Long-term hypothyroidism in patients started on levothyroxine during pregnancy

Sophie Demartin¹, Stefan Matei Constantinescu¹, Kris G Poppe², Dominique Maiter¹, Raluca Maria Furnica¹, Orsalia Alexopoulou¹, Chantal Daumerie¹, Frederic Debiève³, Maria-Cristina Burlacu¹

¹Department of Endocrinology and Nutrition, Cliniques Universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium.

²Endocrine Unit, Centre Hospitalier Universitaire Saint Pierre, Université Libre de Bruxelles (ULB), Rue Haute 322, 1000 Brussels, Belgium.

³Department of Obstetrics, Cliniques Universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium.

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Corresponding Author:

Maria-Cristina Burlacu

Department of Endocrinology and Nutrition

Cliniques Universitaires Saint-Luc

Université Catholique de Louvain

1200 Brussels

Belgium

Tel: 00 322 764 54 75.

E-mail: maria.burlacu@saintluc.uclouvain.be

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Abstract

Background: Current guidelines recommend different post-partum approaches of patients started on levothyroxine (LT4) during pregnancy.

Objective

We studied post-partum management of these patients and determined factors associated with long-term hypothyroidism.

Methods

Retrospective study performed in a tertiary center between 2014 and 2020, with LT4 initiation according to 2014 ETA recommendations. We performed multivariate logistic regression (MVR) and a Receiver Operating Characteristic (ROC) curve analysis to determine variables associated with long-term hypothyroidism and their optimal cut-offs.

Results

LT4 was initiated in 177 pregnant women and 106/177 (60%) were followed at long-term (at least 6 months post-partum) (28.5 [9.0-81.9] months). LT4 could have been stopped in 45% patients who continued it immediately after delivery. Thirty-six/106 (34%) patients were long-term hypothyroid. In them, LT4 was initiated earlier during pregnancy than in euthyroid women (11.7 ± 4.7 vs. 13.7 ± 6.5 weeks, p=0.077), at a higher TSH level (4.1 [2.2-10.1] vs. 3.5 [0.9-6.9] mU/l, p=0.005) and reached a higher dose during pregnancy (62.8 ± 22.2 vs. 50.7 ± 13.9 µg/day, p=0.005). In the MVR only the maximal LT4 dose during pregnancy was associated with long-term hypothyroidism (OR=1.03, 95% CI 1.00-1.05, p=0.003). The optimal cut-offs for predicting long-term hypothyroidism were a LT4 dose of 68.75 µg/day (87% specificity, 42% sensitivity; p=0.013) and a TSH level ≥ 3.8 mU/l (68.5% specificity, 77% sensitivity; p=0.019).

Conclusion
One-third of patients started on LT4 during pregnancy had long-term hypothyroidism. The TSH level at treatment initiation and the LT4 dose during pregnancy could guide the decision for continuing long-term LT4.
Introduction

Hypothyroidism diagnosed during pregnancy, whether subclinical and overt, is associated with adverse pregnancy and neonatal outcomes (1). Existing guidelines unanimously recommend the treatment of overt hypothyroidism (OH) in this setting but some controversy remains about the management of subclinical hypothyroidism (SCH). The European Thyroid Association (ETA) recommends treatment of SCH with levothyroxine (LT4) to normalize maternal serum TSH values within the trimester-specific pregnancy reference range or, when not available, to the following reference range upper limits: first trimester, 2.5 mU/l; second trimester, 3.0 mU/l; third trimester, 3.5 mU/l (2). The more recent American Thyroid Association (ATA) guidelines recommend LT4 treatment in patients with TSH levels above pregnancy trimester-specific reference range and to be considered in women with thyroid autoimmunity (TAI) with a serum TSH ≥ 2.5 mIU/L (3), giving the association between thyroid autoantibodies, miscarriage, and preterm birth (4). Where pregnancy trimester-specific reference range is not available, the ATA suggests an upper limit of about 4 IU/mL for the first trimester, based on newer data on factors influencing the upper reference range of normal TSH. The same cut-off was recently advocated by the ETA guideline for the management of thyroid disorders in women undergoing assisted reproduction (5). At the difference of the ETA, ATA does not recommend the treatment of first trimester isolated hypothyroxinemia (2,3).

