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Postpartum thyroid function following LT4 treatment from infertility treatment to delivery in women with subclinical hypothyroidism or high-normal TSH: a retrospective study

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Abstract

Background Levothyroxine (LT4) therapy is commonly initiated in women undergoing infertility treatment who have high-normal thyroid-stimulating hormone (TSH) levels (HN) or subclinical hypothyroidism (SCH). However, there are no clear postpartum management guidelines for these patients.

Methods We retrospectively analyzed 155 women (56 with HN, 99 with SCH) who initiated LT4 therapy during infertility treatment, discontinued it immediately after delivery, and underwent TSH measurement within 6 months postpartum. We evaluated postpartum TSH levels and their association with pre-treatment TSH, LT4 dose at delivery, thyroid volume, body weight, and thyroid autoantibodies. Receiver operating characteristic (ROC) curve analysis was performed to predict postpartum SCH.

Results Postpartum TSH levels were significantly lower than pre-treatment levels (median 2.57 vs. 4.30 mIU/L, $p < 0.001$). TSH remained within the reference range in 78% of participants, while 15.7% had SCH and 6.3% had thyrotoxicosis. Higher pre-treatment TSH and higher LT4 dose at delivery were significantly associated with postpartum SCH ($p < 0.001$ for both). ROC analysis identified cutoff values of 4.82 mIU/L for pre-treatment TSH (area under the curve [AUC] = 0.785) and 71.4 µg/day for LT4 dose (AUC = 0.753). Postpartum thyrotoxicosis occurred in 6.3% of participants, all of whom were antibody-positive. Only two women required LT4 resumption after one year postpartum due to TSH ≥ 10 mIU/L.

Conclusions For women with HN or SCH who initiated LT4 therapy during infertility treatment, immediate discontinuation of LT4 after delivery appears generally safe. Nevertheless, postpartum thyroid function should be closely monitored, particularly in antibody-positive patients or those with elevated pre-treatment TSH.

Keywords Infertility treatment, Subclinical hypothyroidism, High-normal TSH, Levothyroxine therapy, Postpartum thyroid function

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Background

Elevated serum TSH is observed in 2–3% [1, 2] of healthy, nonpregnant women of reproductive age, with a similar prevalence (2.3%) [3] reported in infertile women. The association between SCH and adverse pregnancy outcomes remains inconclusive due to heterogeneous TSH thresholds and variable consideration of TPOAb status. Nevertheless, levothyroxine (LT4) therapy is widely administered to women undergoing infertility treatment who are diagnosed with high-normal thyroid-stimulating hormone (TSH) levels (HN) or have subclinical hypothyroidism (SCH), as low-dose LT4 is safe and commonly used to prevent progression to overt hypothyroidism during pregnancy. According to the 2017 American Thyroid Association guidelines [4], in pregnant women treated with LT4 for hypothyroidism, it is recommended to revert the LT4 dose to the pre-pregnancy level after delivery. For those who initiated LT4 therapy during pregnancy, especially at doses ≤ 50 μg/day, discontinuation postpartum and reevaluation of TSH approximately six weeks later are advised. However, no clear guidelines exist for patients who began LT4 therapy for HN or SCH during infertility treatment, and post-delivery management often relies on individual physician judgment.

Therefore, this study aimed to examine whether LT4 therapy should be continued postpartum in women with HN or SCH who started LT4 after beginning infertility treatment, based on postpartum TSH levels.

Methods

Study design and participants

This study was a single-center retrospective analysis of electronic medical records. Among 1,703 women referred to Okamoto Thyroid Clinic from assisted reproductive technology facilities between January 2019 and December 2021, we selected 155 patients (56 with HN, 99 with SCH; 159 deliveries) who met the inclusion criteria: initiation of LT4 therapy for previously untreated HN (TSH 2.5–4.0 mIU/L) or SCH (TSH > 4.0 mIU/L), discontinued LT4 immediately after delivery, and had TSH measured within six months postpartum. A total of 159 deliveries were included, as four patients had two separate deliveries meeting the inclusion criteria during the study period. Patients with FT4 values below our institution's reference range (9.1–21.8 pmol/L) were classified as having overt hypothyroidism and excluded from the study. LT4 treatment was initiated at a dose of 1.0 μg/kg/day, using a combination of 12.5 μg to 100 μg tablets adjusted to the required dosage. The dosage was subsequently adjusted to maintain serum TSH levels within the range of 0.5–2.5 mIU/L. We examined the relationship between postpartum TSH and pre-treatment TSH, body weight at the first visit, thyroid volume, presence of anti-thyroglobulin antibody (TgAb) and anti-thyroid peroxidase antibody (TPOAb), and LT4 dose immediately before delivery.

