Postpartum Thyroid Dysfunction in Pregnant Thyroid Peroxidase Antibody-Positive Women Living in an Area with Mild to Moderate Iodine Deficiency: Is Iodine Supplementation Safe?

SUSANNE B. NØHR, ANNEMETTE JØRGENSEN, KLAUS M. PEDERSEN, AND PETER LAURBERG

Departments of Obstetrics and Gynecology (S.B.N., A.J.) and Endocrinology and Medicine (K.M.P., P.L.), Aalborg Hospital, DK 9000 Aalborg, Denmark

ABSTRACT

In moderately iodine-deficient, pregnant, thyroid peroxidase antibody (TPO-Ab)-positive women the role of iodine supplementation in the development of postpartum thyroid dysfunction (PPTD) was studied in a placebo-controlled, randomized, double blind trial. Screening for TPO-Ab was performed in early pregnancy in a population of healthy pregnant Danish women with no previous diagnosed thyroid disease (prevalence, 117 of 1284; 9.1%). The participants were randomized, stratified according to TPO-Ab level, to three groups. All participants received a daily vitamin and mineral tablet with 150 μg iodine or no iodine. The +/+ group received iodine during pregnancy and the postpartum period, the +/− group received iodine during pregnancy only, and the −/− group received no iodine supplementation. A total of 66 TPO-Ab positive women were followed, and in the postpartum period sera were collected at 8-week interval for biochemical evaluation of thyroid function and antibody level. Compliance was evaluated by 24-h urinary iodine measurements.

PPTD developed in 55% of the participants. In 67% of the cases abnormal TSH was accompanied by abnormalities in thyroid hormones, whereas 33% had abnormal serum TSH only. There was no statistically significant difference in the frequency of PPTD in the three groups: +/+ group, 59% (95% confidence interval, 36–79%); +/− group, 60% (36–81%); and −/− group, 46% (26–67%). There were also no differences in the severity of the PPTD, as evaluated by duration and grade of deviation of TSH and thyroid hormones from normality. The occurrence, severity, and type of PPTD predominantly depended on the TPO-Ab level: TPO-Ab below 200 U/L at screening, 35% developed PPTD; TPO-Ab of 200–900 U/L, 54%; and TPO-Ab above 900 U/L, 75% developed PPTD. Women with low levels of antibodies predominantly remained euthyroid or had hyperthyroidism only, whereas women with high antibody levels had hyperthyroidism followed by hypothyroidism or hypothyroidism only. We conclude that iodine supplementation (150 μg) during pregnancy and the postpartum period to TPO-Ab-positive women living in an area with mild to moderate iodine deficiency did not induce or worsen PPTD. The study confirmed that screening for TPO-Ab in early pregnancy can predict women at high risk for development of PPTD. (J Clin Endocrinol Metab 85: 3191–3198, 2000)

Marginally low iodine intake is found in many parts of the world, including European countries (1). In such areas pregnant and lactating women and their neonates may be at special risk of developing iodine deficiency (2–5). As sufficient iodine is important for normal brain development of the fetus as well as the newborn child, recommendation of individual iodine supplementation to pregnant and lactating women, therefore, might be considered. It is, however, important to exclude that this involves a risk for the mother or the child.

One possible side-effect of iodine is aggravation of thyroid (autoimmune) dysfunction, which has been demonstrated in experimental animals and in patients with thyroid disorders (6–8). Subclinical autoimmune thyroid disease with measurable antibodies against thyroid peroxidase (TPO-Ab) in serum is common in pregnant women, and many of these develop postpartum thyroid dysfunction (PPTD). A study performed in an iodine-sufficient population showed that iodine given to women with TPO-Ab in the postpartum period might aggravate thyroid dysfunction if they develop postpartum thyroiditis (9). In a previous intervention study we found that iodine supplementation (200 μg) given to pregnant women living in an area of moderate iodine deficiency may ameliorate some of the pregnancy-associated variations in maternal thyroid function (10). However, this study aroused suspicion that iodine supplementation could induce PPTD in women who were TPO-Ab positive (10).