There are also differences in the postpartum management of patients started on LT4 during pregnancy. According to the ETA, LT4 treatment could be discontinued at delivery in women with TSH less than 5 mU/l and negative thyroperoxidase antibodies (TPOAb) at diagnosis, whereas the ATA consider treatment discontinuation in women requiring a LT4 dose ≤ 50 µg/day during pregnancy, after discussion between patient and the caregiver (2,3). Few studies have investigated the evolution of post-partum thyroid function in women in whom LT4 was initiated during pregnancy, but the incidence of persistent hypothyroidism after delivery could be as high of one-third of patients (6-8), calling for a more accurate management of LT4 treatment started during pregnancy.
The aim of our study was to determine the post-partum management and long-term evolution of thyroid function of women started on LT4 during pregnancy and the predictive factors of persistent hypothyroidism.

**Materials and Methods**

We retrospectively analyzed the medical records of 985 pregnant women treated with LT4 during pregnancy and followed at a single tertiary center between January 2014 and December 2020 in Brussels, Belgium. From these women, 500 were excluded because of LT4 initiation before pregnancy, 94 patients for known thyroid disease or taking drugs interfering with thyroid function and 214 patients because of missing data (149/214 (69%) because of no information on LT4 dose (these were patients seen in our hospital during the last trimester of pregnancy, with treatment initiated in another hospital), 10/214 (5%) because of no information on thyroid function at LT4 initiation, 42/214 (20%) because of no information about the timing of LT4 initiation (before or during the pregnancy) and 13/214 (6%) because of follow-up during pregnancy in another hospital).

Patients treated with LT4 during or outside a previous pregnancy in whom the treatment was withdrawn were included. The final analysis included 177 patients in whom LT4 was initiated during pregnancy. One hundred and six of these patients were followed for 6 months or more after delivery and analyzed for “long-term” persistent hypothyroidism. **Figure 1** illustrates the study selection process in detail.

**Thyroid function tests and criteria for LT4 initiation during pregnancy**

In our hospital, thyroid function (TSH and freeT4) and presence of TPOAb are routinely tested at the first obstetrical visit during the first trimester of pregnancy. Locally derived trimester-specific reference ranges for freeT4 (FT4) exist in our hospital since June 2014, but for the TSH only non-pregnant reference range is available. Before June 2014, TSH, FT4 and thyroid antibodies were measured with a chemiluminescent immunoassay (DXL, Beckman Coulter) and after June 2014 using an electrochemiluminescent immunoassay on a Cobas e602 analyzer (Roche Diagnostics). The reference ranges were as follows: TSH 0.2-3.5 mU/l before June 2014 and 0.27-4.2 mU/l after June 2014; FT4...
12-22 pmol/l non-pregnant, 12.6-19.7 pmol/l first trimester, 9.7-17.5 pmol/l second trimester, 8.1-15.3 pmol/l third trimester; TPOAb positive > 5.1 U/ml before June 2014 and > 115 U/ml after June 2014.

LT4 treatment was prescribed according to 2014 ETA guidelines recommendations (2). The thyroid status at LT4 initiation was defined as follows: euthyroidism (normal range TSH and normal trimester-specific range FT4); SCH (TSH above upper normal range and normal trimester-specific FT4); OH (TSH above upper normal range and FT4 below normal trimester-specific range); isolated hypothyroxinemia (normal TSH and FT4 below normal trimester-specific range).

**Thyroid status at long-term post-partum follow-up**

Euthyroidism was defined as normal TSH without LT4 treatment, hypothyroidism as normal TSH under LT4 treatment or TSH above upper normal range with or without LT4 treatment and hyperthyroidism as TSH below lower normal range in absence of LT4 treatment.

**Statistical Analyses**

Statistical analyses were performed using the IPSS Statistics© software from IBM© (version 25.0). A p value of less than 0.05 was considered significant. Continuous variables were described either as mean ± standard deviation or median with the percentiles 5 and 95. Discrete variables were described using their frequency. Subgroup analyses were performed using Pearson’s X² test for categorial unpaired variables. Student’s t Test was used for comparing means of continuous unpaired variables. We performed univariate and multivariate logistic regression analysis (MVR) to determine variables associated with long-term hypothyroidism. We included in the MVR only those variables that were significantly associated (p<0.1) with long term hypothyroidism in univariate logistic regression. Finally, we used Receiver Operating Characteristic (ROC) curve analysis to describe optimal cut offs and area under the curve (AUC) for factors significantly associated with long term hypothyroidism in MVR. For MVR, all input variables were entered simultaneously.
Results

