Patterns of Iodine Intake and Urinary Iodine Concentrations During Pregnancy and Blood Thyroid-Stimulating Hormone Concentrations in the Newborn Progeny

Amparo Marco,1 Almudena Vicente,1 Enrique Castro,1 Carmen Eva Perez,2 Olga Rodríguez,3 Maria Angeles Merchan,1 Julia Sastre, Bárbara Cánovas,1 Esther Maqueda,1 Virginia Peña,1 and José López1

Background: Appropriate maternal intake of iodine during pregnancy is essential for maternal thyroxine production and thyroid status of the fetus. It should be possible to enhance iodine intake during pregnancy by using iodine fortified salt or taking iodine supplements. In the present report we determined the status of iodine nutrition in pregnant women who were stratified on the basis of their history of taking or not taking iodized salt or iodine supplements. The study was performed in Toledo (Spain), a region in which prior studies have noted borderline iodine sufficiency. Iodine nutrition was assessed by measuring urinary iodine concentration (UIC) and neonatal thyrotropin (TSH).

Methods: UIC was measured in 525 pregnant women. They were grouped according to their history of iodine intake. Diet Group 1 patients (n = 69) did not take iodized salt or iodine supplements during pregnancy. Diet Group 2 patients (n = 75) took iodized salt but not iodine supplements during pregnancy. Diet Group 3 patients (n = 381) took iodine supplements during pregnancy. Plasma determinations included TSH, free thyroxine, thyroid peroxidase antibody, and thyroglobulin antibody. UIC was measured in a single urine sample from all the pregnant women. Neonatal TSH was measured in capillary spot blood from all the neonates as part of a screening for congenital metabolic abnormalities.

Results: The median UIC in all subjects was 164 μg/L (interquartile range [IR]: 116–245). The median UICs in Diet Groups 1, 2, and 3 were 134.5 (IR: 90–196), 146 (IR: 103–205), and 183 (IR: 124–261) μg/L, respectively (p = not significant [NS] for Diet Group 1 vs. 2; p < 0.01 for Diet Group 2 vs. 3; all other comparisons NS). The median (IR) TSH of the neonates in all Diet Groups was 1.0 (IR: 0.7–1.6) mU/mL. Only 2 neonates had blood TSH concentrations >5 mU/L. Neonatal blood TSH concentrations were similar in all Diet Groups.

Conclusions: In a region with a history of borderline iodine deficiency the UICs were below 150 μg/L in a substantial percentage of pregnant women who did not take iodine supplements, regardless of whether or not they took iodized salt. Our results support the use of iodine supplements from the start of the pregnancy, or even before pregnancy in women who live in regions with a history of even small degrees of iodine deficiency. In addition, neonate TSH screening is not the best tool to assess whether the iodine status in populations is ideal.

Introduction

IODINE DEFICIENCY (ID) is the most preventable cause of thyroid dysfunction in pregnant women worldwide, and of the related psychoneurological impairment in their progeny (1,2). An appropriate level of maternal dietary intake of iodine during pregnancy is essential for maternal thyroxine production and for normal thyroid status in the fetus. Iodine insufficiency results in inadequate production of thyroid hormones during pregnancy, which in turn is likely to cause varying degrees of irreversible brain development in the fetus (3–5). In 2007 the World Health Organization (WHO), United Nations Childrens Fund (UNICEF), and the International Council for the Control of Iodine Deficiency (ICCIDD) drew

1Endocrinology and Nutrition Service, Complejo Hospitalario de Toledo, Toledo, Spain.
2Biochemistry Service, Institute of Health Sciences, Talavera de la Reina, Spain.
3Obstetrics and Gynecology Service, Complejo Hospitalario de Toledo, Toledo, Spain.
up new consensus guidelines and recommended nutrient intake for iodine during pregnancy of 250 μg/day (6). Universal salt iodization is recommended as a strategy to eliminate ID disorders, particularly in countries and regions where the normal dietary sources are poor (7,8). Unfortunately, in many such regions iodized salt distribution has lapsed or is uneven leaving pregnant women and their fetuses at risk.

Currently in European countries, there are proposals that iodine be given to pregnant women and breast-feeding mothers by systematically administering multivitamin tablets containing iodine, to reach the recommended dietary allowance of 250 μg iodine per day (9).