The aim of the present study was to evaluate whether iodine supplementation during pregnancy and the postpartum period to TPO-Ab-positive women living in an area in Denmark with mild to moderate iodine deficiency imposes any danger of worsening PPTD.

Subjects and Methods

Study design and population (Fig. 1)

Screening for TPO-Ab in serum was performed in early pregnancy (median, 11th gestational week) in a consecutive cohort of 1284 healthy pregnant Danish women (age, 18–35 yr) referred to Aalborg Hospital for an obstetrical routine ultrasound investigation. TPO-Ab was found in 117, corresponding to a prevalence of 9.1%.

Seventy-two of the TPO-Ab-positive women agreed to participate in a placebo-controlled, randomized, double blind trial evaluating the impact of iodine supplementation during pregnancy and the postpartum period on PPTD. None had previously diagnosed thyroid disease or
clinical symptoms of thyroid dysfunction. The participants were randomized, stratified according to TPO-Ab level, to three groups. All participants received a daily vitamin and mineral tablet with 150 µg iodine or no iodine. Group +/+ (n = 22/22) (pregnancy/postpartum) received iodine during pregnancy and the postpartum period. Group +/− (n = 24/20) received iodine during pregnancy only. Group −/− (n = 26/24) received no iodine supplementation. Six women were censored from the postpartum part of the study. In four women no blood tests postpartum were available, and two women with only one test 3 months postpartum were excluded. They differed only in smoking habits (83% were smokers compared to 20% in the remaining group).

Basic characteristics of the remaining cohort (n = 66) within the three groups are shown in Table 1. There were no statistically significant differences among the groups at the start of the study. The study had a power of 90% for detecting a doubling of the frequency of PPTD.

Before inclusion, 45 (68%) of the women had taken vitamin and mineral supplements, and 34 of these had taken iodine-containing tablets, whereas 32 had no history of previous iodine supplementation (Table 1). At inclusion, all participants stopped their previous intake of supplements.

All thyroid function tests were performed after closure of the study, and the occurrence of postpartum thyroid dysfunction was not evaluated during the study period, except in one woman. She presented with symptoms of hypothyroidism and had PPTD with a biphasic course. She recovered within the study period, and substitution with thyroid hormone was not necessary. The supplement code was not broken, nor was supplement ceased.

Iodine supplement

The vitamin tablets (Livol Super) were provided by Dansk Droge A/S (Copenhagen, Denmark) and contained the recommended daily allowances of various vitamins and minerals, including 50 µg selenium. The iodine content was 150 µg (which is the traditional iodine content of such tablets in Denmark), except in the batches where iodine was omitted.

Biochemical evaluation

TPO-Ab at screening was measured by routine biochemical procedures. Women with TPO-Ab of 100 U/mL or more were considered TPO-Ab positive and met the criteria for inclusion. In the randomized study, serum for biochemical evaluation of thyroid function and antibody level was collected at inclusion, at the 35th week of gestation, and at 3, 5, 7, and 9 months postpartum. Compliance was evaluated by 24-h urinary iodine measurements at time of inclusion, during pregnancy (35th week), and during the postpartum period (7 months postpartum). Blood samples were centrifuged shortly after sampling, and serum and urine were stored at −20°C until analysis. In all assays samples from one individual were analyzed in the same assay.

Total T4 (reference range, 60–140 nmol/L) and total T3 (1.2–2.7 nmol/L) were measured by RIAs (Amerlex-M, Ortho-Clinical Diagnostics, Amersham Pharmacia Biotech, Aylesbury, UK). TSH (detection limit, 0.008 mU/L; reference range, 0.40–4.0 mU/L), thyroglobulin (Tg; detection limit, 0.2 µg/L), and free T4 (FT4; reference range, 10–25 pmol/L) were measured by immunoluminometric assays, and free T3 (FT3; reference range, 3.4–7.1 pmol/L) was measured by a luminescence immunooassay (Lumitest, Brahms Diagnostica GmbH, Berlin, Germany). At screening, TPO-Ab were measured initially by luminescence immunooassay (detection limit, 100 U/mL; Lumitest anti-TPO, Henning Berlin GmbH & Co., Berlin, Germany) and later by a radioimmunoprecipitation assay (detection limit, 5.5 U/mL; Dynotest anti-TPOAb, Brahms Diagnostica). For analyses of samples from the randomized study, the Dynotest Anti-TPO-Ab assay was used. Tg antibodies (Tg-Ab; detection limit, 5.5 U/mL) were measured by radioimmunoprecipitation assays (Dynotest anti-TgAb, Brahms Diagnostica). Although Tg-Ab may influence Tg values (11), the Tg data presented here were not adjusted for interference. In women with a hyperthyroid episode, TSH receptor autoantibodies (TRAb) were measured by RRA (detection limit, 2.4 U/L; reference range, <9 U/L; TRAK-Assay, Brahms Diagnostica).