Characteristics of patients started on LT4 during pregnancy

The general characteristics of the 177 patients initiated on LT4 during pregnancy were in majority similar to those of the pregnant population in Brussels area for reference year 2021. The mean age at diagnosis was 30.9±4.9 years, the pre-conception BMI 24.5±4.8 kg/m² and 94/177 (53%) of women were multiparous. Twenty-three of 147 (15.5%) patients had a history of LT4 treatment during a previous pregnancy. There were more women with infertility history in our population (32/177 (18%)) than in the reference Belgian population (5.4%). The pregnancy and neonatal outcomes were similar in term of gestational diabetes, birth weight, prematurity, pre-eclampsia and there were less macrosomia and neonatal unit admissions in our population (11/172 (6.5%) vs. 13% and 12/172 (7%) vs. 10.1%, respectively).

At LT4 treatment initiation, 24/177 (13.5%) of patients were euthyroid, 105/177 (59.5%) had SCH, 31/177 (17.5%) had OH and 17/177 (9.5%) had isolated hypothyroxinemia. LT4 treatment was initiated at a mean gestational age of 13.1 (9-16.8) weeks, at a median TSH of 3.6 [1.2-7.1] mU/l and a mean FT4 of 12.6±2.5 pmol/l. TPOAb were measured at the time of LT4 treatment initiation and were positive in 75/168 (45%) of patients (Table 1). Among the 24 women initiated on LT4 while being euthyroid, 14/24 (58%) were TPOAb positive and in most of them the treatment was initiated for that reason. The reason for LT4 initiation in euthyroid TPOAb negative patients was not always specified, but 3/10 patients had an IVF procedure and 2/10 patients were TgAb positive. The LT4 treatment was initiated by the endocrinologist in only 37/177 (21%) of patients, but the majority of patients (139/177 (78.5%)) was further followed by the endocrinologist during pregnancy. The maximal mean LT4 dose reached during pregnancy was 54.2±16.2 µg/day.

Characteristics of patients started on LT4 during pregnancy and followed at long-term after delivery

One hundred and six of patients (106/177; 60%) initiated on LT4 during pregnancy had long-term post-partum follow-up (Figure 1). Forty-nine of the 177 (28%) patients had no post-partum follow-up. There
were no differences in term of general characteristics, thyroid function tests or LT4 treatment between patients with or without follow-up, except that followed patients have been more frequently managed by endocrinologists during pregnancy (85/106 (80%) vs. 32/49 (65%), p=0.045).

The median post-partum follow-up time was 28.5 [9.0-81.8] months. Among the 106 women treated with levothyroxine during pregnancy and followed at long-term after delivery, 13/106 (12.5%) were euthyroid at LT4 initiation, 11/106 (10.5%) had isolated hypothyroxinemia, 66/106 (62%) had subclinical hypothyroidism and 16/106 (15%) had overt hypothyroidism. At the last visit, 68/106 (64%) of patients were euthyroid, 36/106 (34%) were hypothyroid and 2/106 (2%) were thyrotoxic. Among women with long-term follow-up, 36/86 (42%) of those with TSH>2.5 mU/l and 20/44 (45%) of those with TSH>4mU/at diagnosis were long-term hypothyroid. Thirty-four of 106 (32%) patients continued or restarted LT4, at a mean dose of 57.9±24.5 µg/day.

**LT4 treatment discontinuation after delivery**

Of the 106 long-term followed patients, 22/106 (21%) continued LT4 after delivery and only 49 patients discontinued the treatment. There was no information on how the remaining 35 patients were managed immediately after delivery, but most of them (24 patients;68.5%) were euthyroid with no LT4 treatment at long term follow-up (Figure 1). Among the 22 patients who continued the treatment, 12 (55%) received a LT4 dose ≥ 50 µg/day during pregnancy at the difference of only 8/49 (17%) of women who discontinued it (p=0.001). The median TSH at LT4 initiation was higher in patients who continued the treatment vs. those who discontinued it (5.1[2.6-8.8] mU/l vs. 3.5[1.4-9.9] mU/l, p=0.010) (Table 2).

At long-term follow-up, there were more hypothyroid patients among those that continued the treatment than among those that discontinued it (14/22 (64%) vs. 13/49 (26.5%), p=0.003) (Figure 1).