The present report attempts to identify, using measurements of urinary iodine concentration (UIC), the status of iodine nutrition in pregnant women in Toledo. Toledo is a province in central Spain where iodine intake is considered to be borderline iodine sufficient. In addition, we determined the relationship between UIC and thyrotropin (TSH) concentrations in neonates residing in this area.

Methods

The subjects were a cross section of 525 pregnant women who consecutively attended the metabolic unit of Complejo Hospitalario de Toledo from January to June 2007 to have a 100 g oral glucose tolerance test to rule out gestational diabetes. All pregnant women in the area sanitaria of Toledo who were positive for a 50-g 1-hour glucose tolerance screening test (the O’Sullivan test) had been sent to the metabolic unit to rule out gestational diabetes. The diagnosis of gestational diabetes was based on National Diabetes Data Group criteria. All the women who participated in our study gave their informed consent and the study was approved by the Ethics Committee of the Hospital.

Each patient completed a questionnaire that explored dietary habits, especially with respect to consumption of iodized salt or of potassium iodide tablets or of vitamin tablets containing iodine. Participants were asked whether they received any information from health-care personnel regarding the importance of iodine intake during pregnancy or whether they had received similar information from other sources such as publicity campaigns or magazines. Women with a history of thyroid dysfunction were excluded from the study.

After participants were identified a recommendation was made to them that they take potassium iodide or multivitamin tablets containing iodine, up until the end of the pregnancy. Women who were noted to have hypothyroxinemia or hypothyroidism were started on substitution treatment with levothyroxine sodium.

Plasma concentrations of TSH, free thyroxine (FT4), thyroid peroxidase antibody (anti-TPO), and anti-thyroglobulin (anti-Tg) antibodies were measured using chemiluminescent micro particle immunoassay. UIC was determined by a modification of the method of Benotti and Benotti (10) in an isolated urine sample from each of the pregnant women. Neonatal TSH levels were measurements in heel prick capillary blood spots collected 3 days after birth. The analyses were performed in the Health Science Institute of Talavera de la Reina of Toledo. The reference ranges were 0.5–4 μU/mL for TSH, 0.8–2 ng/dL for FT4, 0–5.6 IU/mL for anti-TPO antibodies, and 0–4.1 IU/mL for anti-Tg. The cut-off point for neonate TSH, which permits detection of transient hyperthyro-

topinemia, was established as >5 mU/L. According to the WHO recommendations, a median UIC of >500 μg/L is considered indicative of excessive iodine intake, 251–500 μg/L is indicative of more-than-adequate iodine intake, 151–250 μg/L is indicative of appropriate iodine intake, 101–150 μg/L is indicative of slightly deficient iodine intake, 50–100 μg/L is indicative of moderate ID, and <50 μg/L is indicative of severe deficiency (6).

Statistical analyses

For those quantitative variables that did not follow normal distributions, as assessed by the Kolmogorov–Smirnoff test, comparisons of means were calculated with the Mann–Whitney U-test. Chi-squared test was used to compare proportions. Statistical significance was set at p < 0.05. All statistical analyses were performed with the SPSS package (version 15).

Results

The mean age ± standard deviation of the pregnant women was 32 ± 4.9 years (range 15–45 years); 70% of them were >30 years old. The mean gestational age was 26.3 ± 6 weeks. Of the study sample, 42.7% were primipara. Of the pregnant women, 15.2% had a family history of thyroid disease.

A regular intake of iodized salt was reported by 56.6% of the pregnant women. 72.4% consumed potassium iodide tablets or multivitamins, and 77.0% took any of both forms of supplements. Twenty-five percent of the women had received information from a health-service provider on the importance of iodine during pregnancy, whereas 14.3% had received this information from health-related publicity programs or from other media.

The median (interquartile range [IR]) of maternal TSH and FT4 was 1.7 (1.2–2.4) μU/mL and 0.9 (0.8–1.0) ng/dL, respectively. The proportion of women who were anti-TPO positive was 11.6% and the proportion that was anti-Tg positive was 9.9%. TSH levels above the normal range were observed in 4.8% of the study sample, and 15.1% had maternal hypothyroxinemia, that is, FT4L levels <0.4 ng/dL. Of the total sample, 16.4% of the women were found to be having gestational diabetes. The median (IR) TSH of neonates was 1.0 (0.7–1.6) μU/mL (Table 1).