Iodine in urine was measured in duplicate by the Ce/As method after alkaline ashing, using a modification of the method of Wilson and van Zyl (12) as previously described (13). The detection limit was 2 µg/L, and the recovery of added 127I and 125I was greater than 95% and not corrected for.

Urinary iodine excretion in the two groups (+/+ and +/− groups) that received 150 µg iodine during pregnancy was (median) 187 µg/24 h (105 µg/L; n = 41) in the 35th gestational week, whereas it was 71 µg/24 h (53 µg/L) in the −/− group. In the +/+ group that received iodine supplementation postpartum as well, it was (median) 124 µg/24 h (75 µg/L; n = 21) 7 months postpartum, whereas it was 65 µg/24 h (43 µg/L) in the women not receiving iodine (+/+ and −/− groups). The relatively low urinary iodine excretion 7 months postpartum could be due to rebuilding of thyroid hormone stores after previous loss of hormone due to thyroiditis (14, 15), or it could be explained by loss of iodine in breast milk in mothers still nursing the child. Finally, a fail in compliance of some mothers when they resumed work (usually about 5–6 month postpartum) has to be considered.

Outcome measurements

PPTD was defined as abnormal TSH in the postpartum period. It was classified as subclinical if only TSH was abnormal and clinical if also thyroid hormones were abnormal (subclinical hypothyroidism: TSH, >4.0 mU/L and normal thyroid hormones; clinical hypothyroidism:
TABLE 1. Basic characteristics of the cohort in the randomized study (n = 66)

<table>
<thead>
<tr>
<th></th>
<th>++ group (n = 22)</th>
<th>+/− group (n = 20)</th>
<th>−/− group (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>29 (26–31)</td>
<td>29 (26–31)</td>
<td>30 (27–32)</td>
</tr>
<tr>
<td>Paritya</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
<td>2 (1–2)</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>67 (63–78)</td>
<td>68 (63–73)</td>
<td>67 (60–72)</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>27</td>
<td>25</td>
<td>13</td>
</tr>
<tr>
<td>Iodine status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subgroup with no previous iodine supplementation</td>
<td>n = 9</td>
<td>n = 10</td>
<td>n = 13</td>
</tr>
<tr>
<td>µg/24 h</td>
<td>86 (66–147)</td>
<td>83 (54–145)</td>
<td>88 (68–123)</td>
</tr>
<tr>
<td>µg/L</td>
<td>50 (35–101)</td>
<td>52 (36–81)</td>
<td>51 (30–80)</td>
</tr>
<tr>
<td>Thyroid antibodies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPO-Ab at screening (U/mL)</td>
<td>441 (125–1054)</td>
<td>324 (151–1579)</td>
<td>374 (148–1254)</td>
</tr>
<tr>
<td>Tg-Ab detectable (%)</td>
<td>64</td>
<td>65</td>
<td>63</td>
</tr>
<tr>
<td>Thyroid function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH (mU/L)</td>
<td>1.45 (0.96–2.02)</td>
<td>1.45 (0.97–2.23)</td>
<td>1.42 (1.14–1.84)</td>
</tr>
<tr>
<td>TT₄ (nmol/L)</td>
<td>144 (137–168)</td>
<td>142 (121–154)</td>
<td>136 (121–152)</td>
</tr>
<tr>
<td>TT₃ (nmol/L)</td>
<td>2.53 (2.16–2.76)</td>
<td>2.33 (1.93–2.55)</td>
<td>2.27 (1.93–2.57)</td>
</tr>
<tr>
<td>FT₄ (pmol/L)</td>
<td>11.8 (10.5–13.5)</td>
<td>13.4 (11.3–14.5)</td>
<td>13.0 (10.9–14.9)</td>
</tr>
<tr>
<td>FT₃ (pmol/L)</td>
<td>5.41 (4.53–6.11)</td>
<td>4.87 (4.49–5.40)</td>
<td>5.25 (4.49–5.48)</td>
</tr>
<tr>
<td>Tg (µg/L)</td>
<td>22.5 (12.0–30.9)</td>
<td>13.4 (3.5–21.4)</td>
<td>17.1 (7.4–22.9)</td>
</tr>
</tbody>
</table>