Thyroid function testing and statistical analysis

Free T4 (9.1–21.8 pmol/L), TSH (0.41–4.0 mIU/L), TgAb (< 5 U/mL), and TPOAb (< 3 U/mL) were measured using AIA-Pack CL® reagents (Tosoh Corporation, Tokyo, Japan). Serum samples were analyzed immediately following collection according to our institution's standard clinical laboratory procedures; no long-term storage was performed before analyzing. Thyroid volume (mL) was calculated using ellipsoid approximation based on ultrasound measurements. Ultrasound examinations were performed with an Aplio 400 system (Canon Medical Systems). The volume of each thyroid lobe was calculated as length×width×depth×0.7, and total thyroid volume was calculated by summing the volumes of the right and left lobes. Data are presented as median (interquartile range). The Wilcoxon signed rank test was used for paired comparisons, the Mann–Whitney U test for comparisons between two groups, the Kruskal–Wallis test for comparisons among three or more groups, and Fisher's exact test for contingency tables. A p-value < 0.05 was considered statistically significant. All analyses were performed using EZR software [5]. This study was approved by the Ethics Committee of Okamoto Thyroid Clinic (Clinical trial number: 2024002).

Results

Patient characteristics

At baseline, the median age was 36 years (32–38.25) in the HN group and 34 years (33–38) in the SCH group ($p = 0.463$). The median weight was 54 kg (49.75–58.25) in HN and 51 kg (47.0–57.0) in SCH ($p = 0.108$), and the median thyroid volume was 12.1 mL (9.40–14.20) in HN and 12.2 mL (9.45–14.05) in SCH ($p = 0.963$). TgAb and/or TPOAb positivity was observed in 30 HN patients (53.6%) and 42 SCH patients (42.4%) ($p = 0.241$). LT4 doses before delivery were < 50 μg/day in 36 deliveries, 50–74 μg/day in 82, 75–99 μg/day in 32, and ≥ 100 μg/day in 9.

Association between pre-treatment TSH and postpartum TSH

The median pre-treatment TSH level was 4.30 mIU/L (3.60–5.65). Postpartum TSH measured within six months (in 91.3% of cases at 2–3 months), excluding 10 cases of thyrotoxicosis, was significantly lower at 2.57 mIU/L (1.96–3.44) ($p < 0.001$), with a maximum postpartum TSH of 9.17 mIU/L (Fig. 1).

TSH remained within the reference range in 78%, elevated (SCH) in 15.7%, and suppressed (thyrotoxicosis) in 6.3%. When a ± 20% change from baseline TSH

