The magnitude of increased Levothyroxine dose during pregnancy in patients on thyroid-stimulating hormone (TSH) suppression treatment after total thyroidectomy for papillary carcinoma

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Abstract. The dose of L-T₄ replacement for hypothyroidism often needs to be increased after pregnancy. In our institution, patients are instructed to double the dose 2 days a week after pregnancy. However, there is scarce evidence supporting the need for a dose increase after pregnancy in patients with preconception thyroid-stimulating hormone (TSH) suppression (TSH <0.3 μ IU/mL). This study aimed to determine the need for a dose increase in L-T₄ among women with a TSH-suppressive dose of L-T₄ before pregnancy. In this retrospective observational study, between January 2008 and December 2018, we analyzed 166 pregnancies in 134 patients on TSH suppression treatment after total thyroidectomy for papillary carcinoma. Thyroid function tests were performed before and in the first trimester of pregnancy. The dose was adjusted and maintained during the first trimester of pregnancy in 76 pregnancies (group A) and 90 pregnancies (group B), respectively. The median serum TSH level was significantly lower in group A than that in group B (0.014 μ IU/mL (IQR, 0.005–0.071) vs. 0.155 μ IU/mL (IQR, 0.021–0.657), $p < 0.001$). TSH suppression could not be maintained after pregnancy in 15.8% and 38.9% of the pregnancies in groups A and B, respectively. Increasing the post-pregnancy dose by an average of 27.4% resulted in maintenance of TSH suppression after pregnancy in 84.2% of pregnancies. In conclusion, this study suggests that increasing the L-T₄ dose after pregnancy may be appropriate in postoperative thyroid cancer patients whose serum TSH levels should be suppressed.

Key words: Thyroid-stimulating hormone suppression, Pregnancy, Papillary carcinoma, Levothyroxine

THYROID HORMONES are important for normal pregnancy and fetal development [1, 2]. During pregnancy, maternal thyroid hormone requirements increase [3, 4]. Reference levels of TSH, free T₄ (FT₄) and free T₃ (FT₃) differ between pregnant and non-pregnant populations. The National Health and Nutrition Examination Survey (NHANES) database, a cross-sectional ongoing study, determined trimester-specific means and medians for TSH levels in the U.S. population. In this survey, mean TSH levels were 0.91, 1.03, and 1.32 μ IU/mL, in each trimester, respectively. Panesar *et al.* reported trimester-specific TSH reference ranges of the population

without history of thyroid disease were 0.03–2.3 μ IU/mL in the first trimester, 0.03–3.1 μ IU/mL in the second trimester, 0.13–3.4 μ IU/mL in the third trimester [5]. Although the downward shift in TSH reference range is seen in essentially all populations, the extent of this reduction varies significantly between racial and ethnic groups. In a small percentage of women, the TSH can be undetectable (<0.01 μ IU/mL) but still represent a normal pregnancy. Subclinical hyperthyroidism has not been associated with adverse pregnancy outcomes. A maternal TSH concentration that is low but detectable is likely not clinically significant [6].

Athyroid patients after total thyroidectomy are dependent on exogenous L-thyroxine (L-T₄). The magnitude of increased L-T₄ requirements in hypothyroid pregnant women depends upon the etiology of the hypothyroidism [7]. However, the appropriate timing for the dose increase is still unclear. Some authors argue that

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L-T₄ dose increases during pregnancy should be determined from thyroid function test results, while others suggest increasing the dose as soon as pregnancy is confirmed [8, 9]. There are no reports directly comparing pregnancy outcomes between these two methods of dose escalation. In addition, there are few studies of pregnancy in postoperative thyroid cancer patients on TSH suppression therapy. Krhin *et al.* reported 36 cases of pregnancy after total thyroidectomy for thyroid cancer [10]. They evaluated patients who had received a TSH-suppressive dose of L-T₄ prior to pregnancy and adjusted their medications to maintain serum TSH levels below 0.3 μ IU/mL by checking blood test every 6 to 8 weeks. Serum TSH levels were adequately suppressed in only 25% of the pregnancies, and the ranges of changes in TSH concentrations during pregnancy varied widely. This study aimed to determine (1) whether there is a need to increase the L-T₄ dose after pregnancy to prevent TSH elevation among postoperative thyroid cancer women who are on TSH suppression prior to pregnancy and (2) the extent of dose increase after pregnancy.

