

Levothyroxine Dosing after Delivery in Women Diagnosed with Hypothyroidism During Pregnancy-A Retrospective, Observational Study

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Abstract

Background: Pregnancy leads to profound alteration in thyroid function and dysthyroidism contributes to adverse pregnancy outcomes. Though the management of hypothyroidism during pregnancy is highlighted, the same is often neglected during postpartum. We have evaluated the postpartum levothyroxine (LT4) dose change in patients with new onset hypothyroidism. **Methods:** We conducted this retrospective, observational study between 2014 and 2016 using the medical records of patients with new onset hypothyroidism during pregnancy. We included patients who continued with LT4 after delivery (as per predetermined protocol) and the availability of 2-year follow up record. We excluded patients who stopped LT4 and use of other drugs that affect the thyroid function tests (TFT) after delivery. The patients were divided into 2 groups for comparison [Group 1-Overt hypothyroidism (OH) and Group 2-Subclinical hypothyroidism (SCH)] based on the initial TFT reports. The data were analyzed using appropriate statistical methods and a *P* value of less than 0.05 was considered significant. **Results:** A total of 159 women continued using LT4 after delivery and the final follow up data were available for 130 patients only. LT4 dose up titration was observed more in group 1 than in group 2 (*P* = 0.0336). In both the groups, the presence of goitre, thyroid autoimmunity and a repeat pregnancy are associated with increasing LT4 requirement. **Conclusion:** Majority of patients with OH during pregnancy require more than half of the final dose after delivery. Goitre and autoimmunity are associated with higher LT4 dose after delivery.

Keywords: Hypothyroidism, levothyroxine, postpartum, puerperium, thyroid

INTRODUCTION

Thyroid disorders are common during pregnancy and its prevalence is increasing exponentially due to increase in the awareness and easy availability of thyroid assays. Hypothyroidism is the most common thyroid disorder and multiple factors like renal iodine loss, foetal demand etc., contribute to the increased thyroid hormone requirement during pregnancy.^[1] As a direct consequence to this, a greater number of patients are being treated with levothyroxine (LT4) during pregnancy. Untreated hypothyroidism leads to adverse pregnancy outcomes and there have been many guidelines in the last decade about the management of hypothyroidism during pregnancy.^[2-4] The guidelines suggest a dynamic approach during pregnancy, with an aim to keep the thyroid stimulating hormone (TSH) in the gestational age specific range till delivery. However, the guidelines have paid little attention to the management of hypothyroidism in the postpartum phase.

The guidelines by the European Thyroid Association (ETA) suggest about the discontinuation of LT4 therapy in a specific subset of patients only (Initial TSH <5 μ IU/ml and negative for thyroid antibody).^[5] American Thyroid Association (ATA) guidelines in 2017 suggest discontinuation of levothyroxine therapy, especially in patients requiring less than 50 μ g of levothyroxine per day.^[6]

The postpartum state lasts for about 8-12 weeks in which the thyroid physiology (thyroxine binding globulin, deiodinase activity etc.) reverts back to normal.^[7] Lactation, akin to

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pregnancy is a state of enhanced requirement of thyroid hormone requirement. Postpartum thyroiditis (PPT) is another disorder that affects the thyroid physiology in these patients and the prevalence is more in patients with positive thyroid peroxidase (TPO) antibody.^[8] PPT may present with the classical tri-phasic course and complicate the thyroid function tests (TFT) in patients using LT₄ therapy. The management of hypothyroidism is often neglected in the post-partum state with increasing focus on the needs of the neonate. The obstetric care in India is compromised by reduced gap between the two pregnancies and it is essential to have an optimum thyroid function to achieve good pregnancy outcomes.^[9] The literature is sparse about the postpartum LT₄ dose adjustment in patients detected with hypothyroidism during pregnancy.^[10,11] Hence, this study was conducted to observe the postpartum changes in the LT₄ dose in patients with new onset hypothyroidism detected during pregnancy.

MATERIALS AND METHODS

Study population

We conducted this retrospective, observational study in a tertiary care, and teaching hospital. The patients who attended the endocrinology clinic for the new onset hypothyroidism during pregnancy between 2013 and 2015 were considered for inclusion in the study. A total of 824 patients with a diagnosis of hypothyroidism during pregnancy were evaluated and the study protocol is shown in Figure 1. We have included patients (Newly diagnosed hypothyroidism during pregnancy, received LT₄ therapy throughout the pregnancy till delivery, continued use of LT₄ after delivery for a period of 2 years thereafter) with records available of serial thyroid hormone evaluation. We excluded patients with known thyroid disease, discontinuation of thyroid hormone therapy after delivery, amiodarone and use of any other drug that could affect the TFT results. The patients were divided into 2 groups for comparison as per the initial diagnosis: Group 1-Overt hypothyroidism (OH) and Group 2-Subclinical hypothyroidism (SCH).

