Clinical studies

Urinary iodine and thyroid function in a population of healthy pregnant women in the North of Spain

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Background: Iodine is an essential trace element for the synthesis of thyroid hormones, which are key in maternal metabolism during pregnancy as well as in neurological development during fetal and postnatal life. This was a prospective study on iodine status and thyroid function in women during pregnancy in the Basque country to assess whether there was any relationship among maternal urinary iodine, maternal thyroid function and thyrotropin (TSH) in newborns, and to explore any difference in women experiencing miscarriages.

Methods: We analyzed TSH, free T4 (FT4), free T3 (FT3), thyroid peroxidase antibody (TPO-Ab) titers in serum and urinary iodine concentrations (UIC) in 2104 women in the first trimester of pregnancy and in 1322 of them in their second trimester. We obtained neonatal TSH levels in 1868 cases.

Results: In the first (T1) and second trimesters (T2), the median UICs were 88.5 μg/L and 140 μg/L, respectively. No relationship was found between UIC and FT4 or maternal and neonatal TSH. In T1 and T2, 9.7% and 7.5% of women were TPO-Ab positive, respectively. The total miscarriage rate was 10%. The percentage of miscarriages in healthy women was 8.9%, lower than in women with overt hypothyroidism (21.2%; p < 0.001) and than in women with subclinical hypothyroidism (15.6%; p < 0.025). The miscarriage rate was not higher in TPO-Ab-positive women.

Conclusions: In this study most women had iodine deficiency during pregnancy. Neonatal TSH is not correlated with maternal UIC during pregnancy. Pregnant women with hypothyroidism have a higher rate of miscarriages.

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Introduction

Iodine is an essential trace element for the synthesis of thyroid hormones, which have a fundamental role in maternal metabolism during pregnancy as well as in the neurological development of the fetus and the newborn [1–3]. Pregnant women have physiological modifications in the regulation of thyroid function. Changes in the peripheral metabolism of thyroid hormones have been described, mainly, increases in thyroxine-binding globulin (TBG), in human chorionic gonadotropin (HCG) which acts on the thyrotropin (TSH) receptors, and in renal filtration which leads to a greater loss of iodine [4]. To cope with these changes and the stress of pregnancy, women must have optimal thyroid function and an adequate iodine intake.

Even within the same country, iodine intake may vary among the population by age, season, geographical location and eating habits. For these reasons, iodine deficiency may be underestimated or hidden [5–7]. In an epidemiological setting, the indicators that have historically been considered to assess the iodine status are: thyroid gland volume, urinary iodine, serum thyroglobulin, and neonatal TSH levels. On the other hand, newborn TSH level solely is not included among the indicators in the latest recommendations of the World Health Organization (WHO), the United Nations Children’s Fund (UNICEF), and the International Council for Iodine Deficiency Disorders (ICIDD) [8].

For pregnant women, WHO, UNICEF, and ICCIDD consider that a urinary iodine concentration (UIC) > 150 μg/L [8] reflects adequate intake of this trace element. Iodine deficiency during pregnancy may cause a wide range of iodine deficiency disorders in both...
the mother and the child [7,9]. In geographical areas with chronic severe iodine deficiency, women may have low blood levels of thyroxin hormones from the beginning of pregnancy with potential effects on the neurological and intellectual development of their offspring. On the other hand, in areas with mild or moderate iodine deficiency it is not clear whether children will suffer from cognitive impairment, hence more long-term studies are required [7].

The objective of this study was to assess prospectively iodine status and maternal thyroid function throughout pregnancy in a sample of pregnant women in the Basque Country (North of Spain). The secondary objectives were:

1. To assess the relationships between UIC, maternal thyroid function and TSH at birth in the newborns.
2. To assess whether there were any differences in the subset of women who had miscarriages.

Population and methods

We conducted a prospective observational study of UIC and thyroid function in pregnant women attending obstetric outpatient appointments in the catchment area of Cruces Hospital (Biscay, the Basque Country, Spain) between April 2002 and October 2004. Pregnant women received the usual obstetric monitoring and we did not intervene in the dietary measures and/or vitamin supplements prescribed. We obtained informed consent and the study was approved by the Clinical Research Ethics Committee of Cruces Hospital. We excluded women with any kind of disease (including thyroid pathology), those receiving any pharmacological agent and multiple pregnancies. At the end of the gestation a random subgroup of women (n = 539) were asked if they had received vitamin supplements containing iodine during pregnancy by indication of their obstetricians.