Materials and Methods

Study design and patients

This retrospective observational study analyzed 166 pregnancies in 134 patients on L-T₄ after total thyroidectomy for papillary carcinoma at Kuma Hospital. The patients were selected from those who visited the hospital during their pregnancy between 2008 and 2018. Eligible patients were identified through a search of the computerized medical record system, and only those who were followed for postoperative hypothyroidism prior to pregnancy and were on a TSH-suppressive dose of L-T₄ before pregnancy were included. The preconception goal for TSH was less than 0.3 μ IU/mL in the absence of recurrence based upon imaging studies and stimulated thyroglobulin levels. Some patients were instructed in advance to self-titrate their L-T₄ to double their dose 2 days a week after pregnancy. Meanwhile, the dose was only adjusted in some patients after their serum TSH levels were checked at the time of pregnancy visits. In either case, patients came to the hospital for consultation in the first trimester of pregnancy and continued to have regular visits during pregnancy and after childbirth. Thyroid function tests were performed before and during pregnancy.

The patients were divided into two groups based on whether they self-adjusted their L-T₄ dose in the early pregnancy period (group A) or not (group B). Specifically, group A involved patients who self-increased their dose before they first visit to the hospital in the first trimester of pregnancy. Meanwhile, group B involved

patients who maintained their dose before consultation. In each group, the L-T₄ dose was adjusted individually to maintain the serum TSH below 0.3 μ IU/mL during pregnancy.

We evaluated thyroid function in the first trimester of pregnancy and L-T₄ dose change in both groups. Percent increases in L-T₄ dose were calculated as cumulative increases from baseline.

This study was reviewed and approved by the Ethical Committee at Kuma Hospital (the approval number 20200709-1), and all patients gave written informed consent.

Serum hormone measurements

All blood samples for all hormone levels were obtained at Kuma Hospital. TSH, FT₄ and FT₃ levels were measured using chemiluminescent immunoassays with ARCHITECT i2000SR (Abbott, Japan) (normal range: TSH, 0.3–5.0 μ IU/mL; FT₄, 0.7–1.6 ng/dL; and FT₃, 1.7–3.7 pg/mL).

Statistical analysis

Data in both groups were not-normally distributed, and thus the Mann-Whitney *U* test was used for between-group comparisons. L-T₄ dose changes throughout the pregnancy in each group were analyzed using the Wilcoxon signed rank test. All statistical analyses were performed using the Excel statistical software package (BellCurve for Excel; Social Survey Research Information Co., Ltd. Tokyo, Japan). A *p*-value of <0.05 was considered statistically significant.

Results

In total, 107 patients were followed through one pregnancy; 23 patients, two pregnancies; 3 patients, three pregnancies; and 1 patient, four pregnancies. The mean patient age was 32.7 years (range, 19–43 years). At the point of pregnancy, three patients had lung metastasis and three patients had mediastinal or cervical lymph node metastasis. However, there was no evidence of progression during pregnancy by thyroid ultrasonography or serum thyroglobulin levels.

Groups A and B involved 76 and 90 pregnancies, respectively. There was no significant between-group difference with respect to the maternal age, pre-pregnancy L-T₄ dose, and serum TSH level (Table 1). Only the serum FT₃ level was higher in group B. Table 2 shows the gestational weeks; L-T₄ dose before consultation; L-T₄ dose instructed by the individual practitioners at consultation; the serum TSH, FT₄ and FT₃ levels in the first trimester of pregnancy; and L-T₄ dose at delivery.