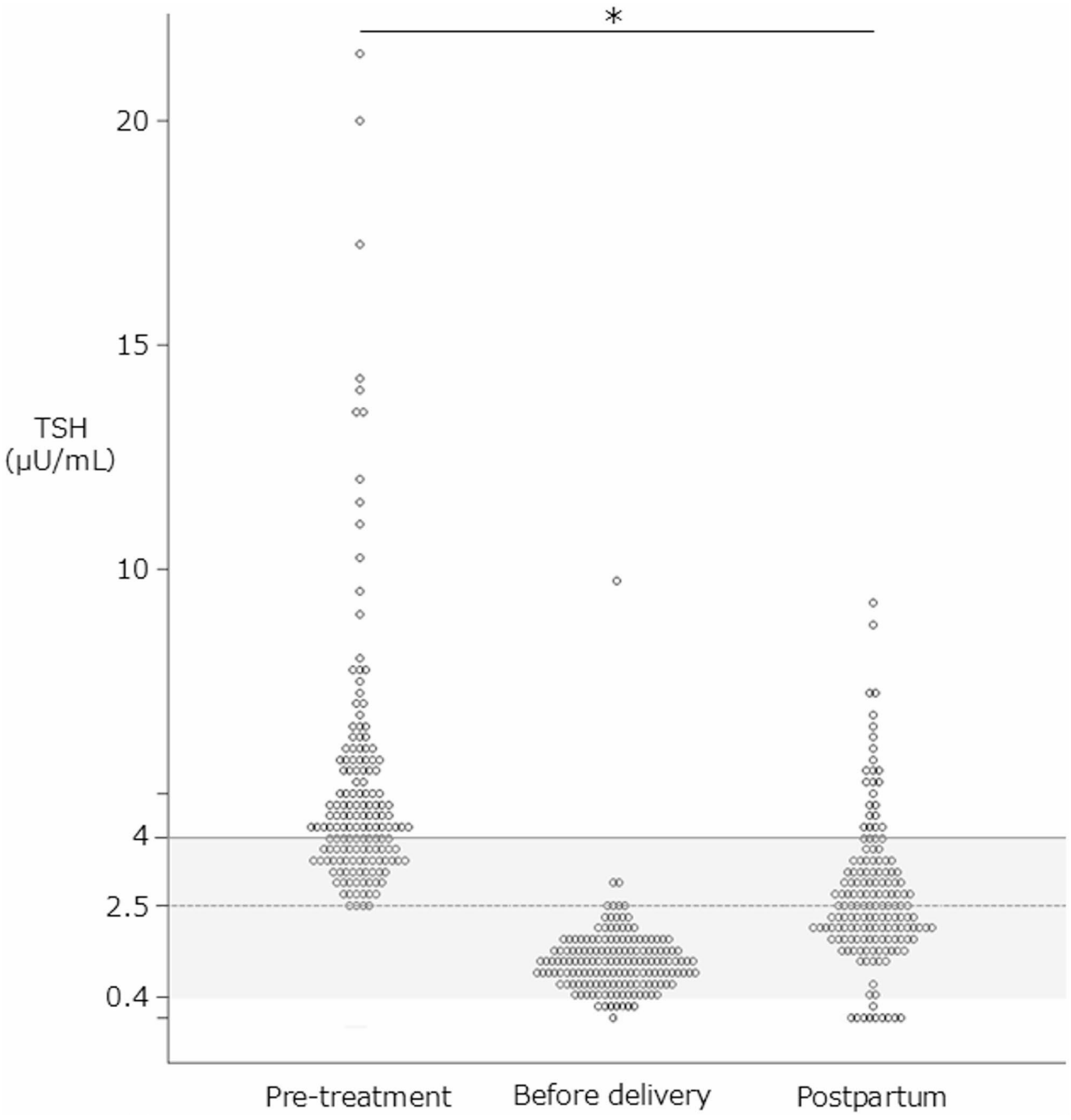

Fig. 1 Trends in TSH Levels at Pre-Treatment, Before Delivery, and Postpartum ($n = 159$). LT4 therapy was discontinued immediately after delivery, and TSH levels were measured within six months postpartum. The shaded area indicates the reference range (0.4–4.0 mIU/L). TSH significantly decreased postpartum (*$p < 0.001$), as calculated by the Wilcoxon signed rank test, excluding 10 postpartum thyrotoxicosis cases.

was considered "unchanged," TSH decreased in 76.6%, remained unchanged in 19.3%, and increased in 4.1%. Table 1 shows factors associated with elevated postpartum TSH (>4.0 mIU/L). Patients with elevated postpartum TSH had significantly higher pre-treatment TSH ($p < 0.001$) and higher LT4 doses before delivery ($p < 0.001$). No significant differences were observed in baseline body weight, thyroid volume, or antibody status. Multivariate logistic regression analysis identified pre-treatment TSH levels (OR = 1.21, 95% CI: 1.05–1.39, $P = 0.0077$) and LT4 dose before delivery (OR = 1.04, 95% CI: 1.02–1.07, $P = 0.0017$) as independent predictors of subclinical hypothyroidism after LT4 withdrawal in the postpartum period.