The median UIC was 164 μg/L (IR: 116–245). About 33.5% of subjects had UIC levels 151–250 μg/L, 24.6% had UIC levels 101–150 μg/L, 16.9% had UIC levels 50–100 μg/L, and 1.1% had UIC levels <50 μg/L. In addition, 20.3% of the sample had UIC levels between 251 and 500 μg/L and 3.4% had UIC levels >500 μg/L. Subjects not consuming iodized salt or iodine supplements constituted 13.1% of the subjects (Group 1), those consuming iodized salt but not iodine supplements constituted 13.8% of the subjects (Group 2), and those consuming iodine supplements constituted 73.1% of subjects (Group 3). There were no significant differences in the median UIC of the group that did not consume iodized salt or iodine supplements compared to the group that consumed only iodized salt (134.5 vs. 146 μg/L; p = not significant [NS]). However, the mean UIC in women who consumed iodine supplements was higher than that in women who consumed iodized salt (183 vs. 146 μg/L; p < 0.01). There were no significant differences between the three groups with respect to median maternal TSH, median maternal FT4, the presence of
The results of the present study show that the iodine intake in pregnant women of Toledo (Spain), expressed as the median UIC, is adequate overall at >150 µg/L. However, when we classify UIC according to the recommended ranges of the WHO, we observe that there is an elevated proportion of pregnant women, around 45%, in whom the iodine intake is insufficient, that is, only those women who are regular consumers of iodine supplements, in the form of potassium iodide or multi-vitamin tablets containing iodine, reach UIC ≥150 µg/L. This does not apply to those consuming iodized salt as the only source of iodine, in which case the iodine intake is insufficient.

These data are coincident with those from some European countries (14,18–20) and other regions of Spain such as Extremadura (13) in which there is a slight or moderate ID in whom a supplement of iodine is required to increase the median UIC.

In Europe there have been eight randomized clinical trials published in which iodine supplements were administered to >600 pregnant women who had slight or moderate ID, although doses and timing of iodine supplementation varied (21–28). In all these trials, the supplementation increased the UIC. However, not all of them coincided with respect to the effects on maternal TSH (29). Effects on maternal thyroid function have been mixed, with significant maternal TSH decreases with supplementation described in four of the eight published studies and increases in maternal T4 or FT4 noted in just two. In our study of the pregnant women of Toledo, we observed a significantly greater UIC in those taking iodine supplements, without any relationship with the concentrations of maternal TSH or of FT4. Conversely, Moleti et al. recently published their results in which it was shown that the consumption of iodized salt over the long-term period, even before the pregnancy (>2 years), increased the concentrations of FT4 during pregnancy. This could contribute to avoiding maternal hypothyroxinemia responsible for neurobehavioral and intellectual disorders in the progeny (1). Most recently, in

Table 2. Results in the Three Diet Groups

<table>
<thead>
<tr>
<th>Determination</th>
<th>Diet Group 1 (n = 69)</th>
<th>p</th>
<th>Diet Group 2 (n = 75)</th>
<th>p</th>
<th>Diet Group 3 (n = 381)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UIC (µg/L), median (IR)</td>
<td>134.5 (90–196)</td>
<td>NS</td>
<td>146 (103–205)</td>
<td>p &lt; 0.01</td>
<td>183 (124–261)</td>
</tr>
<tr>
<td>Maternal TSH (µU/mL), median (IR)</td>
<td>2.51 (1.3–0.9)</td>
<td>NS</td>
<td>1.67 (1.1–2.3)</td>
<td>NS</td>
<td>1.73 (1.2–2.4)</td>
</tr>
<tr>
<td>Maternal FT4 (ng/dL), median (IR)</td>
<td>0.9 (0.8–1.0)</td>
<td>NS</td>
<td>0.9 (0.8–0.9)</td>
<td>NS</td>
<td>0.9 (0.8–1.0)</td>
</tr>
<tr>
<td>TSH &gt;4 (%)</td>
<td>3.0</td>
<td>NS</td>
<td>3.0</td>
<td>NS</td>
<td>5.5</td>
</tr>
<tr>
<td>FT4 &lt;0.4 (%)</td>
<td>12.1</td>
<td>NS</td>
<td>22.7</td>
<td>NS</td>
<td>13.7</td>
</tr>
<tr>
<td>Anti-TPO (%)</td>
<td>9.1</td>
<td>NS</td>
<td>8.1</td>
<td>NS</td>
<td>12.7</td>
</tr>
<tr>
<td>Anti-Tg (%)</td>
<td>4.5</td>
<td>NS</td>
<td>7.6</td>
<td>NS</td>
<td>11.4</td>
</tr>
</tbody>
</table>