Data are given as medians or percentage and 25–75% percentiles (in parentheses). There were no statistically significant differences between the treatment groups, although the figures show a trend toward a lower frequency of smokers in the control group (by x² test, P = 0.42).

a Parity includes the pregnancy in question.

TSH, >4.0 mU/L; and FT₄ <10 pmol/L; or TT₄ <60 nmol/L; subclinical hyperthyroidism: TSH, <0.4 and normal thyroid hormones; clinical hyperthyroidism: TSH, <0.4 mU/L; and FT₄ ≥25 pmol/L, or TT₄ ≥140 nmol/L; or FT₃ ≥2.7 pmol/L, and/or TT₃ ≥2.7 nmol/L. The severity of the PPTD was estimated by a biochemical dysfunction score, taking both duration and grade of deviation of thyroid function from normality into account. At each time of evaluation, a clinical abnormality gave a score of 1, and a clinical abnormality gave a score 2, or 3 if all measured hormones were abnormal. A biochemical hypothyroid score of 3 was given if TSH was elevated and FT₄, TT₄, FT₃, and TT₃ were below the reference ranges. Free T₃ was not used for evaluation of hypothyroidism because the FT₃ assay suffered from lack of precision in the low range of measurements. This biochemical grading taking a low T₃ into account correlated to a clinical score of hypothyroidism in a study by Zulewski et al. (16).

Results

PPTD developed in 55% of the participants. In 67% of the cases, abnormal TSH was accompanied by abnormalities in thyroid hormones (clinical PPTD), whereas 33% had abnormal serum TSH only (subclinical PPTD).

Iodine supplementation and PPTD

There was no statistically significant difference in the frequency of PPTD in the three groups (by x² test, P = 0.56): ++ group, 59% (95% confidence interval, 36–79%); +/− group, 60% (36–81%); and −/− group, 46% (26–67%), although a small trend was observed. One of the six women leaving the study had evidence of PPTD (abnormal TSH 3 months postpartum), and one had normal TSH 3 months postpartum (no further test available). Neither these data nor intention to treat analysis including all six censored women altered the outcome.

The types of PPTD in the three groups are depicted in Fig. 2. There were no differences among the groups. Neither were there any differences in the severity of the PPTD, as evaluated by the duration and grade of deviation of TSH and thyroid hormones from normality by the biochemical dysfunction score. Scores from the women in relation to treatment groups are depicted in Fig. 3a.

