Levothyroxine Treatment in Euthyroid Pregnant Women with Autoimmune Thyroid Disease: Effects on Obstetrical Complications

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Context: Euthyroid women with autoimmune thyroid disease show impairment of thyroid function during gestation and seem to suffer from a higher rate of obstetrical complications.

Objective: We sought to determine whether these women suffer from a higher rate of obstetrical complications and whether levothyroxine (LT₄) treatment exerts beneficial effects.

Design: This was a prospective study.

Setting: The study was conducted in the Department of Obstetrics and Gynecology.

Patients: A total of 984 pregnant women were studied from November 2002 to October 2004; 11.7% were thyroid peroxidase antibody positive (TPOAb⁺).

Intervention: TPOAb⁺ patients were divided into two groups: group A (n = 57) was treated with LT₄, and group B (n = 58) was not treated. The 869 TPOAb⁺ patients (group C) served as a normal population control group.

Main Outcome Measures: Rates of obstetrical complications in treated and untreated groups were measured.

Results: At baseline, TPOAb⁺ had higher TSH compared with TPOAb⁻; TSH remained higher in group B compared with groups A and C throughout gestation. Free T₄ values were lower in group B than groups A and C after 30 wk and after parturition. Groups A and C showed a similar miscarriage rate (3.5 and 2.4%, respectively), which was lower than group B (13.8%) (P < 0.05; relative risk [RR], 1.72; 95% confidence interval [CI], 1.13–2.52; and P < 0.01; RR = 4.95; 95% CI = 2.59–9.48, respectively). Group B displayed a 22.4% rate of premature deliveries, which was higher than group A (7%) (P < 0.05; RR = 1.66; 95% CI = 1.18–2.34) and group C (8.2%) (P < 0.01; RR = 12.18; 95% CI = 7.93–18.7).

Conclusions: Euthyroid pregnant women who are positive for TPOAb develop impaired thyroid function, which is associated with an increased risk of miscarriage and premature deliveries. Substitutive treatment with LT₄ is able to lower the chance of miscarriage and premature delivery. (J Clin Endocrinol Metab 91: 2587–2591, 2006)

Another matter of concern is the relationship between thyroid function and obstetrical complications. Several studies confirmed that not only is overt hypothyroidism associated with maternal and fetal adverse consequences, but also subclinical hypothyroidism or euthyroidism in patients affected by TAI may adversely affect the mother or fetus (4–8). Additionally, unfavorable obstetric events appear to be more frequent when hypothyroidism is diagnosed too late and/or when the levothyroxine (LT₄) replacement is not adequate to ensure euthyroidism during pregnancy (7). The dual aims of the present study are to assess whether euthyroid women positive for thyroid peroxidase antibodies (TPOAb⁺) are affected by a higher rate of obstetrical complications and to explore the hypothesis that LT₄ treatment may improve the outcome of affected patients.

Subjects and Methods

A total of 1074 Caucasian pregnant women who attended the Department of Obstetrics and Gynecology were screened for TPOAb. Levels of TSH and free T₄ (FT₄) were also determined. The study was carried out from November 2002 to October 2004. Forty-five of 1074 (4.2%) women were excluded for overt hypo- or hyperthyroidism or for preexisting thyroid dysfunction. A total of 1029 women participated in the study, and 984

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Abbreviations: CI, Confidence interval; FT₄, free T₄; LT₄, levothyroxine; RR, relative risk; TAI, thyroid autoimmunity; TPOAb, thyroid peroxidase antibodies.

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completed it. TPOAb titers were checked and thyroid function tests were performed at the first gynecological visit, at 20 and 30 wk gestation, and 3 d after delivery. One hundred fifteen of 984 (11.7%) subjects were TPOAb+. The 115 TPOAb+ women were divided into two groups, an intervention group (group A, n = 57) treated with LT4 and another group (group B, n = 58) without treatment. The TPOAb+ women (group C, n = 869) served as a normal control group. In group A, the patients treated with LT4 received a dose of 0.5 μg/kg/d if they had TSH less than 1.0 mIU/liter, 0.75 μg/kg/d for TSH between 1.0 and 2.0 mIU/liter, and 1 μg/kg/d for TSH higher than 2.0 mIU/liter or a TPOAb titer exceeding 1500 kIU/liter. These dosages were maintained throughout gestation.

LT4 administration was started on the first endocrinological visit, which occurred 3–7 d after the first gynecological visit. A computer program was used to randomly assign the TPOAb+ patients to either group A or group B. A sealed opaque envelope was assigned to each patient; only the doctor treating the patient, who did not participate in any subsequent phase of the study, knew which group the patient was in. Medical doctors participated in different phases of the protocol, so that each was unaware of which group the patients belonged to. If hyperthyroidism was observed, the patient was excluded from the study protocol.