Among 42 pregnancies in Group A, the median

Table 1 Baseline characteristics of the patients

Characteristics	Group A (n = 76)	Group B (n = 90)	p value
Age (years)	33 (30–37)	31 (29–35)	0.06
Baseline L-T ₄ dose (µg/day)	125 (100–128)	125 (100–134)	0.7
Baseline TSH level (µIU/mL)	0.025 (0.009–0.062)	0.028 (0.011–0.099)	0.7
Baseline FT ₄ level (ng/dL)	1.44 (1.33–1.54)	1.44 (1.34–1.58)	0.5
Baseline FT ₃ level (pg/mL)	2.77 (2.52–2.95)	2.91 (2.71–3.16)	0.02
Radioiodine ablation			
Treated (n)/untreated (n)	14/62	21/69	0.3

Statistical significance was analysed using the χ^2 test (radioiodine treatment), unpaired *t*-test, or *Mann–Whitney *U* test. Values are expressed as the median (IQR).

Table 2 Adequacy of L-T₄ dose and thyroid function at the time of consultation in the first trimester of pregnancy

	Group A (n = 76)	Group B (n = 90)	p value
Pregnancy weeks in the first trimester (week)	7 (6–9)	6 (5–8)	<0.001
L-T ₄ dose before consultation (µg/day)	161 (129–165)	125 (100–134)	<0.001
L-T ₄ dose after consultation (µg/day)	150 (129–161)	129 (125–158)	<0.001
Changes in L-T ₄ dose before and after consultation (n, %)			
increase	7 (9)	53 (59)	
same dose	48 (63)	36 (40)	
decrease	21 (27)	1 (1)	
TSH levels in the first trimester (µIU/mL)	0.014 (0.005–0.071) *	0.155 (0.021–0.657)	<0.001
TSH <0.003 (n, %)	8 (10.5)	2 (2.2)	
TSH >0.3 (n, %)	12 (15.8)	35 (38.9)	
TSH >2.5 (n, %)	0 (0)	11 (12.2)	
FT ₄ level in the first trimester (µIU/mL)	1.53 (1.41–1.67)	1.33 (1.19–1.51)	<0.001
FT ₃ level in the first trimester (pg/mL)	2.70 (2.51–3.00)	2.64 (2.45–2.82)	0.2
L-T ₄ dose at the time of delivery (µg/day)	150 (129–162)	150 (125–161)	0.03

Statistical significance was analyzed using the unpaired *t*-test, or Mann–Whitney *U* test. Values are expressed as median (IQR). *In 42 pregnancies in group A, we were able to identify how many days after self-increasing L-T₄ dose patients visited the hospital, with a median of 18 days (IQR, 10–30 days).

number of days from self-increasing L-T₄ dose by patients to hospital visit was 18 days (IQR, 10–30 days). Patients in group B visited the hospital earlier than in group A during the first trimester of pregnancy ($p < 0.001$). At the time of consultation, patients in group B had significantly lower L-T₄ dose ($p < 0.001$), higher serum TSH levels ($p < 0.001$), and lower serum FT₄ levels ($p < 0.001$) than those in group A.

The L-T₄ dose of all patients was adjusted by their attending physician in the first trimester of pregnancy and increased if TSH suppression was not maintained at the time of the visit, or TSH suppression was maintained at a very mild degree. In group A, the dose was decreased in 21 pregnancies and increased in 7. In group B, the dose was decreased in 1 pregnancy and increased in 53 pregnancies. The dose in group A was reduced

because 12 of 21 patients had serum FT₄ level >1.6 ng/dL at the time of visit and were judged to have excessive doses. The convenience of medication administration was considered in the remaining 9 pregnancies. TSH suppression therapy was unsuccessful in the first trimester of pregnancy in 12 (15.8%) pregnancies in group A and 35 (38.9%) pregnancies in group B.