Diet Group 1 subjects did not use iodized salt or iodine supplements during pregnancy. Diet Group 2 subjects used iodized salt but not iodine supplements during pregnancy. Diet Group 3 subjects used iodine supplements during pregnancy.

NS, not significant.
Spain, Berbel et al. supplemented 92 women with 200 mcg/day starting at 4–6-week gestation, 102 women starting at 12–14-week gestation, and 131 women only after delivery. Supplementation was continued in all women until the end of lactation. At term, FT4 was higher in the two supplemented groups, whereas serum TSH values did not differ. In neurocognitive testing that was carried out, mean developmental quotients were higher in children whose mothers were supplemented starting in week 4–6 of pregnancy (27).

Apart from the determination of UIC in pregnant women, the screening of TSH in newborns can be useful in assessing the nutritional iodine status of women in the final weeks of pregnancy (26,30–33). The neonatal TSH concentration reflects the saturation of brain cell receptors with thyroid hormones, and constitutes the single best indicator of the risk of brain damage and mental retardation (34,35). Under normal conditions, the proportion of neonates with a concentration of TSH >5 mU/L in whole blood (or 10 mU/L in plasma) is <3% (36).

In addition to nutritional iodine status, other factors can influence the concentrations of TSH in the neonates. Among these are the timing of the sample collection, the exposure of the mother or the neonate to antiseptics that contain iodine, the method of measuring TSH, and the role of the filter used in the method of neonate TSH measurement (33). For these reasons, the cut-off point to define the severity of the ID based on the concentrations of neonatal TSH that was proposed originally by the WHO (36) is not included in the more recent recommendations (8). In our case, despite the percentage of women with UIC <150 µg/L being high, the proportion of neonates with TSH >5 mU/L was very low. Further, the TSH levels of the newborns were not correlated with the UIC. This was probably due to the collection of the samples from the pregnant women. For example, it was recommended to all the women that iodine needs to be taken as supplements containing iodine; hence, at the time of parturition the nutritional iodine status had improved in all women compared to the original status. These results support those published by Zimmermann, who, in a prospective study in Switzerland over 5 years (1999 to 2004), demonstrated that an increase in the intake of iodine in women increased the UIC, and that this improvement was reflected in the frequency of neonates with TSH >5 mU/L. The percentage of neonates above this cut-off was 2.9% in the years 1992–1998 and 1.7% between the years 1999–2004 (37). Conversely, data published recently by Rajatanavin in Thailand showed that the concentration of TSH in whole blood collected on filter paper from 1182 neonates in 2002–2003 did not correlate with the UIC of the pregnant women, but did correlate significantly with the TSH in serum from neonates (38).

In conclusion, we consider that pregnant and lactating women as well as the neonates are groups of the general population that are most sensitive to the effects of ID. This is due to the impact of maternal, fetal, and neonatal hypothyroxinemia on brain development. As such, we consider that apart from universal iodization of salt, the use of supplements of iodine as vitamin complexes or as potassium iodide tablets are necessary from the start of gestation, or earlier in the case of planned pregnancy, even where iodine intake appears adequate, like in Toledo, because not everybody consumes iodized salt and there is an elevated proportion of pregnant women in whom the iodine intake is insufficient.

Neonatal screening using the blood concentration of TSH is not the best tool to determine if the iodine status of populations is ideal.

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Disclosure Statement

The authors declare that there are no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported.

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Address correspondence to:
Amparo Marco, M.D.
Servicio de Endocrinología
Servicio de Endocrinología y Nutrición del Complejo Hospitalario de Toledo
Complejo Hospitalario de Toledo
Avda Barber n° 30
45004 Toledo
Spain

E-mail: amparo.marco@terra.es