**Comparisons of long-term hypothyroid and euthyroid patients**

The general characteristics of long-term euthyroid and hypothyroid patients at LT4 treatment initiation during pregnancy are presented in Table 3. There were no differences in term of gestational age, BMI, parity, previous LT4 treatment, infertility and pregnancy and neonatal outcomes between the two groups.
In long-term hypothyroid patients, LT4 was initiated earlier during pregnancy than in euthyroid patients (11.7±4.7 vs. 13.7±6.5 weeks, p=0.077), at a higher TSH level (4.1 [2.2-10.1] vs. 3.5 [0.9-6.9] mU/l, p=0.005) and reached a higher dose during pregnancy (62.8±22.2 vs. 50.7±13.9 µg/day, p=0.005). LT4 dose distribution for each group was significantly different (p=0.038). There were less euthyroid patients at LT4 initiation in the long-term hypothyroid patients (3% vs. 17.5%, p=0.029). There were no differences in term of TPOAb positivity, level or tertile between the long-term hypothyroid and the euthyroid patients.

Predictive factors of persistent hypothyroidism

In the univariate logistic regression, TSH level at LT4 initiation and the maximal LT4 dose during pregnancy were predictive for the risk of long-term hypothyroidism (OR=1.37, 95% CI 1.08 -1.73, p=0.009 and OR=1.04, 95% CI 1.01-1.06, p=0.003, respectively), while gestational age, pre-conception BMI or TPOAb level or positivity at LT4 initiation were not (Table 4). However, only the maximal LT4 dose during pregnancy (OR=1.03, 95% CI 1.00-1.05, p=0.003) was associated with long-term hypothyroidism in multivariate logistic regression. ROC curve analysis showed that a maximal LT4 dose of 68.75 µg/day during pregnancy (87% specificity, 42% sensitivity; AUC=0.649, 95% CI 0.53-0.76; p=0.013) and a TSH level ≥3.8 mU/l at treatment initiation (68.5% specificity, 77% sensitivity; AUC=0.723, 95% CI 0.53-0.91; p=0.019) were the optimal cut-offs for predicting long-term hypothyroidism. (Figure 2 A and B)

Discussion

We show in our study of a population of pregnant women representative for our area (9) that one-third of patients initiated on LT4 during pregnancy had long-term persistent hypothyroidism, but this proportion could vary according to the severity of hypothyroidism at LT4 initiation and different TSH cut-offs used to define it (6-8,10). Shields et al. found that 16.5% of patients with SCH and isolated hypothyroxinemia had persistently TSH levels >4.5 mU/l over 5 years postpartum follow-up, but the proportion increased to 24.5% when only women with pregnancy SCH were considered (6). The prevalence of long-term hypothyroidism increases with the increasing cut-off of diagnostic TSH, from
18% in a large Indian study of 467 women with SCH (7) when trimester specific TSH reference range was used, up to 39% in a recent prospective Chinese study that defined SCH as TSH > 4 mU/l (8). Although we used a lower diagnostic TSH cut-off, the rather high proportion of persistent hypothyroidism found in our study could be explained by the inclusion of a significant proportion of patients with OH. At a much higher TSH level at diagnosis during pregnancy (mean TSH 13.2 mU/l), 64% of patients developed OH over >10 years follow-up in the seminal study by Haddow et al (11).

Another confounding factor for the prevalence of persistent hypothyroidism is the continuation of LT4 treatment after delivery. In our study, there were significantly more patients who continued the treatment after delivery in the long-term hypothyroid than in the euthyroid group. The reason for treatment continuation was not always known and we cannot rule out a therapeutic inertia, as almost half of those who continued the treatment had a TSH <4.0 mU/l at LT4 initiation and received during pregnancy a maximal LT4 dose of 50 µg/day or less, that should have been stopped according to current recommendations (3, 12). These patients account for almost one third of long-term hypothyroid patients and could lead to an overestimation of the persistence of hypothyroidism. In the study by Linardi et al, the prevalence of persistent hypothyroidism goes down from 75.5% to 28% when only the patients who discontinued the treatment are analysed (10).