The changes in serum TSH, FT₄, and FT₃ levels before pregnancy and in the first trimester in each group are presented in Figs. 1 and 2. Group A showed no significant difference in serum TSH levels between before and during the first trimester of pregnancy ($p = 0.4$). The serum FT₄ and FT₃ levels were slightly elevated in the first trimester of pregnancy ($p < 0.001$, $p = 0.006$, respectively). Meanwhile, the serum TSH levels were significantly higher ($p < 0.001$) and the serum FT₄ and

Fig. 1 TSH, FT₄ and FT₃ levels in group A before and after pregnancy.

The serum TSH levels were measured in all 76 cases in group A (range: before pregnancy <0.003–0.277 μ IU/mL, after pregnancy <0.003–1.4 μ IU/mL). The serum FT₄ levels were measured in 66 cases before pregnancy and in 63 cases during the first trimester of pregnancy. The serum FT₃ values were measured in 41 cases before pregnancy and in 46 cases in the first trimester of pregnancy. The serum TSH, FT₄ and FT₃ levels before and after pregnancy were compared using Wilcoxon's signed rank test.

Fig. 2 TSH, FT₄ and FT₃ levels in group B before and after pregnancy.

The serum TSH levels were measured in all 90 cases in group B (range: before pregnancy <0.003–0.293 μ IU/mL, after pregnancy <0.003–16.6 μ IU/mL). The serum FT₄ levels were measured in 81 cases before pregnancy and in 78 cases during the first trimester of pregnancy. The serum FT₃ values were measured in 39 cases before pregnancy and in 43 cases in the first trimester of pregnancy. The serum TSH, FT₄ and FT₃ levels before and after pregnancy were compared using Wilcoxon's signed rank test.

FT₃ levels were significantly lower ($p < 0.001$ and $p < 0.001$) in the first trimester of pregnancy in group B.

The changes in L-T₄ dose before and during pregnancy in each group are presented in Fig. 3. The L-T₄ dose after consultation in the first trimester was significantly higher than that before pregnancy in both groups (all $p < 0.001$). The L-T₄ dose was self-increased by an average of 27.4% in group A. In detail, 71 of the 76 patients in group A took the double dose two days

weekly, two took the dose at the time of their previous pregnancy. One accidentally took the double dose one day weekly, one increased the double dose from one day weekly before pregnancy to three days, and one took the dose as directed by the obstetrician. The dose was increased after consultation in the first trimester to 24.5% and 14.6% higher than that before pregnancy in groups A and B, respectively. The mean increase in L-T₄ dose after pregnancy was lower in group B than in group

Fig. 3 Changes of L-T₄ dosage during pregnancy of each group.

The bottom and top of the box are the 25th and 75th percentile (the lower and upper quartiles, respectively). The band near the middle of the box is the 50th percentile (median). The ends of the whiskers represent the minimum and maximum of all the data. The Cross marks are outliers. The number of weeks of pregnancy in “After consultation” corresponds to “Pregnancy weeks in the first trimester” in Table 2.

A because 40% of the patients continued the same dose. However, when restricted to only those patients who increased their dose at the time of consultation, the average increase in L-T₄ dose from pre-pregnancy to the first trimester in group B was 25.6%. The median L-T₄ dose in the overall pregnancies with suppressive TSH levels was 125 µg/day before pregnancy and was 142.9 µg/day in the first trimester of pregnancy.

The miscarriage rate was 7.9% in group A and 18.9% in group B (odds ratio: 2.7, 95% confidence interval: 1.01–7.28), and was significantly higher in group B. The preterm birth rate was 5.7% in group A and 13.7% in group B (odds ratio: 2.6, 95% confidence interval: 0.78–8.78), without significant difference. The median L-T₄ dose at delivery was 150 µg/day (IQR: 129–162 µg/day) in group A and 150 µg/day (IQR: 125–161 µg/day) in group B. The L-T₄ dose at delivery was significantly higher in group A than that in group B ($p = 0.03$). No patients in both groups had any new cancer recurrence or metastatic growth findings during pregnancy.