The sample included 2104 women in the first trimester of pregnancy and 1322 were tested again in their second trimester. Blood samples were taken during routine tests in both trimesters, and the following parameters were analyzed: TSH, free T₄ (FT₄) and free T₃ (FT₃) and anti-thyroid peroxidase antibodies (TPO-Ab). The same day of the blood test, a morning urine sample was collected for measuring UIC. Serum samples were stored at −80 °C and urine samples at −20 °C until processing, the analysis being carried out after completion of the pregnancy.

We assessed the levels of iodine in urine on the basis of UIC measured in a spot urine sample using paired-ion, reversed-phase, high-performance liquid chromatography with electrochemical detection at silver working electrodes [10] (Waters Chromatography, Milford, MA). UIC was expressed in micrograms of iodine per 1000 ml of urine (µg/L).

We determined serum FT₃, FT₄ and TSH levels by chemiluminescence with an automated immunoassay system (IMMULITE 2000, Siemens-Healthcare Diagnostic, Los Angeles, CA). TSH levels were measured using a third generation, solid-phase, two-site immunometric assay, with a reference range of 0.4–4.5 mIU/L (IMMULITE 2000 Third Generation TSH, Siemens-Healthcare Diagnostic). FT₄ and FT₃ were measured using solid-phase competitive analog chemiluminescence immunoassays, with reference ranges of 10.3–24.5 pmol/L and 2.8–6.5 pmol/L, respectively (IMMULITE 2000 Free T₄ and IMMULITE 2000 Free T₃, Siemens-Healthcare Diagnostic). Lastly, TPO-Ab titers were conducted using a solid-phase enzyme-labeled chemiluminescent sequential immunoassay with 35 IU/ml cut-off for normal (IMMULITE 2000 Anti-TPO Ab, Siemens-Healthcare Diagnostic).

The iodine status of the women was classified according to the WHO/UNICEF/ICCIDD guidelines [8]. Specifically, iodine intake was defined as insufficient for UICs < 150 µg/L; adequate for UICs of 150–249 µg/L; above the requirements for UICs of 250–499 µg/L; and excessive for UICs ≥ 500 µg/L.

We used the criteria proposed by the American Thyroid Association [11] to define overt and subclinical hypothyroidism in pregnant women. We considered the participants to have: overt hypothyroidism when TSH levels were above 10 mU/L or 2.5–10 mU/L with FT₄ below the fifth percentile; and subclinical hypothyroidism when TSH levels were 2.5–10 mU/L with normal FT₄ levels. Hyperthyroidism was diagnosed if TSH was < 0.1 mU/L with an FT₄ level > 25.7 pmol/L.

We used neonatal TSH screening for detecting iodine deficiency as it is one of the methods previously proposed by WHO/UNICEF/ICCIDD [12]. They suggest that the level of deficiency in a population could be characterized as a function of frequency of neonatal TSH concentrations >5 mU/L: mild deficiency for frequencies of 3–19.9%; moderate deficiency for 20–39.9% and severe deficiency for ≥40%. We evaluated the TSH results of 1868 live newborns of the women participating in this study, through the local screening program for congenital metabolic disorders. Total blood samples were obtained from newborns between the 2nd and 3rd day after birth by lancet puncture of the heel, spotted on filter paper and delivered to the reference laboratory (Normative Public Health Laboratory of Bilbao, Basque Country). Blood TSH was measured by a solid-phase, time-resolved sandwich fluorimunoassay (AutoDELFIA, PerkinElmer Life and Analytical Sciences, Wallac Oy, Turku, Finland) using a lanthanide metal (europium) label.

Statistical analysis was performed using the Statistical Package for Social Sciences SPSS® (version 18 for Windows; Chicago, IL). Quantitative variables that followed a normal distribution were analyzed using the Student’s t-tests, while non-parametric Wilcoxon test and Spearman correlation coefficients were used for non-normally distributed quantitative variables. Qualitative variables were analyzed using the McNemar tests, χ² or Fisher exact tests. We selected a level of significance of p < 0.05.

Results

Results were obtained from 2104 women in the first trimester of pregnancy and from 1322 of them, in the second one. Their mean age at delivery was 32.6 ± 4.2 years. We did not find statistically significant differences between women who completed the study and those who did not, with regards to TSH, FT₄, or FT₃ levels, UIC or age.