Table 1 Comparison of patient characteristics according to postpartum TSH levels ($n = 149$)

Variable	Postpartum TSH 0.4–4.0 mIU/L ($n = 124$)	Postpartum TSH > 4.0 mIU/L ($n = 25$)	*p*-value
Pre-treatment TSH (mIU/L)	4.22 (3.56–5.10)	6.04 (4.86–8.03)	< 0.001
Body weight at first visit (kg)	52.9 (48.0–57.0)	51.6 (47.0–58.0)	0.665
Thyroid volume (mL)	12.1 (9.6–13.9)	10.4 (8.6–12.7)	0.142
TgAb and/or TPOAb positive [n (%)]	54 (43.5%)	9 (36.0%)	0.515
LT4 dose before delivery (μg/day)	50 (50–62.9)	75 (62.5–87.5)	< 0.001

Ten cases that developed postpartum thyrotoxicosis were excluded from the comparison. Values (except for antibody positivity) are expressed as median (interquartile range). Comparisons were performed using the Mann–Whitney U test. Antibody positivity was analyzed using Fisher's exact test.

Table 2 Association between LT4 dose before delivery and patient characteristics ($n = 159$)

Variable	LT4 < 50 μg/day ($n = 36$)	50 ≤ LT4 < 75 μg/day ($n = 82$)	75 ≤ LT4 < 100 μg/day ($n = 32$)	LT4 ≥ 100 μg/day ($n = 9$)	*p*-value
Pre-treatment TSH (mIU/L)	3.66 (3.29–4.47)	4.32 (3.71–5.50)	4.98 (4.18–7.40)	4.87 (3.76–6.41)	< 0.001
Body weight at first visit (kg)	50.5 (48.8–56.0)	52.5 (48.0–57.8)	51.5 (46.7–58.0)	54.0 (51.6–56.0)	0.747
Thyroid volume (mL)	11.55 (8.78–14.88)	12.20 (9.15–14.28)	12.40 (9.90–13.75)	11.40 (10.60–12.80)	0.955
TgAb and/or TPOAb positive [n (%)]	17 (47.2%)	36 (43.9%)	15 (46.9%)	5 (55.6%)	0.919
TSH before delivery (mIU/L)	1.09 (0.67–1.45)	1.26 (0.90–1.62)	1.17 (0.84–1.87)	1.30 (1.11–1.52)	0.435

Values (except for antibody positivity) are expressed as median (interquartile range). Comparisons were performed using the Kruskal–Wallis test. Antibody positivity was analyzed using Fisher's exact test.

Factors influencing LT4 dose at delivery

We further analyzed factors influencing LT4 dose at delivery by dividing patients into four groups: <50, 50–74, 75–99, and ≥ 100 μg/day (Table 2). Higher LT4 doses were associated with significantly higher pre-treatment TSH ($p < 0.001$). No significant differences were observed among the four groups in baseline body weight, thyroid volume, antibody positivity, or TSH before delivery.

Prediction of postpartum TSH

ROC curve analysis for predicting postpartum SCH using pre-treatment TSH and LT4 dose before delivery revealed cutoff values of 4.82 mIU/L (AUC = 0.785) for pre-treatment TSH and 71.4 μg/day (AUC = 0.753) for LT4 dose (Fig. 2).

Postpartum thyrotoxicosis

Postpartum thyrotoxicosis was observed in 10 of 159 deliveries (6.3%), all of whom were antibody-positive. Of these, 9 had postpartum thyroiditis (PPT) and 1 had Graves' disease. Among 72 antibody-positive patients, the incidence of PPT was 12.5%.

Discussion

In this retrospective study, we evaluated postpartum TSH levels and various factors in women with HN or SCH who initiated LT4 therapy after beginning infertility treatment and discontinued it immediately after delivery. Patients with TSH ≥ 10 mIU/L were included in this study, as per the Japanese guidelines on thyroid function classification, which categorize such cases as SCH when FT4 remains within the normal range. This inclusion strengthens the study's real-world applicability and allows for findings that align with established practices in Japan. The postpartum TSH level was significantly lower than the pre-treatment value, and 78% of patients remained within the reference range. Notably, even among those with pre-treatment TSH ≥ 10 mIU/L ($n = 11$), 5 had normal postpartum TSH and 6 had SCH. Among those receiving ≥ 100 μg/day LT4 before delivery ($n = 9$), 5 had normal postpartum TSH and 4 had SCH. All SCH cases had TSH levels that remained under 10 mIU/L, suggesting none required immediate resumption of LT4 [6].