Thyroid antibodies and PPTD

The occurrence and severity of PPTD predominantly depended on the TPO-Ab level. The well known pattern of a decline in TPO-Ab during pregnancy and a postpartum surge was observed. There were no statistically significant differences in TPO-Ab among the treatment groups at any time of evaluation, nor were there any differences in the absolute or fractional increment in TPO-Ab (maximum levels...
The TPO-Ab values at screening correlated to the postpartum surge in TPO-Ab (Spearman's $r = 0.87; P < 0.001$). The TPO-Ab level at screening was also a good predictor of the PPTD risk, as shown in Fig. 4, and it correlated to the severity of PPTD, as evaluated by the biochemical dysfunction score (Fig. 3b).
The relationship between antibody level and the course of PPTD is further illustrated in Fig. 5, showing the variations in thyroid function, TPO and Tg autoantibodies (85% of the women had detectable Tg-Ab in the postpartum period), and serum Tg in relation to the four types of postpartum thyroid function ( euthyroidism, hypothyroidism only, hyperthyroidism only, and biphasic course). Parallel variations were observed in TPO-Ab and Tg-Ab, and the variations in antibody quantity were essentially the same in all four types, but at different levels. Antibody levels were high in women with a biphasic course of PPTD and with hypothyroidism only and were much lower in the hyperthyroidism only and euthyroid groups. The indication of a less severe abnormality in women with hyperthyroidism only was further substantiated by the variations in thyroid hormones and Tg. Only 20% had thyroid hormone abnormalities, e.g. clinical PPTD, as opposed to 75% in the hypothyroidism only group and almost 90% in women with a biphasic course. The debut and duration of deviations were similar in the hyperthyroidism only and the biphasic groups, whereas the hyperthyroidism only group manifested later, as evaluated by both TSH and Tg variations. One woman had an unusual biphasic course, with hypothyroidism (5 month postpartum) followed by hyperthyroidism. She was transiently TRAb positive during the postpartum period and had clinical hyperthyroidism at the end of the randomized study. She later reported that she had been followed by her general practitioner because of fatigue until 16 months postpartum, when thyroid hormone levels normalized and she became TRAb negative. None of the other women with a hyperthyroid episode was TRAb positive.

As the occurrence of clinical hypothyroidism was the most striking outcome in women with high TPO-Ab levels, it was tested in a multivariate analysis if other factors with possible impact on thyroid function contributed. The independent significance of the TPO-Ab level was confirmed. Smoking showed a trend, whereas supplement group, age, and parity had no significance. Surprisingly, iodine supplementation before entering the study was TRAb positive. For the development of clinical hypothyroidism. Further studies are needed to confirm this finding.

Long-term consequences

Although abnormalities in thyroid function mostly were transient and tended to normalize 9 months postpartum (Fig. 5), 14 women (21%) still had abnormal serum TSH at the end of the randomized study (9 months postpartum). Twelve had hypothyroidism (9 subclinical and 3 clinical), and 2 had hyperthyroidism (1 subclinical and 1 clinical). Follow-up 3 yr postpartum (median) of the initial cohort (n = 72) showed that four women later had a registered diagnose of thyroid disease. From the +/− group, the woman with symptoms of PPTD during the study period had transient hypothyroidism 1.5 yr later, one woman developed euthyroid goiter, and one developed permanent hyperthyroidism due to Graves’ disease (she left the study after pregnancy and therefore was excluded). From the −/− group, one woman had hypothyroidism due to toxic adenoma.

Of the remaining 68 women, 67 completed a questionnaire and had a test of thyroid function. Four women had either subclinical (n = 2) or clinical (n = 2) hypothyroidism. These 4 women were all subclinically hypothyroid at the end of the randomized study. Thus, a total of 8 women (11%) had evidence of thyroid disease at follow-up.

Iodine supplementation and thyroid function in late pregnancy

Measurements of TSH, thyroid hormones, and thyroid antibodies in week 35 of pregnancy in women receiving iodine (+/+ and +/− groups) and women not receiving iodine (−/− group) are shown in Table 2. There were no statistically significant differences when comparing absolute values at 35 weeks gestation. Iodine supplementation modified changes in TSH and Tg during pregnancy. In the group without iodine there was a small, but systematic, increase in TSH during pregnancy, whereas the TSH al-
terations during pregnancy in the group with iodine showed a more diverse pattern, with no significant difference between early and late pregnancy. The small increase in Tg during pregnancy reverted to a considerable fall after iodine supplementation. FT₄ declined during pregnancy, and iodine supplementation made no signif-

Fig. 5. The four types of postpartum thyroid function in relation to thyroid function parameters and antibody levels. Curves are medians. Note that serum TSH, TPO-Ab, and Tg-Ab levels are shown on logarithmic scales. The figures illustrate that the course of PPTD was dependent on the antibody level, but that the antibody course was essentially the same. The TPO-Ab levels (upper right panel) in the hypothyroidism only group and the biphasic group were statistically significantly different from those in the euthyroid group at all time points (P < 0.01), whereas levels in the hyperthyroid group were not.
Iodine and Postpartum Thyroiditis 3197

TABLE 2. Iodine supplementation and maternal thyroid function in late pregnancy (35th week)