Obstetrical complications were classified as follows. Gestational hypertension was defined as an intrapartum systolic blood pressure of at least 140 mm Hg or a diastolic blood pressure of at least 90 mm Hg. Severe preeclampsia was diagnosed in women with hypertension who had at least one of the following: blood pressure higher than 160/110 mm Hg, serum creatinine greater than 1.0 mg/dl, a platelet count less than 100,000/μl, serum aspartate aminotransferase level at least twice the normal value, persistent headache or scotomata, 2+ or greater proteinuria, or more than 2 g protein excreted in 24 h. A birth before 37 wk gestation was considered to be a preterm birth.

Serum TSH and FT4 were measured using a third-generation electrochemiluminescence immunoassay (Roche, Basel, Switzerland). The reference values were 0.27–4.2 mIU/liter for TSH and 0.3–18.0 ng/liter (12–33.5 pmol/liter) for FT4. Intra- and interassay coefficients of variation were 2.4 and 9.5% for TSH and 4.7 and 6.9% for FT4. TPOAb titers were determined using a RIA kit (Brahms DIAGNOSTICA, Berlin, Germany). The reference range was 0–100 kIU/liter. TPOAb titers of more than 100 kIU/liter were considered positive.

Statistical analysis was performed using an SPSS (SPSS Inc., Chicago, IL) program, by means of Fisher’s exact test. Correlations between variables were assessed using Spearman’s test, and differences between mean values were determined by the Mann-Whitney U test. A multivariate approach was used, starting with a univariate model for each individual variable. Mean TSH values were calculated after log transformation. All statistical tests were considered statistically significant whenever P < 0.05.

This study was conducted in accordance with guidelines in the Declaration of Helsinki. The Institutional Review Board approved the study protocol, and all the participants gave a written informed consent.

Results

The age range was 17–38 yr, with a Gaussian distribution (mean ± SD, 29 ± 5 yr). The average age of group C was significantly lower than groups A and B taken together: 28 ± 5 vs. 30 ± 6; P < 0.05. The first endocrinological visit took place at gestational wk 10.4 ± 3.1 in group A, at wk 10.3 ± 3.1 in group B, and at wk 10.4 ± 3.3 in group C (mean ± SD) (Table 1). Ninety-two percent of the women consulted the endocrinologist before the 20th wk of gestation (Fig. 1, top).

![Fig. 1. Gestational time of the first endocrinological visit for all patients participating in the study (top) and for group A (TPOAb+ treated with LT4) (bottom).](image)

The LT4 administered in group A was 49.7 ± 14 μg/d; eight patients received 0.5 μg/kg/d (30.6 ± 4.9 μg/d), 35 received 0.75 μg/kg/d (47.7 ± 6.0 μg/d), and 14 received 1 μg/kg/d (64.7 ± 8.7 μg/d). When the LT4 treatment was started, the gestational ages were similar in the three subgroups submitted to the three different dosages (9.6 ± 5, 10.1 ± 3.7, and 10.9 ± 3.8 wk, respectively). In group A, 23 of 45 patients (40%) started LT4 treatment by the 8th week and 45 (79%) by the 12th week (Fig. 1, bottom).

Thyroid function tests

Whether they had extremely or moderately elevated TPOAb titers, women in groups A and B showed a 62% decrease in TPOAb titers at delivery compared with the initial values.

Initially, the mean TSH values were significantly higher in groups A and B compared with group C (1.6 ± 0.5 and 1.7 ± 0.4, respectively, vs. 1.1 ± 0.4 mIU/liter; P < 0.05 and P < 0.05, respectively). In group A, TSH baseline values were significantly different between the three subgroups given 0.5, 0.75, and 1.0 μg/kg/d dosages of LT4 (0.7 ± 0.2, 1.4 ± 0.3, and

### TABLE 1. Characteristics of patients at 10, 20, and 30 wk gestation and delivery (D)

<table>
<thead>
<tr>
<th>TSH (mIU/liter)</th>
<th>FT4 (ng/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n Age (yr)</td>
<td>10 wk</td>
</tr>
<tr>
<td>TPOAb+ LT4</td>
<td>57</td>
</tr>
<tr>
<td>TPOAb+</td>
<td>58</td>
</tr>
<tr>
<td>TPOAb</td>
<td>869</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD.
2.6 ± 0.7 mU/liter; P < 0.01). However, at 20 and 30 wk gestation and after parturition, TSH values were similar in the three subgroups (Fig. 2). The TSH values of group B remained significantly higher than those of groups A and C during the entire gestation period, with a sharp increase at parturition (3.5 ± 0.7 mU/liter; P < 0.01). At delivery, 19% of group B showed a TSH value higher than the normal range (Fig. 3, top).