In this study, both pre-treatment TSH levels (OR = 1.21) and LT4 dose before delivery (OR = 1.04) were identified as statistically significant independent predictors of SCH after LT4 withdrawal in the postpartum period. While these factors were significantly associated with an increased risk, the effect sizes were modest and clinically anticipated. More importantly, most cases of SCH observed after LT4 discontinuation were mild and did not require immediate treatment. This suggests that although certain baseline characteristics may be associated with a higher likelihood of postpartum thyroid dysfunction, the clinical impact remains limited in most patients. Given these findings, it may be reasonable to discontinue LT4 therapy after delivery in women with HN or SCH TSH levels undergoing infertility treatment, regardless of pre-treatment TSH levels or LT4 dose before delivery, provided that careful follow-up is ensured. Close monitoring of thyroid function in the postpartum period remains essential to detect any cases that may eventually require treatment.

The significant decrease in postpartum TSH levels may be attributed to physiological changes in the thyroid during pregnancy, such as stimulation by human chorionic gonadotropin. In a prospective study [7] of 118

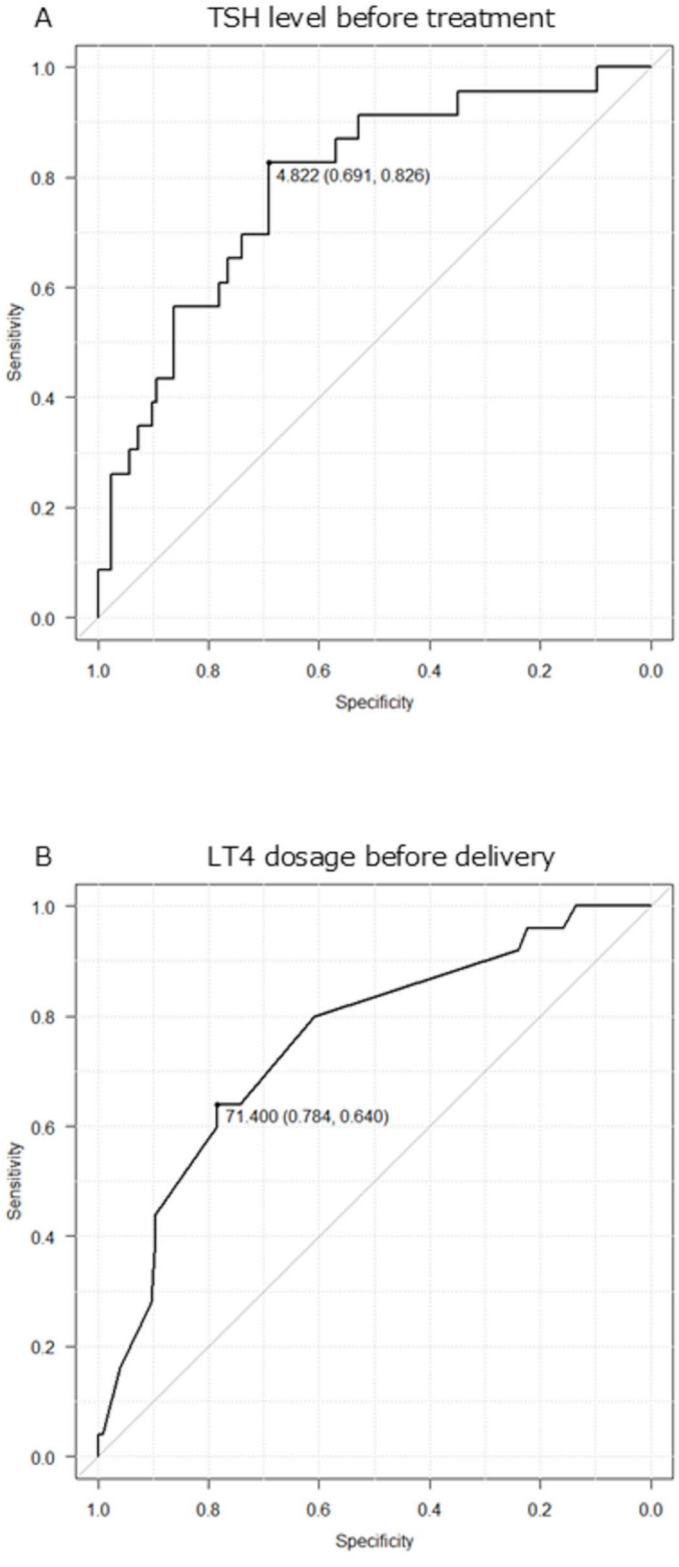

Fig. 2 ROC Curve Analyses for Predicting Postpartum SCH ($n = 149$). (**A**) The area under the curve (AUC) for pre-treatment TSH was 0.79 (cutoff, 4.82 mIU/L). (**B**) The AUC for LT4 dose before delivery was 0.75 (cutoff, 71.4 μg/day). Ten cases that developed postpartum thyrotoxicosis were excluded from the analyses.

healthy pregnant women in iodine-sufficient Slovenia, thyroid volume increased during pregnancy (first trimester: 8.7 ± 2.5 mL; third trimester: 11.3 ± 3.1 mL) and then decreased postpartum (4 months: 8.6 ± 2.5 mL; 14 months: 7.8 ± 2.4 mL). Using the 14-month postpartum volume as a nonpregnant reference suggests that the thyroid gland enlarges during pregnancy to meet elevated hormone demands and remains enlarged until at least 4 months postpartum. These findings imply that thyroid hormone secretion may stay elevated even after delivery.