<table>
<thead>
<tr>
<th>Thyroid antibodies</th>
<th>+ Iodine (n = 42)</th>
<th>− Iodine (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPO-Ab (U/mL)</td>
<td>161 (16–276)</td>
<td>106 (38–304)</td>
</tr>
<tr>
<td>Tg-Ab detectable (%)</td>
<td>41</td>
<td>54</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thyroid function</th>
<th>+ Iodine (n = 42)</th>
<th>− Iodine (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (mU/L)</td>
<td>1.60 (1.09–2.07)</td>
<td>1.56 (1.21–2.30)</td>
</tr>
<tr>
<td>TT3 (nmol/L)</td>
<td>143 (126–159)</td>
<td>138 (128–149)</td>
</tr>
<tr>
<td>TT4 (nmol/L)</td>
<td>2.50 (2.27–2.93)</td>
<td>2.48 (2.29–2.74)</td>
</tr>
<tr>
<td>FT3 (pmol/L)</td>
<td>11.2 (9.4–12.4)</td>
<td>10.4 (9.3–12.8)</td>
</tr>
<tr>
<td>FT4 (pmol/L)</td>
<td>4.90 (4.32–5.44)</td>
<td>5.30 (4.48–5.57)</td>
</tr>
<tr>
<td>Tg (μg/L)</td>
<td>14.1 (5.0–21.5)</td>
<td>19.4 (8.2–33.5)</td>
</tr>
</tbody>
</table>

Data are given as medians or percentages and 25–75% percentiles (in parentheses). There were no statistically significant differences between absolute values at the 35th week. In the − Iodine group, TSH was significantly higher compared to early pregnancy values [median difference (25–75% percentiles) week 35-inclusion, 0.35 (0.05–0.78) mU/L; P < 0.01] with no significant increase in TSH in the + Iodine group (0.06 (−0.35–0.38) mU/L; P = 0.78 by Wilcoxon signed rank test). The early-late pregnancy difference in TSH was significantly different between groups (P = 0.04). FT4 was significantly lower compared to early values in both groups (P < 0.001), with no difference between groups. In the + Iodine group, FT3 was lower in late than in early pregnancy (P = 0.002), but with no significant difference between groups. Tg was significantly lower (P = 0.003) in the + Iodine group compared to early pregnancy, whereas Tg tended to increase in the − Iodine group (P = 0.06); difference between groups (P = 0.001). TPO-Ab and Tg-Ab decreased in both groups (P < 0.001), with no difference between groups.

Discussion

Iodine requirements are increased during pregnancy and the postpartum period, and consequently, the recommended iodine intake is higher (17). A possible unintended effect of increasing the iodine intake in pregnant and lactating women with mild to moderate iodine deficiency is an increase in postpartum autoimmune thyroid dysfunction.

However, in the current study we found no significant increase in the prevalence, severity, or duration of PPTD when 150 μg iodine were given to TPO-Ab-positive women during pregnancy only or during pregnancy and the postpartum period. Iodine supplementation induced minor late pregnancy differences in thyroid function similar to those found in previous studies of pregnant women in areas of mild to moderate iodine deficiency (10, 18). These variations probably had little clinical significance.

Two randomized studies have previously focused on iodine supplementation and its impact on the prevalence and severity of PPTD (9, 19). Jansson et al. hypothesized, based on their observation of low iodine excretion during the hypothyroid phase of PPTD (14), that iodine deficiency might worsen this phase of PPTD. In a subsequent study performed in Sweden, an iodine-sufficient area, they randomized 58 TPO-positive women to receive no supplement, 0.1 mg l-T4, or 150 μg iodine/day during the postpartum period (9). Contrary to their hypothesis, they found an aggravation of the hypothyroid phase of PPTD in the iodine group. The frequency of PPTD was not different from those in the control and l-T4 groups. They recommended that iodine should not be given during the postpartum period.