If discontinuation of LT4 treatment after delivery is not considered, this could lead to long-term overtreatment, especially when the indication for LT4 initiation during pregnancy is not justified. In our study, LT4 was started in 13.5% of patients although they were euthyroid according to 2014 ETA criteria. If the 2017 ATA criteria had been applied, 50/177 (28%) of patients would have been treated. Recent evidence does not support LT4 treatment in euthyroid women, whether TPOAb positive or not, including those with a miscarriage history (13,14). Moreover, LT4 treatment was initiated in 9.5% of patients of our study for isolated hypothyroxinemia, according to 2014 ETA guidelines. Although isolated hypothyroxinemia in pregnancy has been associated with adverse maternal metabolic profile and obstetrical outcomes (15,16) and intellectual disability in offspring (17), current evidence does not support LT4 treatment for this indication (16).
We show in our study that the TSH level at treatment initiation and the maximal LT4 dose during pregnancy are predictive of persistent hypothyroidism. Previous studies have found associations between long-term hypothyroidism and TSH >5 mU/l at diagnosis (6,7,10), LT4 dose at the end of pregnancy (7), TPOAb (6-8) or TgAb (8) positivity at diagnosis and at 6 weeks post-partum follow-up (8), gestational age at treatment initiation (8), multiparity (10) or maternal age (7). TSH was significantly higher at LT4 initiation in patients who were long-term hypothyroid in our study and a TSH level >3.8 mU/l was predictive of this evolution. This value is also close to the 4.0 mU/l cut-off beyond which epidemiology studies have shown association between thyroid function and adverse maternal and neonatal outcomes (18-20) and beyond which the 2017 ATA guidelines suggest to initiate LT4 treatment during pregnancy, where pregnancy trimester-specific reference range is not available. In addition, a maximal LT4 dose of 68.57 µg/day was found predictive of long-term hypothyroidism in our study. This dose, larger more than the 50 µg cut-off suggested by ATA guidelines (3), might be explained by the inclusion of OH patients with higher peri-conception TSH levels and greater substitution need during pregnancy. In our long-term hypothyroid patients, like in the study by Li et al (10), the LT4 treatment was initiated at an earlier gestational age, demonstrating the lack of adaptation of these patients to the metabolic stress of the pregnancy.

We were not able to reproduce previous findings about the predictive value of TPOAb regarding long-term hypothyroidism (6-8). TAI impairs the thyroidal response to hCG (21) as a function of TPOAb and/or TgAb levels (22, 23), with higher risk of hypothyroidism during and after pregnancy at higher antibodies levels (23). Although TPOAb positivity was present in almost half of patients started on LT4 in our study and this proportion was numerically higher in long-term hypothyroid patients, TPOAb were not associated with persistent hypothyroidism. This could be explained by the fact that most of our patients had TPOAb in the lowest tertiles. In two previous studies that showed an association between TPOAb and persistent hypothyroidism (6,8), antibodies were measured at a more advanced gestational age than in our study (28 and 22 weeks vs. 13 weeks) and the persistence of a significant TPOAb level
at a late stage of pregnancy could indicate a more aggressive autoimmune phenotype with a higher impact on the subsequent thyroid function.

This study draws also attention on the real-life management after LT4 initiation during pregnancy. Although the control of thyroid function is recommended 6 weeks after delivery (2,3), almost one-third of our patients had no follow-up vs. 16.5% in the study by Neelaveni et al. (7) and 45% in the study by Li et al. (8) and slightly more than half had a long-term follow-up. In our study, being followed-up by the endocrinologist seems to be of added value for the long-term management of these patients. As there were no differences of characteristics at LT4 initiation and during treatment between patients with or without follow-up, one might expect the same long-term evolution in the latter and misdiagnosis of persistent hypothyroidism in women susceptible to be pregnant again. However, a post-partum follow-up might not be necessary in some patients, for instance in those with isolated hypothyroxinemia, giving the low prevalence of persistent hypothyroidism in this group (8, 12). A normal thyroid function at 6 weeks post-partum does not exclude the risk of long-term hypothyroidism, that can develop in 28% of patients followed for a median of 11 (7-19) months (8), especially when thyroid antibodies are positive. Consequently, as suggested by 2014 ETA guidelines, the follow-up should be continued at least for one year after delivery.