Discussion

Current guidelines of American Thyroid Association and the Japanese Association of Endocrine Surgeons state that patients with a history of thyroid cancer should take a substitute or suppressed dose of L-T₄, depending on their risk [11, 12]. However, the appropriateness of a dose increase in L-T₄ in this population is yet to be established. This study found that among patients who

were TSH suppressed before pregnancy, the serum TSH levels were significantly increased and the FT₄ and FT₃ levels were significantly decreased in the first trimester of pregnancy if the L-T₄ doses were not increased after pregnancy. When the average L-T₄ dose was increased by 27.4% immediately after pregnancy, the TSH-suppressed status was maintained after pregnancy in 84.2% of pregnancies.

The Endocrine Society Clinical Practice Guidelines recommended that L-T₄ dose should be increased at 4–6 weeks of gestation [13], with an additional dose of 30–50% required [3, 4]. However, the most appropriate timing for increasing the L-T₄ dose, that is, immediately after pregnancy or when elevation of serum TSH level is observed, is still unclear [14]. Alexander *et al.* prospectively evaluated 20 pregnancies with hypothyroidism, including Hashimoto’s disease, thyroid cancer, Graves’ disease, and benign thyroid nodules [8]. The L-T₄ requirements increased starting from 5 weeks’ gestation, and thus they recommended increasing the dose by about 30% as early as possible after pregnancy. Yassa *et al.* also conducted a prospective randomized trial of increasing L-T₄ in early pregnancy in patients with mostly Hashimoto’s disease [9]. They found that increasing the dose of L-T₄ by 29% immediately after pregnancy could achieve a TSH level of <2.5 µIU/mL in 85% of patients and <5.0 µIU/mL in 100% of the patients.

However, there are few reports on post-pregnancy L-T₄ adjustment in patients who are athyroid and have suppressed TSH levels before pregnancy. Lor *et al.* found

that when postoperative thyroid cancer patients adjusted their L-T₄ dose to maintain their TSH target range of 0.4 to 4.1 $\mu\text{IU/mL}$ during pregnancy, the mean cumulative dose gain during pregnancy was 9%, 21%, and 26% in each trimester [7]. Some patients did not need to increase their doses. Only patients with a pre-pregnancy TSH level of 0.01–0.4 $\mu\text{IU/mL}$ were able to maintain their serum TSH levels in the target range after pregnancy without increasing the L-T₄ dose. However, they considered that if the TSH-suppressed state needs to be maintained during pregnancy, the L-T₄ dose may need to be increased after pregnancy. Krhin *et al.* adjusted the L-T₄ dose after pregnancy to maintain the TSH between 0.01 and 0.29 $\mu\text{IU/mL}$ in patients who underwent total thyroidectomy and radioiodine ablation of the thyroid remnant. The TSH-suppressed status prior to pregnancy was maintained during pregnancy in 25% of the patients, and they did not require an increase in their L-T₄ dose [10]. The degree of dose increase was small (11%), and similar to Loh *et al.* [7], they pointed out that increasing L-T₄ dose immediately after pregnancy can lead to overtreatment and development of thyrotoxicosis. However, the range of changes in TSH level during pregnancy was significantly wide in the patients on suppressive L-T₄ therapy before conception, and the rate at which TSH was adequately suppressed during pregnancy was low.

In our study, among the patients with suppressed TSH levels prior to pregnancy who maintained the same L-T₄ dose after pregnancy, 41% did not require dose escalation in the first trimester of pregnancy. However, if the L-T₄ dose was not increased early in the pregnancy, the rate of failure to achieve TSH suppression during pregnancy was higher. TSH suppression was not achieved in 38.9% of pregnancies in group B. It is assumed that increasing the L-T₄ dose soon after pregnancy may help maintain TSH suppression in the early pregnancy period. However, the normal range of thyroid function indicators during early pregnancy in athyroid patients is unknown. Moreover, the effect of increasing the L-T₄ dose in the early pregnancy on pregnancy outcomes is still unclear. All previous reports have enrolled only a small number of cases in which the cause of hypothyroidism was postoperative thyroid cancer, and there were few miscarriage cases [7, 9, 10]. In our study, the possibility of overtreatment with empirical dose increase of L-T₄ after pregnancy and any adverse effect on pregnancy due to over-supplementation was unclear. Maternal subclinical hyperthyroidism was likely not associated with adverse pregnancy outcomes [6]. TSH level below 0.20 $\mu\text{IU/mL}$ was not associated with an increased risk of miscarriage in patients on L-T₄ supplementation [15].