Reinhard and colleagues addressed the efficacy and safety of iodine given during the postpartum period in an area of mild iodine deficiency (Germany) (19). They randomized 70 women with no previous thyroid disease and no iodine supplementation during pregnancy to receive either 50 or 250 μg iodine/day in the postpartum period (8 months). The study did not include a control group. Thyroid dysfunction developed in 6 women in the group receiving 50 μg iodine and in 5 women in the group receiving 250 μg. Seven had subclinical and 4 had manifest thyroid dysfunction, and 8 of these were either TPO-Ab or Tg-Ab positive. They concluded, on the basis of a prevalence of manifest thyroid dysfunction of 5.7% (4 of 70), that iodine supplementation, up to 250 μg/day, in the postpartum period was safe.

The present study supports that iodine supplementation during pregnancy and postpartum is safe, even in women with circulating TPO-Ab. We did not confirm that women given iodine supplementation during the postpartum period had a more severe hypothyroid phase of PPTD, as found by Kämpe et al. (9). On the contrary, we found that the hypothyroid phase tended to be less severe in women receiving iodine postpartum [significantly higher T4 (P = 0.03) and lower TSH (P = 0.04) in the +/+ group compared to the −/− group, with no significant difference in free T4]. As our study environment is more iodine deficient, the difference in findings could be a matter of substrate availability for hormone synthesis during the period of thyroid regeneration. Several studies have demonstrated high urinary losses of iodine during the previous phase of thyroiditis (14, 15).

The prevalence of TPO-Ab-positive women in early pregnancy (9.1%) and the overall prevalence of PPTD (55%) in TPO-positive women found in the current study are in accordance with general accepted findings (20–22). In Denmark, Lervang et al. (23) and Rasmussen et al. (24) previously reported population-based prevalences of PPTD of 3.9 and 3.3, respectively. In general, the prevalence seems to be slightly lower in areas with mild iodine deficiency, such as Denmark (23, 24), than in iodine-sufficient areas, such as the U.S., Canada, Japan, and Sweden (25–28). However, the influence of dietary iodine intake on the prevalence of PPTD is not clear, and there are considerable differences in selections of study populations and follow-up (22).

The association between TPO-Ab level and the frequency and severity of PPTD found in this study is evident from other studies as well (25, 29, 30). In women with hyperthyroidism only antibody levels were the same as those in euthyroid women, and thyroid dysfunction was mild. Lervang et al. (23) and subsequently other researchers (31–33) reported lower TPO-Ab levels or lower frequency of individuals with detectable TPO-Ab when only a hyperthyroid phase was present. Kuijpers et al. suggested that PPTD in some women with hyperthyroidism only had a different nonautoimmune pathogenesis (33). Our data support that hyperthyroidism only and biphasic PPTD are different degrees of the same abnormality, with low levels of autoimmunity and partial thyroid destruction in the hyperthyroidism only group and more severe affection in the biphasic group, with hyperthyroidism followed by hypothyroidism.

Although symptoms of PPTD may be modest, this is a group of women with increased risk of more permanent
thyroid disease, especially hypothyroidism (34), as also evident from the present study. Furthermore, maternal TPO-Ab during pregnancy is associated with postpartum depressive symptoms and impaired child development (31, 35–37), and new data suggest that low FT4 in the mother in the first trimester of pregnancy is associated with impaired psychomotor development in infancy (38) and a lower IQ in the child when evaluated at school age (39). As a consequence, implementation of routine screening for TPO-Ab in early pregnancy is a topical issue and a matter of current international discussion (20, 40–42).

In conclusion, iodine supplementation (150 μg) during pregnancy and the postpartum period to TPO-Ab-positive women living in an area with mild to moderate iodine deficiency did not induce or worsen PPTD. This study supports that screening for TPO-Ab in early pregnancy can predict women at high risk of developing PPTD, but further studies, including cost-benefit analyses, are needed before consensus about this issue can be made.

Acknowledgments

We are grateful to Danske Drolge for providing the vitamin tablets, and to Brahms Diagnostica for providing reagents for biochemical measurement. We are indebted to Anni Nielsen, Marianne Køthler, and Thea Krag for expert technical assistance, and to the staff at the Department of Clinical Chemistry, Aalborg Hospital, for most helpful assistance during the analyses of thyroid hormones. The staff at the Department of Obstetrical Ultrasound is thanked for their assistance with recruiting the TPO-Ab-positive pregnant women.

References