Our study has several limitations related to its retrospective nature, that could increase the risk of selection and information bias. One fifth of our pregnant patients on LT4 was excluded because there was not enough information about the reasons, timing and importance of LT4 treatment. These patients might have had different clinical characteristics from the patients included. The group of patients included was small and the information on LT4 treatment management after delivery not always available. We did not study the impact of TgAb on the occurrence of long-term hypothyroidism, as they were measured in only 55% of patients at LT4 instauration, nor the impact of iodine supplementation or ferritin levels as possible confounding factors for thyroid dysfunction during pregnancy. Also, there was not enough information about the occurrence of post-partum thyroiditis (PPT) in our population. The
hypothyroidism can persist in up to 40% of women with PPT, especially those TPOAb positive (24) and we cannot rule out that PPT was the cause of LT4 restoration in some of our patients. Based on our findings, LT4 treatment initiated during pregnancy could be reasonably discontinued in patients with TSH <4.0 mU/l at diagnosis and who received less than 68.75 µg/day LT4. We suggest to continue LT4 treatment in patients diagnosed with OH during pregnancy and in patients with SCH defined as a TSH >4.0 mU/l during the first trimester of pregnancy, giving the high prevalence of persistent hypothyroidism (8). The dose to be continued could be reduced by one third to one half of the maximal dose required during pregnancy, depending on the initial TSH elevation, and based on the increased requirement for thyroid hormones during pregnancy (25,26). If the treatment was prescribed for isolated hypothyroxinemia, it should be discontinued after delivery. Thyroid function should be checked at 6 weeks post-partum and until at least 1 year after delivery.

Conclusions

One-third of patients started on LT4 during pregnancy has long-term hypothyroidism, but this proportion could be overestimated by the unjustified continuation of treatment in some patients immediately after delivery. We observe deviations from current recommendations concerning the indications of LT4 initiation during pregnancy, the management of LT4 treatment after delivery and the follow-up strategy. The TSH level at treatment initiation and the LT4 dose during pregnancy could guide the decision for continuing long-term LT4 treatment.

Statements

Statement of Ethics

This study protocol was reviewed and approved by the local Ethics Committee (Comité d’Éthique Hospitalo-Facultaire des Cliniques Universitaires St-Luc, Université Catholique de Louvain, Brussels, Belgium). Written informed consent was not required due to the retrospective nature of the study.
Conflict of Interest Statement

KGP received lecture fees from the IBSA Institut Biochimique SA, Berlin-Chemie AG and the Merck company between 2016-2022. From September 2023 on, he is the secretary of the European Thyroid Association (ETA). Kris Poppe is on the editorial board of European Thyroid Journal. Kris Poppe was not involved in the review or editorial process for this paper, on which he is listed as an author.

Funding Sources

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Author Contributions

M.C.B wrote the first draft. S.D collected the clinical data and D.M and S.M.C performed all statistical analyses. C.D., R.F, O.A, D.M, F.D. cared for patients and K.G.P provided revisions for the manuscript. M.C.B and F.D lead the clinical study. All authors reviewed and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due their containing information that could compromise the privacy of research participants but are available from M.C.B. upon reasonable request.

Legends

Figure 1. Flow-chart of patients started on LT4 during pregnancy and their post-partum long-term thyroid status.

LT4: levothyroxine; long-term follow up: at least 6 months post-partum follow-up

Figure 2. Receiver operating characteristic (ROC) curve for maximal LT4 dose (µg/day) during pregnancy (a) and TSH level (mU/l) at LT4 initiation (b) predictive for long-term hypothyroidism.
LT4: levothyroxine
References [Numerical]


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985 pregnant women on LT4

177 women started on LT4 during pregnancy

106 women with long-term post-partum follow-up

LT4 management at delivery

22 LT4 continuation

49 LT4 discontinuation

35 LT4 missing data

Thyroid status at long-term post-partum follow-up

8 Euthyroid

14 Hypothyroid

36 Euthyroid

13 Hypothyroid

24 Euthyroid

9 Hypothyroid

2 Hyperthyroid

808 Women excluded
500 LT4 initiation before pregnancy
214 missing data
94 other thyroid disease/interfering drugs

71 Women excluded
49 with no post-partum follow-up
22 with < 6 months post-partum follow-up
Figure 2

A

LT4 ≥ 68.75 µg
Sensitivity: 42%
Specificity: 87%

B

TSH ≥ 3.8 mU/l
Sensitivity: 77%
Specificity: 68.5%
**Table 1. Characteristics of patients started on LT4 during pregnancy.** Results are shown as mean ± SD or median (percentile 5–95).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>177</td>
<td>13.1 ± 6.7</td>
</tr>
<tr>
<td>TSH (mU/L)</td>
<td>177</td>
<td>3.6 [1.2-7.1]</td>
</tr>
<tr>
<td>FT4 (pmol/L)</td>
<td>176</td>
<td>12.6 ± 2.5</td>
</tr>
<tr>
<td>TPOAb ULN</td>
<td>168</td>
<td>0.5 [0.14-14.7]</td>
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<tr>
<td>TPOAb +</td>
<td>168</td>
<td>75/168 (45%)</td>
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<tr>
<td>Maximal LT4 dose during pregnancy (µg/day)</td>
<td>177</td>
<td>54.2 ± 16.2</td>
</tr>
<tr>
<td>LT4 prescription by endocrinologist</td>
<td>177</td>
<td>37/177 (21%)</td>
</tr>
<tr>
<td>Follow-up by endocrinologist</td>
<td>177</td>
<td>139/177 (78.5%)</td>
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</tbody>
</table>