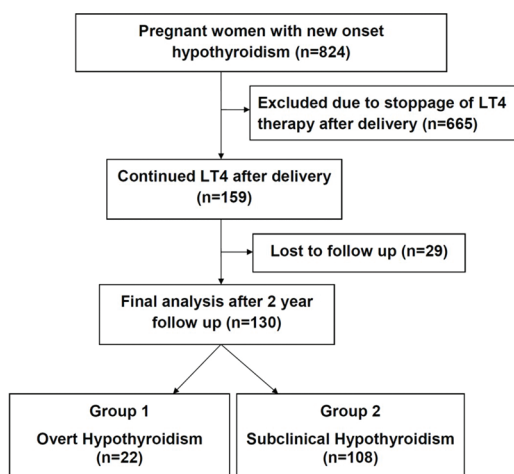


Figure 1: Flow diagram of the study

Study measures

Clinical data were collected from all the participant records, including demographic details like family history of thyroid disorder, gestational age at the time of diagnosis, presence of the goitre, thyroid hormone requirement at the time of delivery, dose modification thereafter in postpartum period for 2 years and peripartum complications. The presence or absence of the goitre was assessed by the endocrinologists as per the World Health Organization (WHO) grading.^[12] The decision to either continue or stop LT₄ after the delivery was taken by the treating endocrinologist. The dose of LT₄ was adjusted after delivery based on a predetermined departmental protocol as shown in Table 1. Subsequently, the LT₄ dose was titrated based on the TSH level of the patient. The number of patients with LT₄ dose increase was noted from the records. All other events of interest retrieved from the records include the occurrence of PPT, repeat pregnancy and the status of TPO antibody. We used chemiluminescence (CLIA) method using the Cobas E411 analyzer (Roche®, Basel, Switzerland) for the estimation of thyroid hormones and antibody titer. The assay did not have a gestational specific range with less than 8% variability in our lab. All the patients were followed up for a period of two years with serial estimation of thyroid hormones at 3-6 monthly intervals depending on the clinical judgement. The institutional ethics committee approved the study protocol for the data analysis and all the patients provided informed verbal consent for the participation in the study.

Study definitions

The subclinical hypothyroidism (SCH) was defined as having normal free thyroxine (FT₄) with elevated TSH (more than 2.5 and 3 μ IU/ml in first and next trimesters respectively) and OH as elevated TSH with low FT₄.^[13] Serial thyroid assessment was done every 3-6 months for all the patients till the end of the follow up period. A TPO antibody titre of more than 30 IU/L was considered as diagnostic of autoimmune thyroid disease (AITD). The LT₄ dose was adjusted to achieve a TSH target of 0.3-4.2 μ IU/ml in the postpartum phase.

Statistical analysis

The continuous variables are presented as mean, standard deviation (SD) and categorical variables using the frequency and percentages. Unpaired t-test and Chi-square test were used to compare the data between the groups. We did not estimate the sample size and power, as our study was retrospective, observational in nature. A two-tailed *P* value of less than 0.05 was considered significant for all the tests. The statistical analysis was done using the Graph Pad Prism Software, Version 6 (Graph Pad Software, San Diego, CA, USA).

RESULTS

A total of 159 out of 824 (20%) women continued to receive LT₄ after delivery. The follow-up data at the end of two years was available for 130 patients only, who are included in the analysis. The study participants had a mean age of 23 ± 2.2 years, gestational age 26.3 ± 4.2 weeks and mean TSH

Table 1: Protocol of LT4 dose modification after delivery

Diagnosis	General considerations	Dose after delivery
OH	Irrespective of the goitre and TPO antibody	Half of the last dose used during pregnancy
SCH	Presence of either goitre or TPO antibody	Half of the last dose used during pregnancy
	Absence of both goitre and TPO antibody	Quarter of the last dose used during pregnancy*

*Excluded patients with daily LT4 dose requirement of <12.5 mcg

Table 2: Comparison between 2 groups regarding clinical and biochemical parameters

Feature	Units	Group 1(OH) n=22	Group 2(SCH) n=108	P
Age	Years	22.8 (1.7) *	23.5 (2)	0.1281
Goitre	N (%)	12 (55)	56 (52)	1.000
TPO Ab Positive	N (%)	8 (67)	34 (61)	0.7563
TPO Ab Negative	N (%)	4 (33)	22 (39)	
Positive TPO antibody	N (%)	11 (50)	48 (44.4)	0.6467
Goitre present	N (%)	8 (73)	34 (71)	0.8674
Goitre absent	N (%)	3 (27)	12 (29)	
Increase of LT4 dose	N (%)	14 (64)	41 (38)	0.0336
Either Goitre or TPO +	N (%)	11 (79)	39 (95)	0.0982
No Goitre and TPO	N (%)	3 (21)	2 (5)	
Another pregnancy	N (%)	3 (14)	5 (5)	0.1334
Postpartum thyroiditis	N (%)	1 (5)	7 (7)	1.0000
Final LT4 dose	µg/day	104.8 (14.5)	51.6 (10.5)	<0.001