A systematic review by Nicholson et al. [8] reported that PPT prevalence ranges from 0.9 to 11.7% (average 8.1%) in the general population, and as high as 33–50% in antibody-positive women [9]. In our study, PPT occurred in 6.3% of all participants and in 12.5% of antibody-positive patients evaluated at 2–3 months postpartum, supporting the rationale for discontinuing LT4 immediately after delivery.

Regarding long-term thyroid function, among 68 of the 155 patients evaluated at least one year postpartum in a non-pregnant state, TSH remained significantly lower than pre-treatment levels. Specifically, the median baseline TSH was 4.22 mIU/L (3.39–4.88), while the median TSH at ≥ 1 year postpartum was 3.07 mIU/L (2.33–4.52) ($p < 0.001$). Only two patients (both antibody-positive) required resumption of LT4 due to TSH ≥ 10 mIU/L. Although baseline and 2-month postpartum TSH levels were not particularly distinctive (4.92 and 8.03 mIU/L at baseline; 3.05 and 5.24 mIU/L at 2-2.5 months postpartum), both individuals exhibited TSH elevations above 10 mIU/L (18.66 and 13.37 mIU/L) at least one year postpartum, requiring LT4 resumption. Due to the small sample size ($n = 2$), no definitive factors could be identified, though autoantibody positivity may be a contributing factor.

This study has several limitations. First, it was a retrospective, single-center analysis, which may introduce selection and information bias. Although the patient population was relatively homogeneous, the generalizability of our findings to other populations or regions with different iodine intake or healthcare systems may be limited. In addition, because of the retrospective design, no prior sample size calculation was performed; all cases meeting the inclusion criteria during the study period were included. Second, there was no comparison group of women who continued LT4 therapy postpartum. Therefore, we could not directly compare the risks and benefits of discontinuation versus the continuation of LT4 after delivery. Third, although we observed postpartum SCH recurrence in some women, the clinical impact was relatively mild in most cases, and only two patients required reinitiation of LT4 therapy for TSH levels above 10 mIU/L. This may limit the strength of our conclusions regarding the necessity of postpartum LT4 management.