Conversely, it has been reported that women on L-T₄ supplementation with TSH below 0.1 $\mu\text{IU/mL}$ have an

increased odds of preterm birth [16]. However, the report by Lemieux *et al.* does not discuss the pregnancy course for each cause of hypothyroidism. It does not evaluate whether there is a correlation between TSH below 0.1 $\mu\text{IU/mL}$ during pregnancy and preterm birth rate in patients even after thyroid cancer surgery. If the L-T₄ dose is not increased early after pregnancy in postoperative thyroid cancer patients, TSH suppression might not be achieved, as reported by Krhin *et al.* [10]. Our study shows that an increase in the average L-T₄ dose by 27.4% immediately after pregnancy results in maintaining TSH-suppressed status after pregnancy in 84.2%. Although pregnancy outcomes, such as birth weight, fetal growth, and perinatal complications, were not compared, there was no increase in miscarriage or preterm birth rates.

Collectively, our findings and those of previous studies [17–19] show that among athyroid patients after total thyroidectomy and are on L-T₄ therapy, those with suppressed serum TSH levels have normal serum FT₃ levels and mildly high serum FT₄ levels. Further, the presence of biochemical markers [19, 20] or symptoms [21] related to thyroid function studies in such patients indicate that patients with a low TSH have lower risks of developing hyperthyroid symptoms. Therefore, a low TSH level with normal serum FT₃ levels and mildly high FT₄ levels during pregnancy may be advantageous for maintaining the pregnancy and providing sufficient T₄ for the fetus. To our best knowledge, there are no studies on the associations between L-T₄ dose adjustment during early pregnancy and miscarriage rate in post-total thyroidectomy patients. This needs to be investigated in future research.

This study has some limitations. First, cases who had miscarried in the very early stage of pregnancy before consultation and whose post-pregnancy serum TSH levels could not be confirmed were excluded. This may have affected the miscarriage rate in each group. Second, the frequency of revisits to the hospital after the first trimester of pregnancy varied with each clinician. Krhin *et al.* reported that post-pregnancy thyroid function testing every 6 to 8 weeks failed to achieve TSH suppression during pregnancy in 75% of the patients, and 14% of them had elevated TSH levels above the normal range [10]. The American Thyroid Association (ATA) guidelines recommend that serum TSH levels should be monitored approximately every 4 weeks until 16–20 weeks of gestation, and at least once between 26 and 32 weeks of gestation [22]. In our study, it cannot be ruled out that the patients in both groups may have been under- or over-treated during pregnancy. This may be avoided by performing thyroid function tests every 4 weeks as recommended by ATA guidelines [22] and Yassa *et al.* [9].

The reason for significantly lower L-T₄ dose at delivery in group B than in group A may be because some patients were not opportune to receive dose adjustment after their hospital visit in the first trimester. If thyroid function tests were performed every 4 weeks during pregnancy, the L-T₄ doses in both groups might have been similar.

In conclusion, postoperative athyreotic patients taking TSH-suppressive dose of L-T₄ need to increase their dose early after pregnancy to prevent TSH elevation. By increasing L-T₄ dose by an average of 27.4% immediately after pregnancy, 84.2% of patients could maintain TSH suppression in the first trimester. The thyroid function of postoperative thyroid cancer patients on high doses of L-T₄ should be closely monitored during preg-

nancy because subsequent dose changes may be required to maintain adequate TSH levels.

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Author contributions: M. Minakata and M. Ito constructed this study design. M. Minakata analyzed the data. The other co-authors contributed by administering patient care.

Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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