FT₄ baseline values were similar in groups A and B, but these groups had FT₄ values lower, although not significantly, than group C. At 30 wk gestation, FT₄ values were lower in group B than groups A and C (P < 0.01 and P < 0.01, respectively), with a marked decrease in group B after delivery, when 53% of cases showed FT₄ values under the normal range (Fig. 3, bottom).

The differentiated LT₄ dosages assigned on the basis of the TSH starting values thus allowed us to obtain, in the intervention group (group A), TSH and FT₄ values that were not significantly different from the normal control group (group C).

**Obstetrical complications**

Group A and group C had a similar miscarriage rate (3.5 and 2.4%, respectively), whereas group B was characterized by a higher percentage of pregnancy loss (13.8%) [P < 0.05; relative risk (RR), 1.72; 95% confidence interval (CI), 1.13–2.25; and P < 0.01; RR = 4.95; 95% CI = 2.59–9.48, respectively] (Fig. 4, top). The difference in miscarriage rates was a result of patients who miscarried within the first trimester of pregnancy; in fact, in groups A and B, all the miscarriages occurred within the first trimester, and in group C, 19 of 21 miscarriages occurred during the first trimester. Consequently, we conclude that LT₄ treatment could not significantly influence the miscarriage rate, if given after 12 wk. The two pregnancy losses observed in group A occurred at 7 and 10 wk gestation (both pregnant women were on LT₄). One of the eight pregnancy losses observed in group B occurred at 6 wk, two at 7 wk, three at 8 wk, and one each at 10 and 11 wk gestation. In group C, two of 21 pregnancy losses occurred at 6 wk, five at 7 wk, eight at 8 wk, two at 10 wk, and one each at 11, 12, 16, and 21 wk gestation. Group B presented a higher number of premature deliveries (22.4%) compared with group A (7%) (P < 0.05; RR = 1.66; 95% CI = 1.18–2.34) and group C (8.2%) (P < 0.01; RR = 12.18; 95% CI = 7.93–18.7) (Fig. 4, bottom). Thus, the LT₄ treatment appeared to be effective in reducing miscarriages whether given before or after the first trimester of pregnancy. Other obstetrical complications (i.e., hypertension, preeclampsia, and placental abruption) (Table 2) and the clinical characteristics of newborns (weight, height, cranial perimeter, and APGAR score) did not vary between groups.

**Discussion**

In this study, we analyzed the outcome of three groups of euthyroid pregnant women. Subjects positive for TPOAb were divided into two groups, one that was given LT₄ treatment; the third group was composed of pregnant women who were TPOAb⁻. The aims were to assess whether TPOAb⁻ pregnant women showed an increased percentage of obstetrical complications in comparison with those without antibodies and whether the LT₄ treatment had some beneficial effects on these events.

The prevalence of TAI in our population was 11.7%, a percentage that is in agreement with the data found in other studies.
Although it is not currently recommended for cases, the thyroid fails to adapt its function to the increased hormone requirement (12). In the TPOAb− group (group C), TSH values increased from 1.1 mU/liter at 10 wk gestation to 2.1 mU/liter at term. The spontaneous increment in serum TSH was, however, quantitatively and significantly less than the one observed in group B (untreated TPOAb+ group). Concerning the adaptation of thyroid function during pregnancy, it has to be taken into account that this study was conducted in Italy, a country that is still characterized by iodine deficiency, because iodized salt is not compulsory by law. On the basis of the results of this study, we speculate that the tendency of hypothyroxinemia in healthy pregnant women presents a strong stimulus for the pituitary to compensate, with a subsequent rise in TSH values.

The development of hypothyroidism can generally be predicted at the beginning of pregnancy on the basis of the TSH value and TPOAb titers, so that patients displaying TSH more than 2.0 mU/liter and/or high TPOAb (>2000 kIU/liter) are more likely to develop overt thyroid dysfunction (8). A secondary endpoint of the present study was to fine tune the LT4 replacement dose and develop, if possible, practical suggestions on how to treat patients at risk of developing hypothyroidism. In fact, the subgroups given three different dosages of LT4 showed a significant difference initially in baseline TSH values that was abolished during gestation. From the data, we can say that the assigned LT4 dose made it possible to maintain the TPOAb− women in a euthyroid state, with TSH and FT4 values that were similar to the ones showed by the TPOAb+ group.