Maternal urinary iodine: Table 1 lists the results of urinary iodine. In the first trimester of pregnancy, the median UIC was 88.5 µg/L (range: 16–875 µg/L). Of all the women, 79.8% had concentrations below what it is considered adequate and 5.7% had concentrations above the normal range. In the second trimester, the median UIC was 140 µg/L (range: 21–880 µg/L), with 54.4% of the women continuing to have UICs below 150 µg/L, while 18.8% had

<table>
<thead>
<tr>
<th>Range (µg/L)</th>
<th>1st trimester</th>
<th>2nd trimester</th>
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<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>1224 (58.2)</td>
<td>428 (32.4)</td>
</tr>
<tr>
<td>100–149</td>
<td>455 (21.6)</td>
<td>291 (22.2)</td>
</tr>
<tr>
<td>150–249</td>
<td>304 (14.4)</td>
<td>354 (26.8)</td>
</tr>
<tr>
<td>250–499</td>
<td>105 (5)</td>
<td>214 (16.2)</td>
</tr>
<tr>
<td>≥500</td>
<td>16 (0.7)</td>
<td>35 (2.6)</td>
</tr>
<tr>
<td>Total</td>
<td>2104</td>
<td>1322</td>
</tr>
</tbody>
</table>

UIC: urinary iodine concentration.

Range (µg/L): Range of urinary iodine concentration.

Table 1: Distribution of UIC in pregnant women during the first and second trimesters of pregnancy.
values of UIC were not significantly different in women with subclinical or overt hypothyroidism compared with healthy women (110.3 ± 91.7 and 107.1 ± 73.4 vs. 111.4 ± 84.8), but were lower in women with hyperthyroidism (71.8 ± 29.6 μg/L vs. 111.4 ± 84.8 μg/L; p = 0.014).

Neonatal TSH: Neonatal TSH measurements were not correlated with maternal UIC in any of the trimesters analyzed. The prevalence of newborn TSH levels >5 mU/L was 2.9%. We did not find any significant differences between their mother and the rest of the group in the variables studied (thyroid function and UIC).

Miscarriages: In the total sample, there were 210 miscarriages (10%). In healthy women the percentage of miscarriages was 8.9%, while in women with overt hypothyroidism it was 21.2% and in women with subclinical hypothyroidism 15.6% ([p < 0.001] and [p = 0.025]). There was not, however, a higher rate of miscarriages in women with hyperthyroidism or those who were TPO-Ab positive.

Discussion

We found a generalized iodine deficiency in the sample of pregnant women studied. In both trimesters, the median UIC was below the recommended levels for considering pregnant women to have an adequate intake of iodine [8]. Comparing this finding to what has been reported for other geographical areas across Spain, our levels of iodine deficiency status can be considered intermediate [13–16]. When we followed UIC through pregnancy, we observed a significant increase in the second trimester. It is well known that the physiological levels of urinary iodine during pregnancy tend to decrease as the demands of mother and fetus increase, in areas with mild and moderate iodine deficiency [17,18]. In our study, the observed increase in UIC in the second trimester may be explained by the practice, of the obstetricians to prescribe vitamin supplements with iodine (100–150 µg/day) during pregnancy because most of the women had received it.

In our study, we observed a decrease in TSH and increase in FT4 levels during the first trimester of pregnancy, consistent with physiological changes secondary to HCG stimulus [13,19,20]. We did not find any correlation between UIC and TSH or FT4, as reported by most authors [21–25]. This lack of correlation could be attributed to pregnancy changes and to the previous amount of iodine storage in the thyroid gland in a population who do not have persistent iodine deficiency, so the thyroid hormone synthesis would be guaranteed [19,20,26]. Other researchers [27,28], have described a positive correlation between UIC and FT4 levels in pregnant women who belong to populations with moderate iodine deficiency and suggested that the fetal neurological development may be compromised by maternal hypothyroxinemia [28]. A recent paper has shown the results of a randomized intervention study using levothyroxine treatment in pregnant women with hypothyroidism or hyperthyrotropinemia, they have not found any improvement in cognitive function of offspring at 3 years of age [29]. We think that there should be more long-term studies to assess the potential impact of iodine deficiency and maternal

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Comparison of urine and blood parameters in the first and second trimesters (n = 1322).</th>
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<tbody>
<tr>
<td></td>
<td>1st trimester</td>
</tr>
<tr>
<td>----------</td>
<td>--------------</td>
</tr>
<tr>
<td>UIC (μg/L)</td>
<td>108.9 ± 88.1</td>
</tr>
<tr>
<td>TSH (mU/L)</td>
<td>1.78 ± 8.9</td>
</tr>
<tr>
<td>FT4 (pmol/L)</td>
<td>17.26 ± 3.1</td>
</tr>
<tr>
<td>FT3 (pmol/L)</td>
<td>6 ± 1.3</td>
</tr>
<tr>
<td>TPO-Ab (+) (%)</td>
<td>9.7</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD or proportion. UIC: urinary iodine concentration. Note to convert pmol/L to ng/dL: FT4 divide by 12.87; to convert pmol/L to pg/ml: FT3 divide by 1.536.

* McNemar test. 