Prospective studies are warranted to clarify the immunological factors and dynamic thyroid hormone requirements in women who experience subsequent pregnancies or develop evolving autoimmune features [10]. Identifying markers predictive of the need for LT4 re-initiation, particularly in antibody-positive patients, may further optimize postpartum thyroid management.

Conclusions

For women diagnosed with HN or SCH who began LT4 therapy during infertility treatment, discontinuation of LT4 immediately after delivery appears to be a safe approach, provided that postpartum thyroid function is monitored, especially in patients who are antibody-positive or present with high pre-treatment TSH levels.

This study was presented at the 67th Annual Meeting of the Japan Thyroid Association (October 4, 2024, Yokohama, Japan).

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Author contributions
Y.T.: Writing-original draft, resources, investigation, data curation, conceptualization. Y.H.: resources, writing-review & editing. Y.F.: resources, Y.W.: resources. K.O.: resources. Y.O.: writing-review & editing, conceptualization, project administration. All authors reviewed the manuscript.

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Data availability
The data that support the findings of this study are available from the corresponding author, YT, upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethical Committee of Okamoto Thyroid Clinic (Clinical Trial Number: 2024002). In accordance with the ethical guidelines established by the Japanese government ("Ethical Guidelines for Medical and Biological Research Involving Human Subjects") (https://www.mhlw.go.jp/content/001457376.pdf), written informed consent was waived based on the opt-out method. Under these guidelines, written informed consent is not required for studies involving retrospective analyses of anonymized patient data, provided that appropriate opt-out procedures are implemented. None of the subjects opted out of participation. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References
1. Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W. Leveno KJ, cunningham. Subclinical hypothy-roidism and pregnancy outcomes. Obstetrics& Gynecol. 2005;105:239–245260.

2. Allan WC, Haddow JE, Palomaki GE, Williams JR, Mitchell ML, Hermos RJ, Faix JD, Klein RZ. Ma-ternal thyroid deficiency and pregnancy complications:implications for population screening. J Med Screen. 2007;7:127–30.
3. Lincoln SR, Ke RW, Kutteh WH. 1999 Screening for hypo-thyroidism in infertile women. The Journal of Reproductive Medicine. 1999; 44:455–457.
4. Alexander EK, Pearce EN, Brent GA, Brown RS, CheHN, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, Peeters RP, Sullivan S. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid. 2017;27(3):315–389. https://doi.org/10.1089/thy.2016.0457. Erratum in: Thyroid. 2017;27(9):1212. doi: 10.1089/thy.2016.0457.correx.
5. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transpl. 2013;48(3):452–8. https://doi.org/10.1038/bmt.2012.244.
6. Bekkering GE, Agoritsas T, Lytvyn L, Heen AF, Feller M, Moutzouri E, Abdulazeem H, Aertgeerts B, Beecher D, Brito JP, Farhoumand PD, Singh Ospina N, Rodondi N, van Driel M, Wallace E, Snel M, Okwen PM, Siemieniuk R, Vandvik PO, Kuijpers T, Vermandere M. Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. BMJ. 2019;365:l2006. https://doi.org/10.1136/bmj.l2006. PMID:31088853.
7. Fister P, Gaberscek S, Zaletel K, Krhin B, Gersak K, Hojker S. Thyroid volume changes during pregnancy and after delivery in an iodine-sufficient Republic of Slovenia. Eur J Obstet Gynecol Reprod Biol. 2009;145(1):45–8. https://doi.org/10.1016/j.ejogrb.2009.03.022.
8. Nicholson WK, Robinson KA, Smallridge RC, Ladenson PW, Powe NR. Prevalence of postpartum thyroid dysfunction: a quantitative review. Thyroid. 2006;16(6):573–82. https://doi.org/10.1089/thy.2006.16.573.
9. Smallridge RC. Postpartum thyroid disease: a model of Immunologic dysfunction. Clin Appl Immunol Rev. 2000;1(2):89–103. https://doi.org/10.1016/S1529-1049(00)00012-5.
10. Korevaar TIM, Medici M, Visser TJ, Peeters RP. Thyroid disease in pregnancy: new insights in diagnosis and clinical management. Nat Rev Endocrinol. 2017;13(10):610–22. https://doi.org/10.1038/nrendo.2017.93.

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