The development of thyroid dysfunction during pregnancy can cause complications. It has been already demonstrated that both overt and subclinical hypothyroidism are associated with obstetrical repercussions. Maternal complications include anemia, postpartum hemorrhage, cardiac dysfunction, preeclampsia, and placental abruption; fetal complications include fetal distress, premature birth, and/or low birth weight, congenital malformations, and fetal/perinatal death (4–8, 14). In our study population sample, treatment with LT4 had a positive effect on reducing the rates of miscarriages and premature delivery. In fact, this group of patients had a significantly reduced risk of miscarriage compared with the TPOAb+ patients who were not treated with LT4 and LT4 treatment reduced the miscarriage rate to a value comparable to that of the TPOAb− patients. Comparing premature delivery rates, the beneficial intervention with LT4 reduced preterm births in TPOAb+ women to a percentage similar to that of the control population. Timing of treatment initiation appears to be of critical importance. In fact, the LT4 treatment turned out to be extremely effective in reducing the number of miscarriages when given during the early stages of pregnancy, because miscarriages generally occurred within the first trimester. On the other hand, the rate of premature deliveries was also significantly reduced in women whose LT4 treatment was started after the first trimester. This allows us to speculate that euthyroxinemia is primarily important in early pregnancy to avoid miscarriages and to maintain normal placental development and function throughout gestation to avoid preterm deliveries.

From the data we observed, we cannot definitively exclude the possibility that the increased miscarriage rate found in TPOAb+ women may be partly because of their older age. The age difference between TPOAb+ and TPOAb− patients was just

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\text{TABLE 2. Pregnancy outcome}
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<table>
<thead>
<tr>
<th>Complication</th>
<th>Group A TPOAb+ LT4 (n = 57)</th>
<th>Group B TPOAb+ LT4 (n = 58)</th>
<th>Group C TPOAb+ LT4 (n = 869)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>5 (8.8)</td>
<td>7 (12)</td>
<td>63 (7.2)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>2 (3.5)</td>
<td>3 (5.2)</td>
<td>32 (3.7)</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>0</td>
<td>1 (1.7)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>2 (3.5)</td>
<td>8 (13.8)</td>
<td>21 (2.4)</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>4 (7)</td>
<td>13 (22.4)</td>
<td>71 (8.2)</td>
</tr>
</tbody>
</table>

Numbers in parentheses represent percentage.
about thyroid function, in this context, not only TSH but also TPOAb+ compared with TPOAb−. However, in that study, LT4 treatment was not found to be beneficial (15). Taking this into consideration, we can speculate that the difference between women undergoing assisted reproduction technologies and the patients examined in this paper is that the populations had differences in fertility. In other words, autoimmunity in infertile women, (with not only TPOAb+ but also antiphospholipid and antinuclear antibodies, for example) may play a major role in fertilization, implantation, and placentation development, so that LT4 treatment alone is not effective. Conversely, in fertile women, as in this study, TAI alone may play a lesser role, and the advantageous effects of LT4 become more evident. Then, although we cannot exclude the influence of age and autoimmunity on obstetrical complications, on the other hand we can confirm that euthyroid pregnant women affected by autoimmune thyroid disease are inclined to develop thyroid dysfunction during gestation.

The TPOAb+ women not treated with LT4 had, as a group, lower FT4 values compared with the other two groups. Considering the fact that basal TSH concentrations in the upper reference range are often associated with subnormal thyroid function, the TPOAb+ women in this study displayed relatively reduced thyroid hormone values (16). There are two undesirable consequences of having low or non-normal FT4 values, the risk of obstetrical complications and the risk of altered fetal brain development. Up to midgestation, when the fetal thyroid begins to work, early fetal brain development depends exclusively on the availability of FT4 in embryonic and fetal tissues; thus, during early gestation, maternal euthyroxinemia appears to be critical for normal fetal brain development (17). Every effort must be made to detect and prevent early maternal hypothyroxinemia to prevent neurodevelopmental defects, which may include an increased chance of lower IQ and a higher risk of cerebral palsy, (18, 19). Furthermore, reports of poor developmental outcomes on the availability of FT4 in embryonic and fetal tissues; thus, during early gestation, maternal euthyroxinemia appears to be critical for normal fetal brain development (17).

- Every effort must be made to detect and prevent early maternal hypothyroxinemia to prevent neurodevelopmental defects, which may include an increased chance of lower IQ and a higher risk of cerebral palsy, (18, 19).

References