FT4: free T4; LT4: levothyroxine; TPOAb: thyroperoxidase antibodies; +: positive; ULN: upper normal limit; TPOAb ULN: a ratio of the absolute TPOAb value to the ULN.
Table 2. Characteristics of patients who continued (N=22) or discontinued (N=49) LT4 treatment immediately after delivery. Results shown as mean ± SD or median (percentile 5–95).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LT4 discontinuation</th>
<th>LT4 continuation</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>General characteristics</td>
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<tr>
<td>Age (years)</td>
<td>30 [21.2-38.6]</td>
<td>29 [23.2-36]</td>
<td>0.876</td>
</tr>
<tr>
<td>Pre-conception BMI (kg/m²)</td>
<td>24 [19.6-36.2]</td>
<td>22 [18.6-25.4]</td>
<td>0.044</td>
</tr>
<tr>
<td>LT4 treatment</td>
<td></td>
<td></td>
<td>0.993</td>
</tr>
<tr>
<td>Previous treatment</td>
<td>9/43 (21%)</td>
<td>4/19 (21%)</td>
<td></td>
</tr>
<tr>
<td>Previous treatment during pregnancy</td>
<td>7/43 (16%)</td>
<td>3/19 (15.5%)</td>
<td></td>
</tr>
<tr>
<td>Multiparous</td>
<td>27/49 (55%)</td>
<td>10/22 (45.5%)</td>
<td>0.383</td>
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<tr>
<td>Infertility treatment</td>
<td>4/49 (8%)</td>
<td>3/22 (13.5%)</td>
<td>0.469</td>
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<tr>
<td>At LT4 initiation during pregnancy</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gestational age (weeks)</td>
<td>11 [5.2-25.1]</td>
<td>9.5 [3.6-21.8]</td>
<td>0.239</td>
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<tr>
<td>TSH (mU/L)</td>
<td>3.5 [1.4-9.9]</td>
<td>5.1 [2.6-8.8]</td>
<td>0.010</td>
</tr>
<tr>
<td>FT4 (pmol/L)</td>
<td>13.8 [8.5-16.3]</td>
<td>12.5 [8.9-17.5]</td>
<td>0.247</td>
</tr>
<tr>
<td>TPOAb ULN</td>
<td>2.7 [0.21-18.12]</td>
<td>0.25 [0.05-27.72]</td>
<td>0.011</td>
</tr>
<tr>
<td>TPOAb +</td>
<td>34/47 (72.5%)</td>
<td>8/22 (36.5%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Maximal LT4 dose during pregnancy (µg/day)</td>
<td>50 [25-75]</td>
<td>50 [50-100]</td>
<td>0.001</td>
</tr>
<tr>
<td>LT4 prescription by endocrinologist</td>
<td>10/49 (20.5%)</td>
<td>8/22 (36.5%)</td>
<td>0.153</td>
</tr>
<tr>
<td>Follow-up by endocrinologist</td>
<td>45/49 (92%)</td>
<td>19/22 (86.5%)</td>
<td>0.669</td>
</tr>
</tbody>
</table>

