>

Our data suggest that recommendations on lower salt intake might result in an even lower iodine supply in pregnant women in countries with mild iodine deficiency.<sup>44</sup> Salt iodization should be adapted to lower the salt intake and UIC in women of childbearing age. The importance of iodine must be conveyed to both women who are already pregnant or planning pregnancy and to their physicians.<sup>31</sup> Pregnant women should generally receive iodine supplements, ideally already starting when planning pregnancy.<sup>7,10–12,14,31</sup> Moreover, the commonly prescribed daily dose of 150 µg of iodine seems to be insufficient to prevent iodine deficiency, at least in Austria, in the light of declining iodine intake.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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