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Relationship between UIC and thyroid function in TPO-Ab-negative women.</th>
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<tbody>
<tr>
<td></td>
<td>1st trimester</td>
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<tr>
<td>----------</td>
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</tr>
<tr>
<td>FT3</td>
<td>0.103</td>
</tr>
<tr>
<td>TSH</td>
<td>−0.284</td>
</tr>
<tr>
<td>UIC</td>
<td>0.001</td>
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<td></td>
<td>0.009</td>
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Spearman “r” correlation coefficient; statistical significance. UIC: urinary iodine concentration. 

* p < 0.01.

concentrations above the recommended levels. Comparing women for which we had data for both trimesters, we observed a significant increase in UIC in the second trimester (108 ± 88.1 μg/L vs. 171 ± 121.9 μg/L; p < 0.001). In the random subgroup of 539 women, 80% had received iodine supplements prescribed by their obstetricians after the first analysis (blood and urine samples) had been collected.

Maternal thyroid function: Among the women with measurements in both trimesters, TSH and FT3 levels increased in the second trimester, while FT4 levels and the rate of positive TPO-Ab titers decreased, as can be seen in Table 2. When we assessed the relationship between UIC and thyroid function in TPO-Ab-negative women, we found a weak correlation between UIC and FT3 levels in the first trimester and between UIC, FT3 and TSH levels in the second trimester, as shown in Table 3.

We analyzed the TPO-Ab-positive subgroup; these were 9.7% of the women in the first and 7.5% of those in the second trimester. As reported in Table 4, this subgroup had higher TSH levels in both trimesters, although no differences were found with regards to UIC.

When we assessed thyroid function of pregnant women in the first trimester, we found that 13.7%, 1.6% and 1% of women had subclinical hypothyroidism, overt hypothyroidism and hyperthyroidism, respectively. In these subgroups, the mean FT4 levels were 16.61 ± 1.9, 11.84 ± 1.8 and 32.36 ± 7.4 pmol/L, respectively, compared to 17.29 ± 2.5 pmol/L in healthy women (p < 0.001). The

hypoxyrogenemia on the neurological and intellectual development of school children in areas with mild or moderate iodine deficiency. In line with this, we are now testing the offspring (currently 7–8 years old) of the women who participated in this study. The prevalence of pregnant women with thyroid autoimmunity during pregnancy was similar to data published on other women of child-bearing age [13,30]. This prevalence decreases throughout pregnancy, and this may be related to the attenuation of the general immune response [31].

The rate of women with overt hypothyroidism, not diagnosed previously in this population of women, was intermediate compared to other series reported in the literature [11,32,33]. The broad range of prevalence published to date may be explained by the diverse methods used as well as differences in the cut-off points applied to define hypothyroidism and subclinical hypothyroidism. If we included the women with subclinical hypothyroidism the prevalence increases to 15.3%, but we do not consider it appropriate to combine the groups.

When we use TSH of the newborn >5 mU/L in the neonatal screening as an indicator of iodine deficiency, we did not reach the established percentage to define a population as having iodine deficiency. These results differ from those found by directly measuring UICs in pregnant women. Further, we did not observe any relationship between neonatal TSH and UIC in any of the trimesters of the pregnancy studied, consistent with other authors [23,33–35]. For this reason, we support the current recommendations of WHO/UNICEF/ICCIDD on neonatal TSH as an indicator of iodine status [8].

Focusing on the subgroup of women who had a miscarriage, we confirm that there is an association between the levels of maternal TSH and miscarriage, as found in other studies [36,37]. Various authors have also found an association between positive TPO-Ab and an increase in the rate of miscarriages, but we did not find this in our study [11,38]. Further, considering the subgroup of pregnant women with hypothyroidism or subclinical hypothyroidism and in agreement with data in the literature [39], we found a higher rate of miscarriages in this subgroup than in pregnant women with no thyroid dysfunction.

Currently there is no consensus on the need to screen for thyroid dysfunction during pregnancy. A study group of the American Thyroid Association did not find sufficient evidence to recommend in favor or against the undertaking of this type of screening [11]. We do believe, however, that it is necessary to screen for thyroid dysfunction in pregnant women to diagnose and treat thyroid disorders, given the high percentage of miscarriages observed in pregnant women with thyroid hypofunction.

Conclusions

The majority of pregnant women in the geographical location studied had iodine deficiency during pregnancy. The UIC increase observed in the second trimester may be due to the intake of supplements containing iodine, prescribed by obstetricians. The results of thyroid function and autoimmunity were not related to UIC in these pregnant women. We confirm that the level of neonatal TSH is not associated with maternal urinary iodine or maternal thyroid function in either of the two trimester studied. Miscarriages are more common in women with overt and subclinical hypothyroidism.

Conflict of interest

No authors have competing financial interests disclosure.