FT4: free T4; LT4: levothyroxine; TPOAb: thyroperoxidase antibodies; +: positive; ULN: upper normal limit; TPOAb ULN: a ratio of the absolute TPOAb value to the ULN.
Table 3. Characteristics of long-term euthyroid (n=68) and hypothyroid (n=36) patients at LT4 initiation during pregnancy. Results shown as mean ± SD or median (percentile 5–95).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Long-term euthyroid</th>
<th>Long-term hypothyroid</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.9 ± 5.2</td>
<td>30.4 ± 3.9</td>
<td>0.620</td>
</tr>
<tr>
<td>Pre-conception BMI (kg/m²)</td>
<td>25.1 ± 5.3</td>
<td>23.4 ± 3.4</td>
<td>0.059</td>
</tr>
<tr>
<td>LT4 treatment</td>
<td></td>
<td></td>
<td>0.675</td>
</tr>
<tr>
<td>Previous treatment</td>
<td>10/55 (18%)</td>
<td>7/32 (22%)</td>
<td></td>
</tr>
<tr>
<td>Previous treatment during pregnancy</td>
<td>9/55 (16.5%)</td>
<td>5/32 (15.5%)</td>
<td></td>
</tr>
<tr>
<td>Multiparous</td>
<td>31/68 (45.5%)</td>
<td>24/36 (66.5%)</td>
<td>0.285</td>
</tr>
<tr>
<td>Infertility treatment</td>
<td>13/68 (19%)</td>
<td>3/36 (8.5%)</td>
<td>0.147</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>13.7 ± 6.5</td>
<td>11.7 ± 4.7</td>
<td>0.077</td>
</tr>
<tr>
<td>TSH (mU/l)</td>
<td>3.5 [0.9-6.9]</td>
<td>4.1 [2.2-10.1]</td>
<td>0.005</td>
</tr>
<tr>
<td>FT4 (pmol/l)</td>
<td>12.7 ± 2.6</td>
<td>12.7 ± 2.4</td>
<td>0.901</td>
</tr>
<tr>
<td>TPOAb ULN</td>
<td>0.53 [0.14-17.64]</td>
<td>2.37 [0.09-20.4]</td>
<td>0.323</td>
</tr>
<tr>
<td>TPOAb+</td>
<td>28/64 (44%)</td>
<td>21/35 (60%)</td>
<td>0.122</td>
</tr>
<tr>
<td>TPOAb tertiles</td>
<td></td>
<td></td>
<td>0.432</td>
</tr>
<tr>
<td>1st tertile: 0.05-0.31 × ULN</td>
<td>21/64 (33%)</td>
<td>12/35 (34.5%)</td>
<td></td>
</tr>
<tr>
<td>2nd tertile: 0.31-3.26 × ULN</td>
<td>24/64 (37.5%)</td>
<td>9/35 (25.5%)</td>
<td></td>
</tr>
<tr>
<td>3rd tertile: 3.26-42.84 × ULN</td>
<td>19/64 (29.5%)</td>
<td>14/35 (40%)</td>
<td></td>
</tr>
<tr>
<td>Maximal LT4 dose during pregnancy (µg/day)</td>
<td>50.7 ± 13.9</td>
<td>62.8 ± 22.2</td>
<td>0.005</td>
</tr>
<tr>
<td>LT4 prescription by endocrinologist</td>
<td>16/68 (23.5%)</td>
<td>9/36 (25%)</td>
<td>0.867</td>
</tr>
<tr>
<td>Follow-up by endocrinologist</td>
<td>55/68 (81%)</td>
<td>30/36 (83.5%)</td>
<td>0.758</td>
</tr>
</tbody>
</table>

FT4: free T4; LT4: levothyroxine; TPOAb: thyroperoxidase antibodies; +: positive; ULN: upper normal limit; TPOAb ULN: a ratio of the absolute TPOAb value to the ULN.
Table 4. Uni- and multivariate logistic regression analysis of factors influencing the risk of long-term hypothyroidism. Values are odds ratio with 95% confidence intervals.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Gestational age</td>
<td>0.944 (0.877-1.017)</td>
<td>0.132</td>
</tr>
<tr>
<td>Pre-conception BMI</td>
<td>0.924 (0.841-1.016)</td>
<td>0.102</td>
</tr>
<tr>
<td>TSH (mU/L)</td>
<td>1.371 (1.083-1.736)</td>
<td><strong>0.009</strong></td>
</tr>
<tr>
<td>TPOAb ULN (continuous)</td>
<td>1.036 (0.969-1.107)</td>
<td>0.301</td>
</tr>
<tr>
<td>TPOAb positivity (categorical)</td>
<td>1.875 (0.810-4.340)</td>
<td>0.142</td>
</tr>
<tr>
<td>Maximal LT4 dose during pregnancy</td>
<td>1.040 (1.014-1.068)</td>
<td><strong>0.003</strong></td>
</tr>
</tbody>
</table>

LT4: levothyroxine; TPOAb: thyroperoxidase antibodies; ULN: upper normal limit; TPOAb ULN: a ratio of the absolute TPOAb value to the ULN.