*Mean (S.D)

of 13.1 ± 4.8 at the time of diagnosis. Out of the 130 patients, a total of 22 and 108 patients had OH and SCH respectively. The details of the TPO antibody, goitre and other relevant parameters between the two groups is shown in Table 2. Goitre and TPO positivity are observed in about half of the study population in both the groups. The dose of LT4 was increased in 14/22 patients and 41/108 patients with OH and SCH respectively ($P=0.0336$). More than 90% of the patients with an increase in the LT4 dose, had either a goitre or TPO antibody positivity. The postpartum thyroiditis (PPT) was seen in both the groups with similar frequency and these patients were stopped with the LT4 for the duration of thyrotoxic phase. About 6 patients with PPT required the thyroid hormone replacement therapy after the phase of thyrotoxicosis due to OH. A total of 8 patients became pregnant again during the observed period. All of them increased their LT4 dose by 25% from the baseline as per the education received during the preconception counselling sessions.

DISCUSSION

The clinical strategy of decreasing the LT4 dose after delivery is always confusing with multiple factors. We have used a simple protocol in our department and evaluated the clinical records of the patients for the usefulness of this strategy. Our study results highlight certain important issues in the levothyroxine dose modification after delivery. Firstly, the reduction of LT4 dose to half of the pregnancy dose results in suboptimal control and majority of them required up titration during follow up. The expert recommendation is to reduce the dose to two-thirds of

the final dose used in the pregnancy.^[14] Secondly, patients with either goitre or TPO antibody had increased LT4 requirement irrespective of the initial diagnosis (OH or SCH). The presence of AITD indicates an ongoing immune mediated destruction of the thyroid follicles and patients may require a higher LT4 dose in these patients.^[15] Thirdly, repeat pregnancy is another major cause of the increased LT4 requirement in our study population. Though the evidence of benefit in continuing LT4 after pregnancy is limited, it is based on the logic and the scientific rationale. Such a strategy ensures follow up of the patients besides reducing the morbidity associated with delayed diagnosis of hypothyroidism. This is relevant in our country, where unplanned pregnancies are common which are often masked by the lactational amenorrhea (or LAM) in postpartum state.^[16]

The guidelines from the learned societies gave conflicting recommendations with regard to the management of the SCH during pregnancy.^[2-6] In general, the endocrine societies recommend LT4 therapy for both OH and SCH, whereas the gynaecological societies do not recommend therapy for SCH patients. The issue becomes even more complicated in the postpartum period and the guidelines are often silent on this issue due to lack of prospective studies addressing this question. The current recommendations are based on the expert opinion keeping in view of the known risk factors that affect the progression of hypothyroidism.^[14] These include higher initial TSH, presence of goitre and positive anti TPO antibodies. The continuation of LT4 therapy is also based on the understanding that these women are at a higher risk of

progression to OH due to altered immunoregulatory network in the puerperium phase.^[17]

The prevalence of PPT varies between 1-15% and the risk is increased with the presence of TPO antibodies and previous history.^[18] Our study showed a prevalence rate of 6.2% (8 out of 130) and all of them showed a thyrotoxic phase necessitating the LT4 withdrawal. The six patients with PPT who developed OH during follow up had both goitre and positive TPO antibodies. PPT has a classical triphasic course with hyperthyroidism, hypothyroidism and euthyroidism. This condition should always be considered during the postpartum management of hypothyroidism, especially when the TFT results don't match with the clinical picture. The strengths of our study include the sizeable number of participants with an appreciable duration of follow up. However, the limitations are the retrospective design and data being derived from a single centre that may not be relevant in other geographical areas. A statistical limitation of our study is the inability to perform the multivariate regression analysis in order to identify the factors responsible for the increasing LT4 dose requirement.

In conclusion, we suggest individualization of LT4 therapy after pregnancy in women who were diagnosed with hypothyroidism during pregnancy. The important determinants are the initial diagnosis (OH or SCH), dose required during pregnancy to maintain euthyroidism, goitre, TPO antibody and a repeat pregnancy. Further prospective studies are required to evaluate the ideal protocol of LT4 dose modification after delivery in patients with hypothyroidism.

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Conflicts of interest

There are no conflicts of interest.

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